HEART DISEASE AND LUNG CANCER RISKS

AFTER RADIOTHERAPY

KATHERINE E HENSON

ST CROSS COLLEGE, UNIVERSITY OF OXFORD

SUBMITTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN POPULATION HEALTH

MICHAELMAS TERM 2014

‘As the creeper that girdles the tree-trunk,

the Law runneth forward and back;

For the strength of the Pack is the Wolf,

and the strength of the Wolf is the Pack.’

-The Jungle Book, by Rudyard Kipling

Heart Disease and Lung Cancer Risks after Radiotherapy

Katherine E. Henson, St Cross College, Doctor of Philosophy, Michaelmas Term, 2014

ABSTRACT

Radiotherapy has been shown to increase the subsequent risk of heart disease among survivors of breast cancer, but little is known about factors, other than the dose of radiation delivered to the heart, which determine the magnitude of the risk. In addition, survivors of teenage and young adult cancer are internationally acknowledged as an understudied population, and limited information is available on their late health risks. This thesis sought to utilise the largest observational datasets available to date for these populations: the Collaborative Group on Observational Studies of Breast Cancer Survivors and the Teenage and Young Adult Cancer Survivor Study. These were used to firstly characterise the radiation-related risks of heart disease and lung cancer, and secondly to provide an overview of the long-term risk of heart disease for the entire spectrum of cancers diagnosed in teenagers and young adults aged 15 to 39.

Initially, a methodology study and systematic review demonstrated that selection effects and other biases can be very problematic during analyses of observational cohorts, particularly when using a radiotherapy comparison. However, in the case of heart disease and lung cancer, one can take advantage of the breast being a paired organ and use a laterality comparison, particularly when laterality played little effect in treatment selection. This comparison was used throughout the analyses of breast cancer patients.

This thesis demonstrated that adjuvant radiotherapy for breast cancer significantly increased the risk of heart disease among women with left-sided breast cancer and those patients with ipsilateral lung cancer. Interestingly, younger women were at the highest risk of heart disease, and a progressive proportional decrease in risk with increasing age at diagnosis was found, which has not been shown before. It also suggested that radiotherapy and chemotherapy combined may further increase the risk of heart disease among breast cancer patients. Survivors of teenage and young adult cancer, particularly Hodgkin lymphoma, were at a significantly raised cardiac mortality risk compared to the matched general population.

The findings of this thesis provide evidence to support continued follow-up for cancer patients, as survivors were found to be at a substantial risk into the second or third decade after treatment. It has permitted the detection of groups of individuals at particularly increased risks, for example younger patients and survivors of Hodgkin lymphoma diagnosed in teenagers and young adults, for whom closer monitoring for late effects or measures to reduce the risk, such as adaptations to treatment, may be appropriate. Finally, evidence was also presented to support the development of clinical follow-up guidelines specifically for survivors of teenage and young adult cancer.

ACKNOWLEDGEMENTS

Firstly, I would like to extend my sincere thanks to my supervisors: Professor Sarah Darby, Dr Paul McGale and Professor Mike Hawkins. Thank you very much for all of your excellent advice, guidance and support throughout my DPhil. Without you this thesis would not exist. I would also like to thank everyone in both of the research teams in Oxford and Birmingham, particularly Dr Raoul Reulen, Dr David Cutter, Dr Carolyn Taylor and David Winter. I have been reliant on many of the member of these teams throughout the past few years, and I would like to thank you all for your help and friendship. Also, I would like to thank Dr Reshma Jagsi for her expert input on my methodology work using SEER.

Secondly, thanks to my family – especially Mum, Dad and Rach - for keeping me sane! Of course, also thank you for your encouragement and general greatness.

Then there is the Wolfpack, and everyone who has made my time in Oxford great - particularly Betts, Bel and Frenchie. Thank you. WCBC and OUWLRC provided me with good times on and off the water, for which I am grateful. Not forgetting, of course, thank you to Mutsa and Ely.

CONTENTS

This thesis contains approximately 39,000 words.

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

AER	absolute excess rate
ALL	acute lymphoblastic leukaemia
AMI	acute myocardial infarction
AML	acute myeloid leukaemia
AP	angina pectoris
BCCSS	British Childhood Cancer Survivor Study
BCS	breast conserving surgery
CAD	coronary artery disease
CCSS	Childhood Cancer Survivor Study
CHF	congestive heart failure
CI	confidence interval
CNS	central nervous system
COBS	Collaborative Group on Observational Studies of Breast Cancer Survivors
CT	computed tomography
E	expected
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ERR	excess rate ratio
FPT	first primary tumour
FU	follow-up
GU	genitourinary
Gy	Gray
HD	heart disease
HES	Hospital Episode Statistics
HL	Hodgkin lymphoma
HSC-IC	Health and Social Care Information Centre
ICD	International Classification of Diseases
IHD	ischaemic heart disease
IMC	internal mammary chain
IMRT	intensity modulated radiotherapy
MCE	major coronary event
MI	myocardial infarction
MR	mortality ratio
NHL	Non-Hodgkin lymphoma
NHS	National Health Service
O	observed
ONS	Office of National Statistics
RCT	randomised controlled trial
RR	rate ratio
RT	radiotherapy
SEER	Surveillance, Epidemiology, and End Results
SHRR	standardised hospitalisation rate ratio
SMR	standardised mortality ratio
STS	soft tissue sarcoma
Sv	Sievert
TYA	teenage and young adult
TYACSS	Teenage and Young Adult Cancer Survivor Study

CHAPTER 1:
INTRODUCTION & LITERATURE REVIEW

1.1 Introduction

Cancer is one of the world's most common diseases, and in 2008 there were an estimated 12.7 million new cancer cases diagnosed. An estimated 7.6 million people died from cancer in 2008, representing 21% of global non-communicable disease deaths[1]. Cancer comprises over a hundred diseases in which abnormal cells divide uncontrollably and invade other tissues. The diagnosis, management and survival vary greatly between different cancer types. However, the current main treatment options are usually a combination of surgery, radiotherapy, chemotherapy and hormonal therapy, and new biological treatments are emerging.

Considering all cancers diagnosed in adults (usually defined as ages 15 years and older) combined, the 5-year survival is now over 50% in developed countries (excluding non-melanoma skin carcinoma). In the USA, 5-year survival was 65.9% (American Cancer Society 2011) and in the UK it was 59% and 49% for women and men, respectively, during 2010-11 (Cancer Research UK 2014). Most types of cancers, apart from cancers of the lung and pancreas, have seen a dramatic increase in survival over the last 40 years. Earlier diagnosis, including the increasing use of screening has contributed to a greater proportion of cancers being diagnosed at an early stage. This improved survival is largely due to advances in techniques which have enabled more effective treatment of the target whilst reducing damage to normal tissue. Figure 1-1 shows breast cancer mortality in middle-aged women in the USA and the UK over the period 1950 to 2010, showing a steep decline in mortality from about 1990 following advances in treatment. However, cancer treatment does carry risks alongside the benefits, and improvements in survival for many cancers mean that quantifying and attempting to minimise long-term adverse health effects is becoming ever more important.

[1] http://www.who.int/gho/ncd/mortality_morbidity/en/
[2] http://www.who.int/healthinfo/statistics/mortality_rawdata/en/

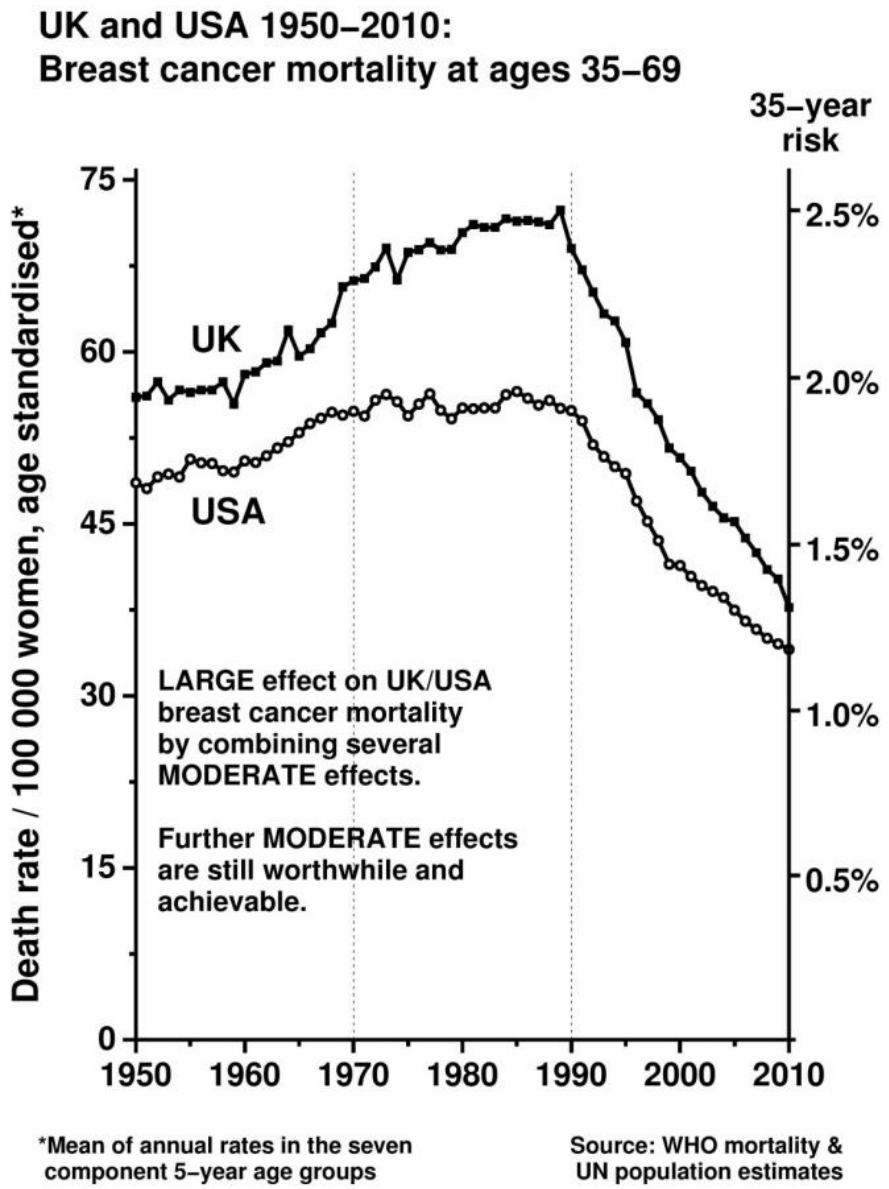


Figure 1-1: Breast cancer mortality in the UK and USA, 1950-2010.

Age-standardised death rate per 100,000 women and 35-year risk (%)
Data sources: the WHO Mortality Database[2] & World Population Prospects: The 2012 Revision[3]

Radiotherapy was first used by Grubbe to treat a patient for breast cancer in 1896, and patients were treated for various cancers throughout the first half of the twentieth century. By 1960, radiotherapy became one of the standard therapies used adjuvantly for breast cancer patients following breast conserving surgery in many countries, with the first randomised trial of breast conserving surgery and radiotherapy versus mastectomy established in 1972 (Rayter

[2] http://www.who.int/healthinfo/statistics/mortality_rawdata/en/
[3] http://esa.un.org/wpp/

2008). It is also often used following mastectomy in node-positive disease. Breast cancer is the most commonly diagnosed cancer among women in the developed world, meaning that a small improvement in patient survivorship could result in a large public health impact. Survival in breast cancer is also good, with 10-year relative survival around 77% in the UK (Cancer Research UK 2014). As a consequence, there are large numbers of breast cancer survivors in the population who are at risk of late effects of their cancer treatment. Thus, the first half of this thesis will focus on the late adverse effects of cancer in breast cancer patients.

Overviews of the randomised trials of radiotherapy for early breast cancer have been conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) since 1985. The first meta-analysis of local therapy randomised trials for local therapies was published by EBCTCG in 1995. As demonstrated by Figure 1-2, radiotherapy after breast conserving surgery (BCS) has been shown to have a significant benefit on both recurrence and breast cancer mortality over a period of 15 years following treatment (Early Breast Cancer Trialists' Collaborative Group 2011). Among 10,801 women with node-negative breast cancer (i.e. no spread of disease to the axillary lymph nodes), radiotherapy reduced the 5-year local recurrence by 15.4% (15.6% risk of any first recurrence after breast cancer in women randomised to radiotherapy versus 31.0% in women randomised to not receive radiotherapy), and the 15-year absolute gain in breast cancer mortality was 3.3% (17.2% risk of breast cancer death in women randomised to receive radiotherapy vs 20.5% in women randomised to not receive radiotherapy). Among women with node-positive breast cancer (i.e. spread to the axillary lymph nodes), the absolute benefits of radiotherapy after breast conserving surgery were much larger: the 5-year absolute gain in local recurrence was 21.2% (42.5% vs 63.7%), resulting in a 15-year absolute gain in breast cancer mortality of 8.5% (42.8% vs 51.3%). The most recent EBCTCG overview included individual patient data from 8,135 women randomised in 22 trials of radiotherapy after mastectomy and axillary surgery (Early Breast Cancer Trialists' Collaborative Group 2014). Post-mastectomy radiotherapy demonstrated

clear gains in women with node-positive disease, with a 10-year absolute gain of any first recurrence of 10.6% (51.9% vs 62.5%), and a 20-year absolute gain of 8.1% (58.3% vs 66.4%) in breast cancer mortality.

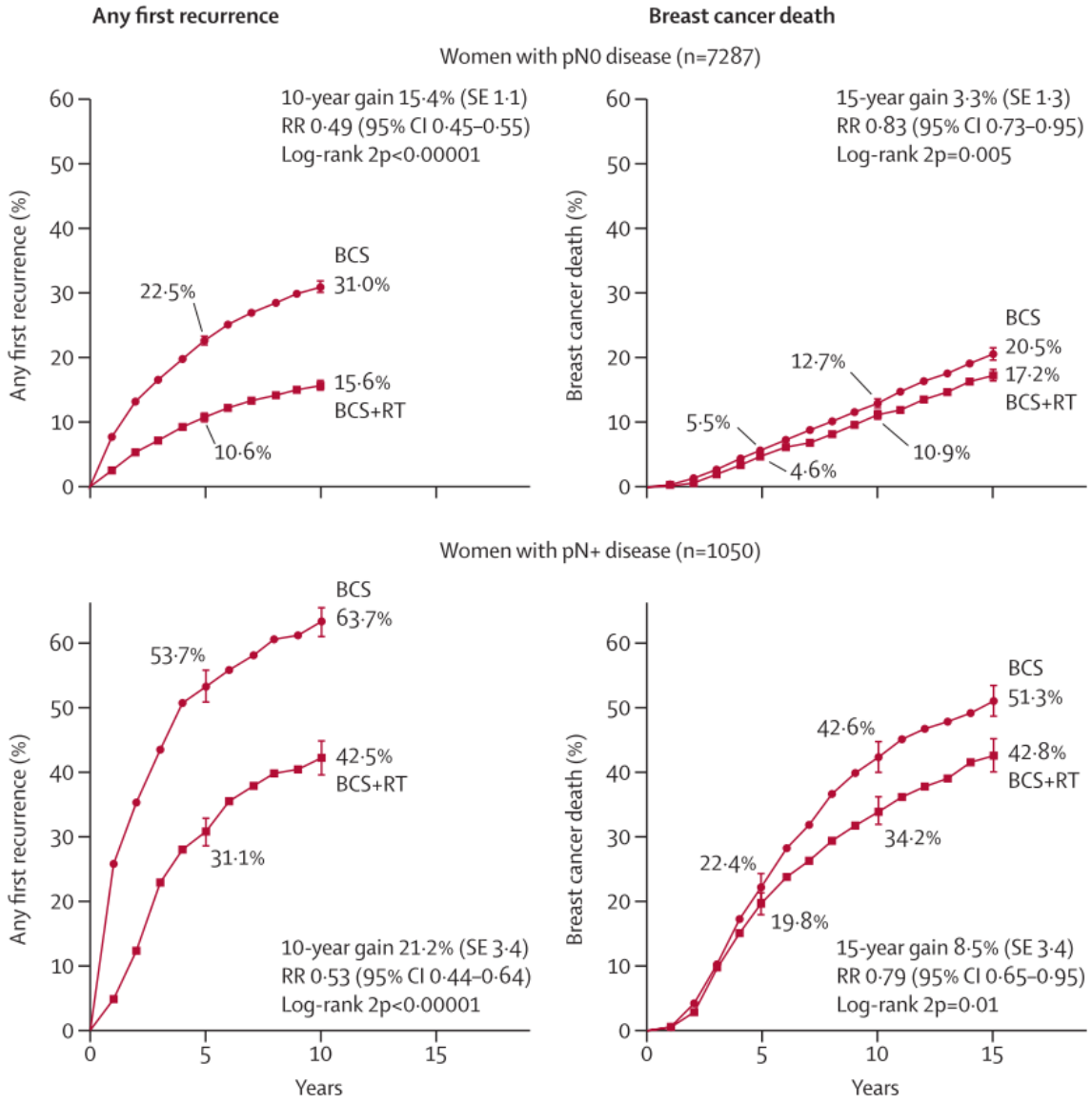


Figure 1-2: Effect of radiotherapy after breast conserving surgery (Early Breast Cancer Trialists' Collaborative Group 2011).

15 year probabilities (%) of isolated local recurrence (left-hand panel) and breast cancer mortality (right-hand panel) for women with node-negative and node-positive disease. Data from 10 trials. Vertical lines indicate 1 SE above or below the 5, 10 and 15 year percentages. BCS = breast conserving surgery

Despite its clear benefits, it has been shown that women who received radiotherapy after surgery can be at an increased risk of death from all causes other than breast cancer. This has been shown to be largely due to heart disease and second primary cancers, mainly lung cancer (Early Breast Cancer Trialists' Collaborative Group 2005), see Table 1-1. The focus of this thesis will therefore be on the largest causes of increased mortality following radiotherapy from causes other than breast cancer: heart disease and lung cancer.

Cause of death or site of cancer (ICD-9 categories)	Events	Logrank O-E*	Variance of (O-E)	Ratio of rates†	2p
Incidence of contralateral breast cancer:					
- by years since randomisation (and, for cases, mean year of randomisation)					
0-4 (1980)	673	1.3	161.1	1.01 (0.08)	0.9
5-14 (1980)	627	53.5	150.2	1.43 (0.10)	0.00001
15+ (1975)	151	2.1	33.4	1.06 (0.18)	0.7
- by age at randomisation					
<50	600	11.7	143.0	1.09 (0.09)	0.3
50+	851	45.1	201.3	1.25 (0.08)	0.002
- by use of systemic therapy					
with chemotherapy or tamoxifen	649	21.7	158.0	1.15 (0.09)	0.08
without chemotherapy or tamoxifen	802	35.1	186.4	1.21 (0.08)	0.01
Total contralateral breast cancer	**1451**	**56.9**	**344.4**	**1.18 (0.06)**	**0.002**
Incidence of other specified cancers: ‡					
Lung cancer (162)	215	24.3	51.1	1.61 (0.18)	0.0007
Oesophagus cancer (150)	31	5.4	7.5	2.06 (0.53)	0.05
Leukaemia (204-208)	59	7.5	13.9	1.71 (0.36)	0.04
Soft-tissue sarcoma (158, 171)	26	5.4	6.4	2.34 (0.62)	0.03
Thyroid cancer	26	-2.3	6.2	0.69 (0.34)	0.4
Bone cancer	28	1.7	6.9	1.28 (0.43)	0.5
Other specified malignancy	966	16.4	220.7	1.08 (0.07)	0.3
Total other specified cancers	**1351**	**58.4**	**312.7**	**1.20 (0.06)**	**0.001**
Mortality before recurrence from causes other than breast cancer:					
- by cause					
Circulatory disease	**1510**	**77.6**	**345.4**	**1.25 (0.06)**	**0.00003**
Heart disease, etc §	1106	60.7	252.7	1.27 (0.07)	0.0001
Stroke	345	9.1	80.9	1.12 (0.12)	0.3
Pulmonary embolism	59	7.8	11.8	1.94 (0.41)	0.02
Other specified cause	**1455**	**6.4**	**335.8**	**1.02 (0.06)**	**0.7**
Lung cancer	156	21.7	37.5	1.78 (0.22)	0.0004
Oesophagus cancer	23	4.9	5.6	2.40 (0.68)	0.04
Leukaemia	31	2.4	7.0	1.40 (0.45)	0.4
Soft-tissue sarcoma (158, 171)	7	1.3	1.7	2.13 (1.14)	0.3
Respiratory disease (460-519, 786)	241	-1.0	55.5	0.98 (0.13)	0.9
Other known cause	997	-22.9	228.5	0.90 (0.06)	0.1
Unspecified cause, not breast cancer	**701**	**7.8**	**159.4**	**1.05 (0.08)**	**0.5**
- by years since randomisation (and, for deaths, mean year of randomisation)					
0-4 (1976)	756	7.4	176.4	1.04 (0.08)	0.6
5-14 (1975)	1513	37.7	348.4	1.11 (0.06)	0.05
15+ (1970)	1397	46.9	304.8	1.17 (0.06)	0.01
- by age at randomisation					
<50	554	27.4	129.6	1.24 (0.10)	0.02
50+	3112	64.4	699.8	1.10 (0.04)	0.02
Total non-breast-cancer deaths ‖	**3666**	**91.8**	**829.4**	**1.12 (0.04)**	**0.001**

*Approximate excess number of events in radiotherapy group is 2(O-E). †Ratio of annual event rates (and its standard error), irradiated vs unirradiated, stimated from O-E and its variance V as exp([O-E]/V).[20] ‡Primary cancers of all specified sites (140-194, 200-208) except non-melanoma skin (173) and reast. Includes RT vs not: 3 vs 2 thyroid cancer (193), 1 vs 0 bone cancer (170). §All circulatory (390-459, 785, 798) except stroke (430-438) and pulmonary mbolism (415, 451, 453, 673). ‖The analyses in this table (and in the corresponding webfigure 7) are stratified by only 2 groups of age; had they been stratified y 5 age-groups, as in the main analyses, and the node-negative patients from 80 Y Edinburgh appropriately removed (see footnotes "added in proof" to annex-bles 2 & 3), these mortality results would have been only very slightly more extreme (eg, for total non-breast cancer deaths the logrank O-E would have been 3.4 with variance 789.2, rate ratio 1.126 SE 0.04, 2p=0.0009).

Table 1-1: Effect of radiotherapy on incidence of second cancers before recurrence of breast cancer, and on mortality from causes other than breast cancer (Early Breast Cancer Trialists' Collaborative Group 2005).

The second part of this thesis will focus on another population: individuals diagnosed with cancer as teenagers or young adults. This group is internationally acknowledged as understudied, with very few studies published on adults diagnosed with cancer at ages 15-39. An increased risk of heart disease has been demonstrated in both adult and childhood cancer survivors (Moller, Garwicz et al. 2001, MacArthur, Spinelli et al. 2007, Armstrong, Liu et al. 2009, Mulrooney, Yeazel et al. 2009, Reulen, Winter et al. 2010), especially survivors of Hodgkin lymphoma (Ng, Bernardo et al. 2002, Aleman, van den Belt-Dusebout et al. 2003, Swerdlow, Higgins et al. 2007). Yet, there are few published studies that address the late heart disease risk among survivors of cancer diagnosis in teenagers and young adults.

Within the teenage and young adult (TYA) cancer age range of 15-39 years, breast cancer is the most commonly diagnosed cancer relative to the other cancers diagnosed, particularly at the older ages at diagnosis (i.e. 30-39 years). Therefore, investigation of TYA cancer survivors will provide more evidence on late cardiac risks after breast cancer diagnosed during younger ages, and the treatment related effects demonstrated in the breast cancer population could potentially help to inform understanding of the late adverse risks for the TYA cancer population. Therefore, findings from the two parts of this thesis should complement each other.

1.2 Radiation-related heart disease after breast cancer therapy: a review

The position of the heart often results in incidental irradiation during breast cancer treatment. Radiation-related cardiotoxicity is associated with both treatment factors and patient characteristics, for example pre-existing heart disease, breast cancer laterality and use of internal mammary chain (IMC) radiotherapy. Pre-existing heart problems can result in a greater absolute risk of treatment-related heart disease, as shown in a recent study in which the percentage increase in risk per Gray of radiation delivered to the heart was the same in all women regardless of prior heart disease, but the absolute risk was much higher in women with cardiac problems (Darby, Ewertz et al. 2013).

Studies of patients with very high cardiac radiation exposures (for example as delivered in previous decades for Hodgkin lymphoma) show that a variety of cardiac structures, including the myocardium, valves, pericardium and arteries, can be damaged by radiation. The manifestations of radiation-related cardiotoxicity can take many forms, including: coronary artery disease, cardiomyopathy, pericardial disease, valvular disease and conduction system abnormalities. A detailed discussion of the clinical presentation and management of radiation-related heart disease is presented elsewhere (Heidenreich and Kapoor 2009, Cutter, Taylor et al. 2010). There are a number of mechanisms in different heart structures by which radiation causes cardiac damage, these mechanisms and the pathology of radiation-related cardiotoxicity have also been presented elsewhere (Adams, Hardenbergh et al. 2003, Schultz-Hector and Trott 2007, Cutter, Taylor et al. 2010).

Previously, it was believed that radiation-related heart disease usually had a latency period of at least a decade, depending on the type of heart disease involved. For example, radiation-related acute pericarditis has been reported within a few months from exposure, whilst an increased risk of valvular heart disease has been reported at more than 15 years. Recent evidence also suggests that radiation-related ischaemic heart disease can occur within the first five years (McGale, Darby et al. 2011, Darby, Ewertz et al. 2013). The extent and duration of these risks are not yet fully understood and further research is therefore needed.

1.2.1 Cardiac exposure from breast cancer radiotherapy

Cardiac exposure depends on the radiotherapy technique, the laterality of the breast cancer (discussed further in Section 1.2.3) and other factors. The “old era” of radiotherapy used techniques that are now known to be cardiotoxic, including direct megavoltage radiation, which incidentally irradiated large volumes of the heart at high doses (Taylor, McGale et al. 2006). Internal mammary node irradiation also delivered high radiation dose to large volumes of the heart in left-sided breast cancer treatment (Taylor, Nisbet et al. 2007).

In more recent years, radiotherapy techniques have improved and there has been increased awareness of radiotherapy cardiotoxicity and the need to protect the heart (Janjan, Gillin et al. 1989, Fuller, Haybittle et al. 1992, Taylor, Povall et al. 2008). The use of tangential fields became standard practice, leading to a reduced dose to the heart. However, the left anterior descending coronary artery still receives a substantial dose for women with left-sided breast cancer. New techniques, for example intensity modulated radiotherapy (IMRT) have been introduced which expose the whole heart to doses in the order of 5 Gy (Jagsi 2014). The late effects of these treatments are still unknown (Magne, Chargari et al. 2010). More accurate delineation of tumour and normal tissues during treatment planning has been possible by advances in technology. Three-dimensional based computed tomography (CT) planning allows estimation of the dose to the normal tissue surrounding the radiotherapy target and can help limit the dose to the organs at risk. It is currently premature to conclude that recent techniques are not cardiotoxic, highlighting the importance of continued follow-up and updated analyses of patients treated with radiotherapy.

1.2.2 Heart disease mortality associated with radiotherapy: randomised evidence

The cardiotoxicity of breast cancer radiotherapy was first suggested in early randomised trials (Stewart and Fajardo 1984, Høst, Brennhovd et al. 1986, Cuzick, Stewart et al. 1987, Haybittle, Brinkley et al. 1989, Jones and Ribeiro 1989, Corn, Trock et al. 1990, Rutqvist and Johansson 1990, Rutqvist, Lax et al. 1992), and subsequently confirmed by meta-analyses of trials of radiotherapy treatment. Currently, individual patient data meta-analyses are conducted by the Early Breast Cancer Trialists' Collaborative Group approximately every five years. The first EBCTCG meta-analysis to combine all radiotherapy trials found that the increase in survival associated with radiotherapy was offset by an increased risk of mortality from other diseases (Early Breast Cancer Trialists' Collaborative Group 2000). This was largely due to a significant 30% excess in vascular causes. The updated meta-analysis in 2005 was based on 42,080 women in 78

randomised trials which began before 1995. Follow-up extended to 2000 and there were 21,531 deaths recorded. Among patients who were randomised to radiotherapy the death rate from heart disease was increased by 27% (2p=0.0001, see Table 1-1) (Early Breast Cancer Trialists' Collaborative Group 2005). This excess mortality continued to increase into the second decade after exposure.

Two separate randomised controlled trials (RCTs) analysed the morbidity risk from ischaemic heart disease (IHD) and myocardial infarction (MI). The first trial was conducted in Sweden during 1971-76, and presented the findings subdivided by cardiac dose-volume among mastectomy patients randomised to radiotherapy (Gyenes 1998). The trial included 960 women, with median follow-up of 20 years. The second study considered post-mastectomy radiotherapy in high-risk patients from the Danish Breast Cancer Cooperative Group diagnosed with breast cancer during 1982-90, with an average follow-up of 10 years (Hojris, Overgaard et al. 1999). Neither study found a significant excess of either fatal or non-fatal ischaemic heart disease or myocardial infarction events after radiotherapy (IHD mortality relative hazard: 0.84 95% CI 0.38-1.83 in Danish study), yet it was shown that mortality was positively correlated with cardiac dose-volume in the Swedish trial . The non-significance of the hazard ratios presented may have been due to a low number of events, which is a problem overcome by meta-analyses of large numbers of randomised evidence.

1.2.3 Heart disease mortality associated with radiotherapy: observational evidence

The process of randomisation in a clinical trial results in groups of patients where the only difference between them is the treatment they were allocated to receive. All patient characteristics, and other potential confounders, should be evenly distributed between the groups. Thus, randomised results are robust, and viewed as the gold-standard for assessing treatment efficacy and effectiveness. However, patients included in RCTs are a highly selected population, usually of otherwise healthy individuals without comorbidities, and elderly patients

are excluded. A limited number of women were randomised in trials of radiotherapy, and very limited data was collected about each woman. Several of the EBCTCG trials were also conducted in the "old" radiotherapy era, in which the radiotherapy given is now known to give appreciable heart radiation dose. Observational data can complement the randomised evidence and provides essential additional information on radiation-related heart disease risk (Jagsi, Bekelman et al. 2014).

A comparison of heart disease rates in women given radiotherapy versus those not given radiotherapy in observational data tends to be confounded, as there are many factors that influence whether a patient receives radiotherapy, which cannot all be controlled for during analysis. However, the position of the heart to the left-side of the body results in the heart usually receiving a higher radiation dose during treatment for left-sided breast cancer as compared to right-sided breast cancer. In the results chapters it will be shown that laterality did not usually influence the decision to use radiotherapy. Thus, a comparison of heart disease rates in women with left-sided versus right-sided breast cancer can produce reliable results regarding radiation-related heart disease in observational data. This topic has been investigated in 16 published studies using a comparison of left-sided versus right-sided breast cancer (summarised in Table 1-2). The four largest of these found an excess of heart disease following radiotherapy for left-sided breast cancer compared to right-sided (Paszat, Mackillop et al. 1998, Darby, McGale et al. 2003, Darby, McGale et al. 2005, Henson, McGale et al. 2013). Two studies of the US Surveillance Epidemiology and End Results (SEER) data, showed a significant 16% (Darby, McGale et al. 2005) and 8% (Henson, McGale et al. 2013) excess of heart disease deaths following left-sided as compared to right-sided breast cancer. In contrast, no such excess was found for women who were not recorded to have received radiotherapy. Henson et al is an extension of the analysis performed by Darby et al, and confirmed the results in a larger sample size of 558,871 women, with an extended follow-up to 1st January 2009 and extended period of breast

cancer diagnosis, thus including women diagnosed more recently. These studies both showed very clearly the increasing cardiac risk with increasing time since diagnosis, particularly in the early diagnosis periods. The mortality ratio, left-sided vs right-sided, in irradiated women during <10, 10-14, 15-19 and 20+ years since diagnosis were 1.19 (95% CI 1.03-1.38), 1.35 (95% CI 1.05-1.73), 1.64 (95% CI 1.26-2.14) and 1.90 (95% CI 1.52-2.37), respectively (2p for trend <0.001). In both studies, there was evidence of a reduced hazard for women diagnosed more recently; but this finding was limited by a shorter follow-up period. Fatal myocardial infarction was also investigated in the SEER database (Paszat, Mackillop et al. 1998) using women diagnosed during 1973-1992. The cardiac mortality ratio, left-sided versus right-sided, in irradiated ratio was significantly elevated (1.17 95% CI 1.01-1.36), and especially amongst patients aged less than 60 years (RR = 2.24 95% CI 1.38-3.64), particularly in the period 10-15 years after diagnosis.

The remaining studies all found an excess of heart disease mortality following left-sided breast cancer, yet in none of them did the results reach statistical significance (Nixon, Manola et al. 1998, Harris, Correa et al. 2006, Marhin, Wai et al. 2007, Gutt, Correa et al. 2008, Bouchardy, Rapiti et al. 2009, Bouillon, Haddy et al. 2011). All but two of these studies, except for Bouillon and Nixon, included women diagnosed since 1980. This could account for the lack of a significant excess, as improvements in radiotherapy techniques have reduced the mean radiation dose received by the heart and the volume of heart irradiated compared with women irradiated earlier. However, there is also shorter follow-up available for more recent studies so risks may be continuing after the end of follow-up.

A number of the studies in Table 1-2 focused on specific types of heart disease (Rutqvist and Johansson 1990, Paszat, Mackillop et al. 1999, Vallis, Pintilie et al. 2002, Giordano, Kuo et al. 2005). A significant excess of ischaemic heart disease deaths following left-sided breast cancer (1.06 95% CI 1.00-1.12) was present in a study of almost 90,000 women with approximately 4,500

deaths recorded by the Swedish nationwide cancer registry (Darby, McGale et al. 2003). This estimate was for all women, both irradiated and unirradiated, as the cancer registry does not record information on radiotherapy treatment, but it was estimated that a third of the women were irradiated. Ischaemic heart disease risk was analysed using the SEER database of women diagnosed during 1973-1989 with an average follow-up of 9.5 years (Giordano, Kuo et al. 2005). Approximately 2,000 women died from IHD, giving a mortality ratio, left-sided versus right-sided, of 1.16 (95% CI 1.07-1.26). A UK-based study found a non-significant 23% excess of IHD mortality in irradiated women treated during 1971-1988 (Roychoudhuri, Robinson et al. 2007). In addition, four studies have investigated a specific IHD diagnosis, by analysing the rate of fatal myocardial infarction during the 1980s (Rutqvist and Johansson 1990, Paszat, Mackillop et al. 1999, Vallis, Pintilie et al. 2002, Borger, Hooning et al. 2007) in Canada and Sweden. A significant excess of fatal MI (1.09 95% CI 1.02-1.17) was found in left-sided breast cancer patients in a Swedish population of 20,871 women, with an average follow-up of 9 years (Rutqvist and Johansson 1990). This excess was present during the entire follow-up, and increased with time since diagnosis. The smaller study, of 3,006 women diagnosed in Canada, also found a significant excess of fatal MI with a mortality ratio, left-sided versus right-sided, of 2.10 (95% CI 1.11-3.95). In contrast to the study by Paszat and colleagues in 1998, an increased risk was found for Canadian patients older than 60 years at diagnosis.

Paper	Population	Number of women	Treatment Period	Average FU	Outcome	Overall MR (L vs R)
Henson et al (2013)	SEER	558,871	1973-2008	-	Heart disease	1.08 (1.03-1.14)
Bouillon et al (2011)	Institut Gustave Roussy	4,456	1954-1984	28 yrs.	Heart disease	1.28 (0.92-1.78)
Bouchardy et al (2009)	Geneva Cancer Registry, node negative	1,243	1980-2004	7.7 yrs.	Heart disease	0.7 (0.3-1.6)
Gutt et al (2008)	University of Pennsylvania, pre-existing heart disease	41	1980-1994	7.9 yrs. (L) 11.3 yrs. (R)	Heart disease	4.2 (0.9-20.9) ** at 10 years FU*
Borger et al (2007)	5 hospitals, Netherlands & Belgium	1,601	1980-1993	16 yrs.	MI	- p=0.11
Marhin et al (2007)	British Columbia Cancer Agency	7,447	1984-2000	7.9 yrs.	Heart disease	1.07 (0.72-1.59)
Paszat et al (2007)	Ontario Cancer Registry	89	1982-1988	13.5 yrs.	Fatal acute MI	1.07 (0.65-1.72)
Harris et al (2006)	Medical record review, Pennsylvania	961	1970-1994	12 yrs.	Heart disease	1.67 (0.78-3.62)
Darby et al (2005)	SEER	308,861	1973-2001	6.2 yrs.	Heart disease	1.16 (1.08-1.24)
Giordano et al (2005)	SEER	27,283	1973-1989	9.5 yrs.	Ischaemic heart disease	1.16 (1.07-1.26)
Darby et al (2003)	Swedish Cancer Registry	89,407	1970-1996	-	Ischaemic heart disease	1.06 (1.00-1.12)
Vallis et al (2002)	Princess Margaret Hospital, Ontario	2,128	1982-1988	10.2 yrs.	Fatal MI	1.16 (0.91-1.48)
Paszat et al (1999)	Ontario Cancer Registry	3,006	1982-1987	106 months	Fatal MI	2.10 (1.11-3.95)
Nixon et al (1998)	Joint Centre for Radiation Therapy, Harvard	745	1968-1986	Min 12 yrs.	Heart disease	1.03 (0.42-2.59)
Paszat et al (1998)	Ontario Cancer Registry	206,523	1973-1992	7.4 yrs.	Fatal MI	1.17 (1.01-1.36)
Rutqvist et al (1990)	Swedish Cancer Registry	54,617	1970-1985	9 yrs.	Fatal MI	1.09 (1.02-1.17)

Table 1-2: Summary of studies of radiation-related heart disease mortality using a comparison of left-sided versus right-sided breast cancer in irradiated women.

FU = follow-up
MR = mortality ratio
L vs R = left-sided versus right-sided breast cancer
MI = myocardial infarction
yrs. = years

1.2.4 Heart disease incidence associated with radiotherapy: observational evidence

The incidence of heart disease associated with radiation for breast cancer has been investigated in a number of studies which are summarised in Table 1-3. There was an elevated risk of heart disease following left-sided breast cancer in all but one study (Rutqvist, Liedberg et al. 1998), and the excess reached significance in five studies (Harris, Correa et al. 2006, Borger, Hooning et al. 2007, Jagsi, Griffith et al. 2007, McGale, Darby et al. 2011, Darby, Ewertz et al. 2013). The incidence ratios vary widely, and may be due to random variation, but also patient characteristics, follow-up period and treatment received across the study populations may play a role.

The largest study, of 72,134 women in Denmark and Sweden, showed a significant 8% excess of heart disease diagnosed in left-sided patients compared to right-sided (McGale, Darby et al. 2011). No such excess was found for unirradiated women. Upon subdivision by specific categories of heart disease, a significant excess of left-sided events was shown for ischaemic heart disease (1.18 95% CI 1.07-1.30) (including the specific diagnoses of acute myocardial infarction and angina considered individually), pericarditis (1.61 95% CI 1.06-2.43) and valvular heart disease (1.54 95% CI 1.11-2.13). The excess of pericarditis was mainly attributable to acute pericarditis, and the valvular heart disease mainly consisted of aortic valvular disease. A left-sided excess of IHD and MI events has also been found in other studies (Vallis, Pintilie et al. 2002, Harris, Correa et al. 2006, Doyle, Neugut et al. 2007, Jagsi, Griffith et al. 2007, Paszat, Vallis et al. 2007), but the increased incidence of valvular heart disease and pericarditis has yet to be shown elsewhere.

Four studies suggested that there may be an association between patient history and subsequent risk of heart disease (Harris, Correa et al. 2006, Hooning, Botma et al. 2007, Paszat, Vallis et al. 2007, McGale, Darby et al. 2011). Specifically, prior heart disease was associated with an increased risk of radiation-related heart disease events (Paszat, Vallis et al. 2007, McGale,

Darby et al. 2011), as were traditional cardiac risk factors, for example smoking (Harris, Correa et al. 2006, Hooning, Botma et al. 2007, Paszat, Vallis et al. 2007).

Paper	Population	Number of women	Treatment Period	Average FU	Outcome	Overall IR (L vs R)
Darby et al (2013)	Case-control study, Denmark & Sweden	2,168	1958-2001	-	Major coronary event	- (p=0.002)
McGale et al (2011)	Denmark & Sweden	72,134	1976-2006	-	Heart disease IHD MI Angina Pericarditis Valvular HD	1.09 (1.02-1.15) 1.18 (1.07-1.30) 1.22 (1.06-1.42) 1.25 (1.05-1.49) 1.61 (1.06-2.43) 1.54 (1.1102.13)
Borger et al (2007)	5 hospitals, Netherlands & Belgium	1,601	1980-1993	16 years	Ischaemic heart disease	1.35 (0.93-1.98)
Correa et al (2007)	Pre-existing heart disease, USA	82	1977-1995	12 years		
Doyle et al (2007)	SEER-Medicare, USA	48,353	1992-2000	-	MI IHD	0.99 (0.87-1.11) 1.03 (0.93-1.13)
Hooning et al (2007)	Late Effects Breast Cancer Cohort, Netherlands	4,414	1970-1986	17.7 years	MI CHF	0.74 (0.31-1.79) 1.01 (0.40-2.55) --breast RT L vs R
Jagsi et al (2007)	University of Michigan Hospital, USA	834	1984-2000	6.8 years	MI	7.92 (1.01-62.28)
Paszat et al (2007)	Ontario Cancer Registry, Canada	6,680	1982-1988	13.5 years	Acute MI	1.42 (0.92-2.17)
Pinder et al (2007)	SEER-Medicare, USA	43,448	1992-2002	4.7 years	Heart failure	1.04 (0.97-1.10)
Harris et al (2006)	Medical record review, Pennsylvania	961	1970-1994	12 years	CAD MI	2.1 (1.7-4.5) 3.1 (1.5-6.5)
Patt et al (2005)	SEER-Medicare, USA	16,270	1986-1993	9.5 years	IHD Valvular HD Heart failure	- p=0.77 - p=0.93 - p=NS
Vallis et al (2002)	Princess Margaret Hospital, Ontario	2,128	1982-1988	10.2 years	MI	1.11 (0.64-1.93)
Rutqvist et al (1998)	Stockholm Breast Cancer Data Base	684	1976-1987	9 years	Acute MI	0.77 (0.25-2.42)

Table 1-3: Summary of studies of incidence of radiation-related heart disease using a comparison of left-sided versus right-sided breast cancer in irradiated women.

FU = follow-up
IR = incidence ratio
IHD = ischaemic heart disease
MI = myocardial infarction
CHF = congestive heart failures
HD = heart disease
CAD = coronary artery disease

1.2.5 Dose and dose-response relationship

As mentioned in Section 1.2.1, breast cancer radiotherapy can result in substantial radiation doses to the heart. The current average mean heart dose is likely to be 2-7 Gy for left-sided (Taylor, Povall et al. 2008, Jagsi, Abrahamse et al. 2010, Schubert, Gondi et al. 2011) and around 1.5 Gy for right-sided breast cancer. A systematic review of studies published during 2003 to 2013 (Dr Carolyn Taylor provisional work, personal communication, November 2014) demonstrated that the mean heart dose received was 4.8 Gy in women treated for left-sided breast cancer, and 1.6 Gy for right-sided radiotherapy. When dosimetric information is not available, the use of internal mammary chain irradiation may be associated with a higher risk of left-sided breast cancer versus right-sided breast cancer (Hooning, Botma et al. 2007). This is because the internal mammary nodes receive the highest radiation dose in left-sided breast cancer (Taylor, Nisbet et al. 2007) and use of internal mammary chain radiotherapy in left-sided breast cancer is one of the main determinants of mean cardiac dose.

Recently, a key study related an individual patient's cardiac dose and cardiac risk factors to her subsequent risk of a major coronary event (MCE) (Darby, Ewertz et al. 2013). A MCE was defined as a diagnosis of myocardial infarction, coronary revascularisation, or death from ischaemic heart disease. Individual radiotherapy plans were available for all women included in the study, allowing estimation of individual radiation dose received by the heart. The mean cardiac dose received was 6.6 Gy and 2.9 Gy for left-sided and right-sided breast cancer, respectively. The rate of major coronary events increased by 7.4% per Gy increase in mean heart radiation dose received ($p<0.001$) (see Figure 1-3). The percentage increase per Gray did not vary significantly by any tumour, treatment or patient characteristics. There was also no evidence of a threshold dose below which there was no radiation-related risk. The increase in risk started in the first five years after exposure and continued into the third decade. When combined with information on the background risk of heart disease, this dose-response relationship can allow

clinicians to estimate the absolute risk of radiation-related heart disease for their patients. In this study, the cardiac radiation exposure would in many cases be non-uniform, but little information is as yet available regarding the specific critical cardiac substructures that are most radiosensitive.

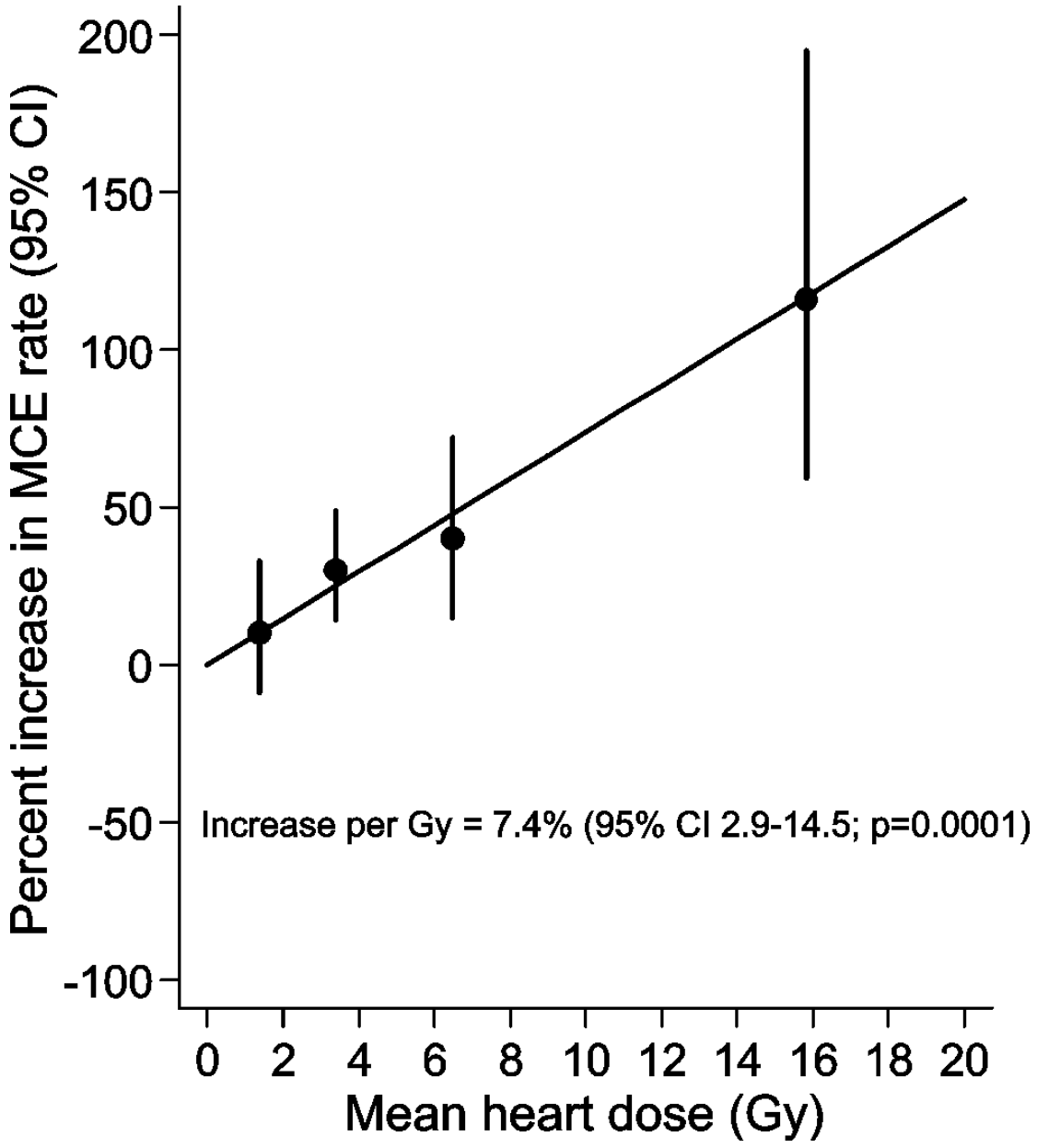


Figure 1-3: Rate of major coronary events according to mean radiation dose to the heart (Darby, Ewertz et al. 2013).

Percent increase in rate of major coronary events by mean dose of radiation received by the heart (Gy). Major coronary event was defined as a diagnosis of myocardial infarction, coronary revascularisation, or death from ischaemic heart disease.

Cardiac doses were retrospectively estimated for women with early breast cancer randomised to radiotherapy or no radiation in 62 trials. In each trial, the extent of surgery and use of adjuvant chemotherapy and hormonal therapy was similar in the two trial arms. The women were divided into three mean heart dose categories: <5 Gy, 5-15 Gy and 15+ Gy and combined with outcome data. It was found that the risk of death from heart disease increased by 31% per 10 Gy mean cardiac dose (Early Breast Cancer Trialists' Collaborative Group 2007). This dose-response relationship was highly significant (2p<0.0001).

1.2.6 Heart disease associated with radiation exposure: other evidence

The Life Span Study is a cohort of approximately 120,000 subjects who were exposed with a whole body uniform dose of 0-4 Gy to the atomic bomb in either Hiroshima or Nagasaki, Japan. The subjects were identified in the 1950 national census, and have subsequently been followed by the Radiation Effects Research Foundation for ascertainment of vital status. This study is one of the major sources of information on the risk of cancer following radiation exposure, and a report was published in 2003 demonstrating a radiation-related risk of heart disease (Preston, Shimizu et al. 2003). A report commissioned by the United Nations concluded that the Life Span Study was the only epidemiological cohort that could provide reliable evidence towards a possible association between radiation and heart disease risk (United Nations Scientific Committee on the Effects of Atomic Radiation 2008) in this low dose range. The risk of cardiovascular disease following cardiac radiation exposures in the range 0.5-5 Gy from other sources has been reviewed systematically elsewhere (McGale and Darby 2005), and since updated (McGale and Darby 2008). In order to evaluate whether information from other studies was consistent with the association reported for the atomic bomb survivors, this review found only six studies (out of a total 27) that were likely to be without substantial biases or confounding (McGale and Darby 2005). The study populations used could be broadly grouped into two exposure categories (other than exposure to atomic bombings): occupational and medical (diagnostic or therapeutic). Examples of these are

nuclear workers and patients irradiated for peptic ulcer, respectively. This review concluded that at that time there was not enough evidence to support the findings of the Life Span Study. However, since this review, a number of studies have suggested that low doses could increase the incidence of heart disease. For example, analyses of nuclear plant workers have suggested that there is an increase incidence of heart disease after radiation doses of less than 1Gy (Azizova, Muirhead et al. 2010).

In a further report from the Life Span Study of atomic bomb survivors, Shimizu et al (2010) reported detailed cardiovascular results and examined dose-response information for heart disease risk using 86,611 subjects with follow-up to 2003. A total of 8,463 heart disease deaths were recorded as the underlying cause. A dose-response relationship was found with an estimated ERR per Gy for all heart disease of 14% (95% CI 6-23, $p<0.001$). An overall association between radiation and all cardiovascular disease was also found (Ozasa, Shimizu et al. 2012). The overall ERR/Gy estimate for all cardiovascular disease was identical to the previous estimate for heart disease (Shimizu, Kodama et al. 2010). Stronger associations were found between radiation and specific diagnoses of heart disease. The accuracy of the diagnosis of heart disease as a whole was found to be high, with a 93% agreement between the autopsy report and the underlying cause listed. The accuracy of the diagnosis of specific types of heart disease was much lower: 69% for IHD, 64% for rheumatic heart disease and 22% for hypertensive heart disease. Therefore, there is reliable evidence for an association and a linear dose-response relationship between radiation and overall heart disease risk, but more evidence is needed before any conclusions can be drawn regarding subtypes of heart disease.

1.3 Radiation-related lung cancer after breast cancer radiotherapy: a review

Lung cancer has, in the past, been a substantial late hazard of radiotherapy for breast cancer. The risk of second primary cancers is a relatively difficult endpoint to study. Within a study population, second primary cancers tend to be relatively rare. Randomised controlled trials

provide an unbiased treatment comparison, and are viewed as the gold standard in analyses of effects of treatment. However, RCTs often have limited follow-up. Therefore, there may not be enough power in randomised evidence to detect trends in the second primary cancer risk. Population-based data often has the statistical power, yet it is limited by selection biases. Careful consideration of its limitations is necessary and the appropriate techniques should be used to minimise the inherent biases. A detailed discussion of the selection biases present in observational data is included in Chapter 3. Analyses of second cancer sites which are a common site of metastatic disease (for example lung cancer after breast cancer) need careful consideration in both observational and randomised data.

1.3.1 Lung cancer mortality associated with radiotherapy: randomised evidence

Radiation-related lung cancer has been considered in the meta-analysis of randomised controlled trials in early breast cancer (Early Breast Cancer Trialists' Collaborative Group 2005). A total of 42,000 women enrolled in 78 randomised trials were included. Both incidence of and mortality from lung cancer were considered. Among women randomised to radiotherapy, there was a 61% proportional increase (2p=0.0007) in lung cancer incidence. A 78% proportional increase was also found in the risk of mortality (before breast cancer recurrence) from lung cancer in those randomised to radiotherapy. This excess of lung cancer deaths was highly significant (2p=0.0004).

There are a number of other randomised trials published in which the radiation-related risk of second primary cancers combined has been studied (Jacobson, Danforth et al. 1995, Marini, Murray et al. 1996, Overgaard, Hansen et al. 1997, Overgaard, Jensen et al. 1999, Fisher, Anderson et al. 2002, Woodward, Strom et al. 2003, Ragaz, Olivotto et al. 2005). The majority found an excess of second primary solid tumours (including lung cancer) among women allocated to radiotherapy. However, specific analyses of lung cancer were not presented.

1.3.2 Lung cancer mortality associated with radiotherapy: observational evidence

When analysing observational data, a comparison of irradiated and unirradiated women needs to be interpreted cautiously due to the effect of selection of women for treatment. As with heart disease, there is an alternative comparison that can be used when analysing the risk of lung cancer: a comparison of ipsilateral to contralateral lung cancer. As the lungs are a paired organ, the lung on the same side as the treated breast will receive a higher dose than the lung on the opposite side. This produces a comparison of higher versus lower dose.

Within the literature there are few studies focusing on mortality risk of lung cancer in breast cancer survivors. Two studies, both using the SEER data, compared the mortality from ipsilateral and contralateral lung cancer in irradiated and unirradiated women separately, see Table 1-4 (Darby, McGale et al. 2005, Henson, McGale et al. 2013). Only women whose lung cancer had been microscopically confirmed previously were included. Henson et al (2013) was an update of the analysis presented by Darby et al (2005). Microscopic confirmation is important, as the lungs are a common site of metastases from breast cancer. Both studies found a significant excess of ipsilateral lung cancer deaths ($2p<0.001$) in women recorded to have received radiotherapy. A trend with increasing follow-up was present for women diagnosed during the first calendar period i.e. 1973-82, with a 4-fold excess by 20+ years of follow-up (Henson, McGale et al. 2013). A substantial increase was also shown for 20+ years of follow-up for women diagnosed during 1983-92, but no increase was detected as yet for women diagnosed more recently.

1.3.3 Lung cancer incidence associated with radiotherapy: observational evidence

The SEER population has also been used to investigate incidence, but no significant excess was found (Neugut, Lee et al. 1993). Data from the Swedish Cancer Registry was used and found no significant excess (Prochazka, Granath et al. 2002). This was followed by a more detailed analysis using a case-only approach, in which each woman contributed a pair of lungs and a pair

of breasts (Prochazka, Hall et al. 2005), enabling a comparison of women with concordant and discordant disease. A significant two-fold excess of concordant events was shown after 10+ years following breast cancer treatment (RR = 2.04 95% 1.24 – 3.36), and significant trend was present across the follow-up period (p=0.005) with the highest excess in the second decade of follow-up. The overall excess did not reach statistical significance for the remaining two studies but was highest in the second decade (Neugut, Lee et al. 1993, Prochazka, Granath et al. 2002).

These studies, of lung cancer incidence and mortality, using a comparison of ipsilateral and contralateral lung cancer, suggested that the radiation-related lung damage can occur in the ipsilateral lung. The contralateral lung also receives some scattered radiation from breast cancer radiotherapy, but has not been studied.

Paper	Type	Population	Number of women	Treatment Period	Average FU	RR in irradiated women (Ip. vs cont.)
Henson et al (2013)	Mortality	SEER	558,871	1973-2008	-	1.30 (1.16-1.45)
Darby et al (2005)	Mortality	SEER	308,861	1973-2001	6.2 years	1.41 (1.19-1.70)
Prochazka et al (2005)	Incidence	Swedish cancer registry	182 lung cancer cases	1958-2000	-	2.04 (1.24-3.36)
Prochazka et al (2002)	Incidence	Swedish cancer registry	141,053	1958-2000	12.2 years	1.26 (0.95-1.68) *estimated
Neugut et al (1993)	Incidence	SEER	56,359	1973-1986	6.9 years	1.1 (0.7-1.7)

Table 1-4: Summary of studies of radiation-related lung cancer using a comparison of ipsilateral and contralateral lung cancer.

FU = follow-up
RR = rate ratio
Ip. vs cont. = ipsilateral versus contralateral lung cancer

1.3.4 Risk factors associated with radiation-related lung cancer

The EBCTCG meta-analysis concluded that the factors associated with increased lung cancer among irradiated patients were: radiotherapy dose, younger age at diagnosis of breast cancer, and the volume of the normal lung tissue in the radiation field (Early Breast Cancer

Trialists' Collaborative Group 2005). The EBCTCG meta-analysis was limited by not having information on the main risk factor for lung cancer: smoking status.

A multiplicative relationship between radiotherapy and smoking status which increased the risk of lung cancer in women treated for breast cancer has been consistently demonstrated in a number of studies (Neugut, Murray et al. 1994, Obedian, Fischer et al. 2000, Ford, Sigurdson et al. 2003, Prochazka, Hall et al. 2005, Kaufman, Jacobson et al. 2008). The authors of one review paper stated that cigarette smoking is "the single most preventable lung cancer risk factor in patients receiving radiotherapy for breast cancer" (Lorigan, Califano et al. 2010).

This multiplicative effect resulted in an increased lung cancer risk in the range of 9-fold to 33-fold in current smokers exposed to radiotherapy compared to unexposed non-smoking women. The case-control study from the Connecticut Cancer Registry demonstrated that among smokers the additional multiplicative effect from radiation was only observed in the ipsilateral lung with no radiation-related risk in the contralateral lung, and that the radiation-related risk did not occur until more than 10 years after exposure (Neugut, Murray et al. 1994). In all studies, smoking was associated with an increased risk of lung cancer, but in all but one (Prochazka, Hall et al. 2005) a radiation-related risk was only observed when smoking status was accounted for. One limitation of these studies is that smoking was recorded only prior to the index breast cancer diagnosis. There was no information available on whether women stopped smoking after their breast cancer diagnosis. Therefore, the risk of radiation-related lung cancer in continuing smokers may be higher than indicated in these papers. In addition, radiation-related lung cancer has been shown to have a latency period of approximately a decade (Lorigan, Califano et al. 2010, Travis, Ng et al. 2012). Therefore, time since cancer diagnosis could be considered to be a risk factor.

1.3.5 Dose-response relationship

Three studies have attempted to quantify the dose-response relationship for radiation-related lung cancer in patients with breast cancer (Inskip, Stovall et al. 1994, Rubino, de Vathaire et al. 2003, Prochazka, Hall et al. 2005). The first of these was based on women diagnosed in the Connecticut Tumour Registry during 1945-1991, and found that the mean dose to the affected lung was weakly suggestive of a dose-response relationship with an excess rate ratio per Gy of 0.20 ($p=0.18$ for slope) (Inskip, Stovall et al. 1994). The case-only analysis of women treated more recently (1958-2000) in Sweden had greater statistical power (182 versus 76 cases, respectively), and showed a significant dose-response relationship with an excess rate ratio per Gy of 0.11 (95% CI 0.02-0.44) for all women combined (Prochazka, Hall et al. 2005). In this study, the excess rate ratio was more than twice the overall value for smokers (ERR/Gy: 0.23 95% CI 0.04-2.13). The French case-control study (Rubino, de Vathaire et al. 2003) found a statistically significant dose-response relationship between radiotherapy dose to the target and the overall risk of a second malignant tumour ($p<0.01$). This relationship became non-significant after excluding lung, soft tissue and bone cancer, suggesting that the dose-response relationship may be related to the lung cancer risk. However, lung cancer was not analysed separately. Dose-response relationships for recent treatment techniques, for example IMRT and proton therapy, are not yet known.

Estimates of recent average mean lung doses from breast cancer radiotherapy are around 7-18 Gy for the ipsilateral lung, and around 0.1-3 Gy for the contralateral lung using moderate deep-inspiration breath hold (Jagsi, Abrahamse et al. 2010) and tangential photon therapy (Schubert, Gondi et al. 2011). However, a significant reduction in lung dose ($p=0.0002$) has been found for women treated using deep inspiration breath hold (Nissen and Appelt 2013). A reduction in ipsilateral lung dose ($p<0.001$) has also been found through use of the prone position

compared to supine position (Ng, Shuryak et al. 2012). These results are promising for a lower lifetime radiation-related lung cancer risk among women treated more recently.

Treatment for Hodgkin lymphoma also involves thoracic radiation. A dose-response relationship for lung cancer has also been demonstrated in survivors of Hodgkin lymphoma (Travis, Gospodarowicz et al. 2002, Gilbert, Stovall et al. 2003). Among individuals irradiated 5 years or more before diagnosis of lung cancer, the excess relative risk per Gy was 0.15 (95% CI 0.06-0.39) (Gilbert, Stovall et al. 2003). Among 19,046 individuals treated during 1965-1994 the relative risks of lung cancer among individuals who received <5 Gy, and 40+ Gy to a specific location in the lung compared to 0 Gy were 1.3 (95% CI 0.3-4.9) and 7.2 (95% CI 2.2-28), respectively (Travis, Gospodarowicz et al. 2002).

As described above, the Life Span Study cohort includes individuals who were exposed to radiation from the atomic bombs in either Hiroshima or Nagasaki. It has been estimated that approximately 5% of the solid cancer deaths in the atomic bomb survivor population could be attributed to radiation exposure, with the majority of solid tumours occurring in the lungs and digestive tract. The mean lung dose received by the atomic bomb survivors was in the order of 0.2 Sv (Howe 1995). The most recent publication presented information on 86,611 subjects, with 1,558 cases of lung cancer. The overall ERR/Gy was estimated to be 0.63 (0.42-0.88) (Ozasa, Shimizu et al. 2012). For women only there were 657 lung cancer events, giving an ERR/Gy of 1.1 (95% CI 0.68-1.6, $p<0.001$). This was comparable to the most recent lung cancer dose-response relationship among irradiated breast cancer survivors (Prochazka, Hall et al. 2005). The Life Span Study also found a declining relative risk of lung cancer with increasing attained age ($p<0.001$) (Preston, Shimizu et al. 2003), with a 7% decrease in the ERR per 10-year increment of age at exposure (Ozasa, Shimizu et al. 2012). The authors noted that the radiation-related lung cancer excess may be partly due to the interaction between radiotherapy and smoking, which had been demonstrated previously (Furukawa, Preston et al. 2010).

1.4 Cancer Diagnosed in Teenagers and Young Adults

Survivors of cancer diagnosed in teenagers and young adults are internationally recognised as an understudied population. They have sometimes fallen into a gap in medical expertise between the childhood and adult cancer survivor populations. Teenage and young adult cancers are distinct in terms of tumour distribution, hormonal factors, tumour biology, potential reluctance to engage with clinicians, socio-economic and lifestyle factors (Scottish Intercollegiate Guidelines Network , Skinner, Wallace et al. , Landier, Bhatia et al. 2004, National Institute for Health and Clinical Excellence 2005, Adolescent and Young Adult Oncology Progress Review Group 2006, National Cancer Research Institute 2008, Tonorezos and Oeffinger 2011). Also, those who survive can expect to live for many decades, giving time for late effects to develop. Thus, there is a need for specialised research of the TYA cancer population, including a focus on late effects.

Improvements in five-year survival have been substantially smaller in populations of individuals diagnosed with teenage and young adult cancer than in either childhood or adult populations for all cancers combined, with the majority of the survival deficit shown among males (Bleyer, Viny et al. 2006). Despite the recognition of the TYA cancer population as distinct, TYA cancer-specific treatment protocols do not tend to be available. This has been argued to be a main contributory factor for the slow improvement of survival in TYA cancers (Fernandez and Barr 2006). Often there are no TYA cancer specialists, in which case they must be treated by specialists in either childhood or adult cancer, and such decisions are currently more often based on the knowledge of the clinician rather than the biology of the tumour (Stock, La et al. 2008, Usvasalo, Raty et al. 2008, Desandes, Lacour et al. 2013).

The TYA cancer population requires a specialised tumour classification scheme. The distribution of TYA cancers includes both embryonic tumours commonly diagnosed in children, and epithelial tumours commonly diagnosed among adults. The widely used TYA cancer

classification scheme comprises ten main diagnostic groups (Birch, Alston et al. 2002, Barr, Holowaty et al. 2006). This classification is a modification of a childhood cancer classification based on histology and morphology and taking into account the frequency of different cancer types in teenagers and young adults.

A substantial challenge in improving the survival of the TYA cancer population is their recruitment into randomised trials (Mitchell, Scarcella et al. 2004, Pearce, Parker et al. 2005, Bleyer, Viny et al. 2006, Burke, Albritton et al. 2007, Bleyer, Barr et al. 2008, Fern, Davies et al. 2008, Whelan and Fern 2008). A study of the inclusion rates of individuals with TYA cancers into National Cancer Research Network phase III intervention clinical trials in England demonstrated that they are less likely than children to be included in trials for the most common cancers for their age groups (Fern, Davies et al. 2008). During 2005-06, 39.9% of patients aged 10-14 were enrolled on trials compared to 23.0% for 15-19 year olds and 13.8% of 20-24 year olds (within the tumour types analysed). This enrolment deficit is believed to be due to trial eligibility and referral patterns. This is in contrast to childhood cancer patients where the majority are enrolled, and this is thought to be one of the main factors for their improved survival. Therefore a substantial challenge is to increase the recruitment of the TYA cancer population into randomised trials.

1.4.1 Incidence and survival

Within the UK, cancer in teenagers and young adults (usually defined as ages 15-24) is rarer than at older ages. However, although it accounts for less than 1% of all cases across all ages, approximately 2,200 cases are diagnosed annually (Cancer Research UK 2014). A table summarising the age-standardised incidence rates from Cancer Incidence in Five Continents Vol X.[4] by first primary tumour (FPT) groups is included in Appendix A1. The overall age-standardised incidence rate was 47.9 per 100,000 for males and 67.5 per 100,000 for females in England and Wales, with variation for specific cancers from 0 to 11.7 per 100,000 for males. Testicular cancer

[4] http://ci5.iarc.fr/CI5-X/Pages/summary_table_pop_sel.aspx

had the highest age-standardised rates for males aged 15-39 years, and breast cancer was highest for females with 15.9 per 100,000. Cancer incidence rates have been shown to be greater for individuals diagnosed with cancer at an older age, in some cases doubling between 15-19 and 25-29 year olds (Bleyer, Viny et al. 2006, van der Horst, Winther et al. 2006, Aben, van Gaal et al. 2012).

Within the UK, the 5-year survival for all teenage and young adult cancers combined (here defined as ages 15-24 years) was 81.4% for males and 84.4% for females diagnosed during 2001-05 (Cancer Research UK 2014). As with incidence, there is wide variation in 5-year survival by cancer group, and a table summarising survival rates seen in various studies is included in Appendix A2. Among all studies, the FPT with the highest survival rate was thyroid cancer with 5-year survival typically greater than 95%, and the FPTs with the lowest rate were leukaemia, bone tumour and soft tissue sarcoma in the range of 40% to 70%. Survival varied across studies, FPT groups and age, with 5-year survival for all cancers combined estimated in the range of 57-80%, 74-85% and 81-84% for 15-19, 20-24 and 25-29 year olds respectively.

1.4.2 Cardiovascular and Cardiac Mortality in TYA Cancer Survivors

1.4.2.1 Studies which Focus on the TYA Cancer Age Range

As yet, few papers have analysed cardiac mortality risk comprehensively for all individuals diagnosed with cancer aged 15-39. Two studies have compared mortality from cardiovascular diseases among individuals diagnosed with cancer as teenagers and young adults with the general population (Prasad, Signorello et al. 2012, Kero, Jarvela et al. 2014) and they are summarised in Table 1-5.

The most detailed paper was published in 2012, and investigated the cardiovascular mortality risk subdivided by first primary tumour group (Prasad, Signorello et al. 2012). As there is a large variation in the cancer type diagnosed within the TYA cancer age range, there is limited

value in investigating all TYA cancers combined due to the large variation in the associated treatments. This analysis of 9,245 5-year survivors diagnosed before age 35 in Finland during 1966-99 found an overall raised cardiovascular mortality risk compared to the general population (SMR (standardised mortality ratio): 1.9 95% CI 1.5-2.3). The cardiovascular deaths most commonly occurred in survivors of Hodgkin lymphoma, which was associated with a 6.6-fold increased cardiovascular mortality risk compared to the general population. Survivors of Non-Hodgkin lymphoma were also at a substantially raised cardiovascular mortality risk, with a SMR of 4.8 (95% CI 2.6-8.1), as were CNS tumour survivors (SMR: 2.6 95% CI 1.3-4.8). None of the remaining FPT groups were at a significantly raised mortality risk. A main limitation of this study for the purpose of this discussion was that individuals diagnosed with cancer in childhood were included.

The most recent paper published characterised the late mortality experience of 5-year survivors of cancer diagnosed before the age of 35 in Finland (Kero, Jarvela et al. 2014). The highest SMRs were found for cancer-related deaths, followed by infectious causes and then cardiac ischemia accounted for the third highest SMR. The SMRs for cardiac ischemia among individuals diagnosed before age 20 was 5.3 (95% CI 2.9 - 7.7), more than double that among those diagnosed aged 20-34 (1.8 95% CI 1.5 - 2.1). This also held true for survivors of CNS tumours, Hodgkin lymphoma and Non-Hodgkin lymphoma when analysed individually. The highest cardiac ischemia SMR was for survivors of Hodgkin lymphoma diagnosed before age 20, taking a value of 16.0 (95% CI 4.9-27.1).

Paper and Country	Population	Number of survivors	Treatment Period	Outcome	Cancer Group	SMR (95% CI)
Kero et al (2014) Finland	5-year survivors diagnosed <35 years	16,769	1971-2012	Cardiovascular	All	1.9 (1.7-2.1)
				Cardiac ischemia / MI	All	1.9 (1.6-2.3)
					All, ages 0-19	5.3 (2.9-7.7)
					All, ages 20-34	1.8 (1.5-2.1)
Prasad et al (2012) Finland	5-year survivors diagnosed <35 years (including children)	9,245	1966-99	Cardiovascular	Bone tumour	1.2 (0.3-3.0)
					Breast cancer	0 (0-3.5)
					CNS tumour	2.6 (1.3-4.8)
					Hodgkin	6.6 (4.8-13.9)
					Leukaemia	1.1 (0.03-6.3)
					Melanoma	0.3 (0.01-1.5)
					NHL	4.8 (2.6-8.1)
					STS	0 (0-2.3)
					Testicular	0.9 (0.3-2.0)
					Thyroid	0.2 (0-1.0)
				IHD	CNS tumour	0.6 (0.01-3.1)
					Hodgkin	10.2 (7.2-14.2)
					NHL	4.0 (1.5-8.6)

Table 1-5: Summary of studies investigating cardiac and cardiovascular mortality using population comparisons in patients diagnosed with cancer within the TYA cancer age range (15-39 years).

CNS = central nervous system
NHL = non Hodgkin lymphoma
STS = soft tissue sarcoma
SMR = standardised mortality ratio
CI = confidence interval
IHD = ischaemic heart disease
MI = myocardial infarction

As mentioned above, the distribution of cancers types varies substantially across the TYA cancer age range of 15-39. A review published in 2011 summarised the variation by age of cancer diagnosis with respect to the risk of late effects after diagnosis of TYA cancer (Woodward, Jessop et al. 2011). Three studies presented SMR estimates subdivided by age (Fossa, Gilbert et al. 2007, Swerdlow, Higgins et al. 2007, Prasad, Signorello et al. 2012). Two of the studies presented data on Hodgkin lymphoma and non-Hodgkin lymphoma, and in these tumour types the mortality risk was greatest in the youngest age group, yet was still raised across all ages (Swerdlow, Higgins et al. 2007, Prasad, Signorello et al. 2012). The most substantial difference was found among survivors of Non-Hodgkin lymphoma in Finland, where individuals diagnosed with cancer aged 15-19 years were at a 19.5-fold raised IHD mortality risk compared to the general population, but individuals diagnosed aged 20-34 years were at a non-significant 2.3-fold raised mortality risk

(Prasad, Signorello et al. 2012). The third study, of testicular cancer survivors, found raised mortality (from both heart disease and IHD) only in males diagnosed before age 35 years (Fossa, Gilbert et al. 2007). Males diagnosed after 35 years were at a decreased risk of cardiac mortality compared to the general population. There was no significant difference in incidence between testicular cancer survivors and the general population, but a significantly increased risk for MI, angina pectoris (AP) and CHF was found for individuals who received both radiotherapy and chemotherapy after orchidectomy, with an SIR of 3.6 (95% CI 2.6 - 4.9) (van den Belt-Dusebout, Nuver et al. 2006).

1.4.2.2 Studies of Cardiac Mortality among All Ages Subdivided by First Primary Tumour Group

There is limited literature available on the cardiac mortality burden in TYA cancer survivors. Within the TYA cancer age range of 15-39 years, a large proportion of the patients would be treated using adult protocols. In addition, the main driver for variations in cardiac mortality seems to be the type of cancer diagnosed, rather than the age of diagnosis. Therefore, in order to get an indication of the expected cardiac mortality risk for each TYA cancer group individually, the literature was searched for papers that investigated cardiac mortality risk using a comparison to the general population in specific cancer groups without a limit on the age of diagnosis (see Table 1-6).

The FPT group most frequently investigated is Hodgkin lymphoma. Ten studies presented cardiac or cardiovascular mortality risk using comparisons to the general population (Hancock, Tucker et al. 1993, Hoppe 1997, Hudson, Poquette et al. 1998, Mertens, Yasui et al. 2001, Aleman, van den Belt-Dusebout et al. 2003, Swerdlow, Higgins et al. 2007, Mertens, Liu et al. 2008, Armstrong, Liu et al. 2009, Baade, Royle et al. 2011, VanderWalde, Sun et al. 2013). The only study to focus on individuals diagnosed with cancer before age 41 during 1965-87 found that 291 individuals had died of heart disease out of 1,261 HL patients (Aleman, van den Belt-Dusebout et

al. 2003). Females were at a greater proportional increased mortality risk, with a cardiovascular SMR of 7.3 (95% CI 3.6-13.0) and 6.0 (95% CI 41-9.4) for males, which translated to an extra 10 and 25 extra deaths per 10,000 person-years for females and males, respectively. The SMR for MI specifically was substantially lower, at approximately 4 for both males and females. The majority of the remaining studies focused on children who were diagnosed with cancer before the age of 21 years. Three recent studies used the CCSS cohort (two of which used the same subset of the cohort) and found a highly raised cardiac mortality risk, with SMRs in the range of 12 – 14 (Mertens, Yasui et al. 2001, Mertens, Liu et al. 2008, Armstrong, Liu et al. 2009). Finally, the only study to investigate cardiac mortality among all ages found a slightly elevated risk among ~2,500 individuals, but it did translate to 28 extra cardiac deaths per 10,000 person-years (Hoppe 1997). The most recent study to investigate cardiovascular mortality found a 4.3-fold increased mortality compared to the general population (VanderWalde, Sun et al. 2013). All other studies found a raised mortality risk, which was greater for heart disease than for all cardiovascular diseases combined.

Five studies investigated cardiovascular or cardiac mortality compared to the general population among survivors of non-Hodgkin lymphoma (Mertens, Yasui et al. 2001, Mertens, Liu et al. 2008, Armstrong, Liu et al. 2009, Baade, Royle et al. 2011, VanderWalde, Sun et al. 2013). All studies found a significantly raised proportional mortality risk, in the range of 1-2.2 for cardiovascular disease among individuals diagnosed before age 79 (Baade, Royle et al. 2011, VanderWalde, Sun et al. 2013), and a 6-fold raised risk of cardiac mortality among individuals diagnosed before age 21 (Mertens, Yasui et al. 2001, Mertens, Liu et al. 2008, Armstrong, Liu et al. 2009). In the childhood population, the 6-fold raised relative risk translated to an absolute 0.43 extra cardiac deaths per 1,000 person-years.

There has been an increase in the worldwide incidence of testicular cancer in the last few decades (Huyghe, Matsuda et al. 2003), and it is currently the most commonly diagnosed cancer

among men aged 15-49 years in the UK (Cancer Research UK 2014). Four studies have analysed the cardiac mortality risk among testicular cancer survivors (Fossa, Aass et al. 2004, Zagars, Ballo et al. 2004, Fossa, Gilbert et al. 2007, Beard, Travis et al. 2013). Out of a total of 3,378 testicular cancer survivors diagnosed before age 55 years, only 107 died from cardiovascular disease during the study period, of which 69 deaths were due to myocardial infarction. The cardiovascular SMR was estimated to be 1.2 (95% CI 1.0-1.5), which was similar to that estimated for testicular survivors in the Finnish study (Prasad, Signorello et al. 2012). This translated to a non-significant 4.5 extra deaths per 10,000 person-years from cardiovascular disease compared to the general population rate (Fossa, Aass et al. 2004). The most recent of the publications studied approximately 10,000 individuals diagnosed with stage I testicular cancer aged 15-71, and found no evidence of an increased cardiovascular mortality risk (Beard, Travis et al. 2013). A collaboration of 14 cancer registries in North America and Europe also found no increased mortality risk of either all heart disease, or IHD specifically (Fossa, Gilbert et al. 2007). However, one study did find a significantly raised cardiac mortality risk compared to the general population (SMR=1.6 95% CI 1.2-2.2), but it was only among 477 men diagnosed during an early diagnosis period (1951-99) with stage I or II testicular seminoma.

A large number of papers have focused on childhood cancer survivors, including investigation of cardiac risk. For all childhood cancers combined, cardiac SMRs varied from 3.5 to 13, while cardiovascular (i.e. including stroke) SMRs were lower, ranging from 2.4 to 9.7 (Green, Hyland et al. 1999, Haupt, Valsecchi et al. 2000, Mertens, Yasui et al. 2001, Moller, Garwicz et al. 2001, Cardous-Ubbink, Heinen et al. 2004, Lawless, Verma et al. 2007, MacArthur, Spinelli et al. 2007, Bluhm, Ronckers et al. 2008, Mertens, Liu et al. 2008, Armstrong, Liu et al. 2009, Reulen, Winter et al. 2010, Castellino, Geiger et al. 2011, Brewster, Clark et al. 2013). A number of other specific tumour sites have been investigated using the Childhood Cancer Survivor Study (CCSS) cohort of 5-year survivors diagnosed before age 21, and in particular, a group from Atlanta, USA

has published two comprehensive papers on cardiac mortality risk (Mertens, Yasui et al. 2001, Mertens, Liu et al. 2008, Armstrong, Liu et al. 2009). The CCSS cohort records information on individuals diagnosed with cancer before age 21 during 1970-86, and is a long-term retrospective cohort from 27 centres in the USA and Canada. The overall cardiac mortality risk was raised for bone cancer, particularly Ewing Sarcoma, CNS tumours, leukaemia (particularly for acute lymphoblastic leukaemia (ALL) survivors), kidney cancer and soft tissue sarcoma.

Paper and Country	FPT	Age at cancer diagnosis	Number of survivors	Treatment Period	Outcome	SMR (95% CI)
Beard et al (2013) USA	Testicular	Aged 15-71 yrs.	9,561	1973-01	Cardiovascular	0.91 (0.80-1.05)
VanderWalde et al (2013) USA	Hodgkin	Aged 6-79 yrs.	2,388	1986-06	Cardiovascular	4.3 (1.7-8.7)
	AML					0.5 (0.1-22)
	NHL					2.2 (1.4-3.3)
Yu et al (2012) USA, SEER	Oral cavity & oropharyngeal	No restriction	32,487	1980-07	Cardiovascular	2.4 (2.1-2.7)
Baade et al (2011) Australia	Hodgkin	Aged 0-79 yrs.	111,432	1983-05	Cardiovascular	1.67 (1.5-1.9)
	NHL					1.09 (1.0-1.1)
Riihimaki et al (2011) Sweden	Breast cancer		3.68 million	1987-06	MI	1.01 (0.98-1.05)
					Heart failure	1.29 (1.22-1.37)
					Other HD	1.24 (1.17-1.32)
Yu et al (2009) USA	Hereditary retinoblastoma	No restriction	1,854	1914-96	Cardiovascular	1.3 (0.3-3.2)
	Non-hereditary retinoblastoma					0.7 (0.2-2.2)
Fossa et al (2007) N. America & Europe	Testicular	No restriction	38,907	1943-02	Cardiac	0.97 (0.92-1.03)
	Testicular				IHD	0.93 (0.88-1.00)
Hisada et al (2007) USA, SEER	Hairy cell leukaemia	No restriction	3,104	1973-02	Cardiovascular	0.67 (0.56-0.80)
Swerdlow et al (2007) Britain	Hodgkin	No restriction	7,033	1967-00	MI	2.5 (2.1-2.9)
Fossa et al (2004) Norway	Testicular	<55 yrs.	3,378	1962-97	Cardiovascular	1.2 (1.0-1.5)
					MI	1.1 (0.9-1.4)
Zagars et al (2004) USA	Testicular seminoma	No restriction	477	1951-99	Cardiac	1.61 (1.21-2.24)
Aleman et al (2003) Netherlands	Hodgkin	<41 yrs.	1,261	1965-87	Cardiovascular	M: 6.0 (4.1-8.4)
						F: 7.3 (3.6-13.0)
					MI	M: 3.9 (2.1-6.7)

						F: 4.2 (0.9-12.4)
Hudson et al (1998) USA	Hodgkin	Paediatric patients	387	1968-90	Cardiac	22 (8-48)
Hoppe et al (1997) USA	Hodgkin	No restriction	2,498	1960-98	Cardiac	3.1 (2.4-3.7)
Hancock et al (1993)	Hodgkin	Diagnosed <21 yrs.	635	1961-97	Cardiac	29.6 (16.0-49.3)
USA	Hodgkin				AMI	41.5 (18.1-82.1)
		Childhood Cancer Survivor Study				
Ginsberg et al (2010) USA	Ewing sarcoma (bone)	<21 yrs.	568	1970-86	Cardiac	12.0 (5.2-23.6)
Armstrong et al (2009) USA	Bone tumour Hodgkin NHL STS	<21 yrs.	20,483	1979-02	Cardiac	3.9 (1.6-8.1) 11.9 (9.1-15.3) 6.3 (3.5-11.1) 4.0 (1.8-7.6)
Mertens et al (2008) USA	Ewing sarcoma Osteosarcoma Astyocytoma Hodgkin ALL AML NHL Kidney STS	<21 yrs.	20,483	1979-02	Cardiac	12.0 (5.2-23.6) 3.9 (1.6-8.1) 6.2 (3.0-11.4) 11.9 (9.1-15.3) 4.2 (2.3-6.9) 5.0 (0.6-18.1) 6.5 (3.5-11.1) 12.7 (6.3-22.8) 4.0 (1.8-7.6)
Mertens et al (2001) USA	Bone tumour CNS tumour Hodgkin Leukaemia NHL Wilms (GU) STS	<21 yrs.	20,227	1970-86	Cardiac	4.9 (1.8-10.5) 7.5 (3.2-14.4) 13.8 (9.3-19.4) 3.8 (1.5-7.6) 6.5 (2.3-14.0) 18.0 (7.1-36.4) 5.7 (2.0-12.2)

Table 1-6: Summary of studies investigating cardiac and cardiovascular mortality in patients diagnosed with cancer outside the TYA cancer age range using a comparison to the general population.

MI = myocardial infarction
HD = heart disease
GU = genitourinary
AMI = acute myocardial infarction
IHD = ischaemic heart disease
CCSS = Childhood Cancer Survivor Study
FPT = first primary tumour
SMR = standardised mortality ratio
CI = confidence interval
yrs. = years
AML = acute myeloid leukaemia
ALL = acute lymphoblastic leukaemia
NHL = non Hodgkin lymphoma
STS = soft tissue sarcoma

1.4.3 Hospitalisation for Cardiovascular Disease in TYA Cancer Survivors

Over the past year, three papers have been published that address the risk of hospitalisation from cardiovascular disease among long-term survivors of cancer diagnosed before age 40 (Kero, Jarvela et al. 2014, Rugbjerg, Mellemkjaer et al. 2014, van Laar, Feltbower et al. 2014). All three studies found significant excesses of cardiovascular hospitalisation among survivors of TYA cancers (see Table 1-7).

The largest of these studies was carried out in Denmark. Cases of cancer were diagnosed from 1943 to 2009 and alive on the 2nd of April 1968 were identified from the Danish Cancer Registry. A comparison cohort was obtained by selecting at random five cancer-free comparison subjects using the Danish Civil Registration System who were born in Denmark, in the same year with the same gender as their matched cancer patient and who were cancer-free at the date of diagnosis of their respective survivor. Due to the wealth of information available in the national Danish Civil Registration System, the authors were able to end follow-up if a second primary cancer was diagnosis in a cancer survivor, or censor controls on the date of their first cancer diagnosis, ensuring that the cardiac late effects were due to the treatment for the first cancer and not confounding by any further treatment. There were 10,591 hospital referrals in cancer survivors, compared with an expected value of 8,124.2 in the matched controls, giving an overall rate ratio of 1.30 (95% CI 1.28-1.33) (Rugbjerg, Mellemkjaer et al. 2014). The Danish cohort found that the hospitalisation rate ratio, and the absolute excess rate was higher at younger attained ages, taking rate ratio values of 6.7 (95% CI 3.7-12.2) and 1.1 (95% CI 1.1-1.2) for ages 16-19 and 70-79, respectively. Among these 1-year cancer survivors, heart disease was divided into 14 different subtypes, and there were significant excesses for all of them. The largest proportionate increase was for endocarditis (RR = 2.16 95% CI 1.62 - 2.88) and the largest absolute excess for cardiomyopathy and arrhythmia (AER per 100,000 person-years = 103 95% CI 86 - 121). Ten different sites of cancers were considered, and across the cancer groups, the subtypes of cardiac

disease with a significant RR varied. For example, among survivors of testicular cancer, a significant excess was found for valvular disease, compared to among breast cancer survivors where a significant excess was shown for cardiomyopathy.

The other two studies presented findings from cohorts on a small scale, with 14,000 survivors in the Finnish study (Kero, Jarvela et al. 2014) and 3,000 survivors in the study of individuals diagnosed in Yorkshire (van Laar, Feltbower et al. 2014). Kero and colleagues compared the mortality experience of cancer survivors to their healthy siblings, who had to be without a cancer diagnosis before age 35, alive in 1971 and at least 5 years old. Mortality outcomes were ascertained from the Finnish National Death Certificate files. The study found that survivors diagnosed before age 20 were at a much greater risk of hospitalisation than that among individuals diagnosed aged 20-34. This held true for both males and females and for all cardiovascular endpoints studied. Substantial variation existed for each of the cardiac endpoints studied by first primary cancer diagnosed, and the risk was greatest amongst survivors of lymphoma, brain tumours, leukaemia and testicular cancer. Van Laar and colleagues matched cancer survivors by age at hospital admission to the general population of Yorkshire during 1996 to 2011 who had an inpatient HES record. This study also found that individuals diagnosed at a younger age were at a greater risk, yet the cohort overall was at an increased hospitalisation rate compared to the general population.

One other study investigated overall hospitalisation of 5-year survivors of childhood, adolescent and young adult cancer, defined as before the age of 25 years (Brewster, Clark et al. 2014). The individuals (n=5,229) were diagnosed in Scotland during 1981-2003 and compared to the general Scottish population. The standardised hospitalisation rate ratio (SHRR) for coronary heart disease after all cancers was 1.4 (95% CI 1.0 - 2.1), and for cardiomyopathy was 5.3 (95% CI 2.8 - 9.0). Investigation of specific cancer types found a significant SHRR for coronary heart disease among survivors of lymphoma (SHR = 3.6 95% CI 2.1 – 5.6), and for cardiomyopathy

among survivors of leukaemia (SHRR = 32.4 95% CI 13.0 - 66.7) and soft tissue sarcoma (SHRR = 17.8 95% CI 2.2 - 64.2). The mortality experience of this population had been previously published, and found an SMR for all circulatory disease of 2.4 (95% CI 1.4 - 3.9) (Brewster, Clark et al. 2013).

Paper and Country	Number of survivors	Treatment Period	Outcome	FPT	SHRR (95% CI)
Rugbjerg et al (2014) Denmark	43,153	1943-2009	Cardiovascular	All	1.30 (1.28-1.33)
				Leukaemia	2.5 (2.1-2.9)
				Hodgkin lymphoma	1.7 (1.6-1.9)
				Brain	1.6 (1.5-1.8)
				Non-Hodgkin lymphoma	1.5 (1.4-1.7)
				Breast	1.4 (1.4-1.5)
				Testis	1.3 (1.2-1.3)
				Cervix	1.2 (1.2-1.3)
				Malignant skin melanoma	1.2 (1.1-1.2)
				Ovary	1.2 (1.1-1.4)
				Thyroid	1.2 (1.0-1.4)
Kero et al (2014) Finland	13,860	1975-2004	Cardiomyopathy / cardiac insufficiency	All	4.6 (3.6-5.8)
			Myocardial infarction / cardiac ischaemia	All	1.8 (1.5-2.2)
			Arrhythmia	All	1.4 (1.2-1.7)
van Laar et al (2014) UK	3,247	1991-2006	Cardiovascular	All ages 0-14	2.6 (1.9-3.6)
			Cardiovascular	All ages 15-29	1.2 (0.9-1.5)
			Cardiomyopathy / heart failure	All ages 0-14	12.7 (7.4-21.9)
			Pericardial disease	All ages 0-14	7.9 (3.3-19.0)
			Hypertension	All ages 0-14	4.0 (2.3-7.1)
			Valvular heart disease	All ages 0-14	3.2 (1.0-10.0)

Table 1-7: Summary of studies investigating cardiac and cardiovascular hospitalisation using population comparisons in patients diagnosed with cancer within the TYA cancer age range (15-39 years).

FPT = first primary tumour
SHRR = standardised hospitalisation rate ratio
CI = confidence interval

1.5 Summary and Unanswered Questions

Over the past few decades it has become clear that the heart is an organ at risk during radiotherapy for breast cancer, and that efforts should be made to minimise the dose that it receives without compromising coverage of the target. The late hazards of recent techniques are still unknown. Recent evidence does not point towards a threshold dose, but it is still unclear which cardiac structures are most radiosensitive. Dose-response relationships from exposure to the whole heart are emerging (Darby, Ewertz et al. 2013), and so the need to identify the critical structures and their associated dose-response relationships is gaining importance. Identification of specific categories of heart disease, for example valvular heart disease and pericarditis, and characterising (trend with age, time since etc.) their associated risk, is needed to help to understand the mechanisms of cardiotoxic damage within structures of the heart. Little is known about factors, other than cardiac dose received, which determine the magnitude of the risk. Although, it seems likely that cardiovascular risk factors will be important. The availability of large-scale observational datasets with extended follow-up should permit the detection of new trends across information routinely collected on groups of individuals, for example age.

There are a limited number of studies that directly assess the risk of radiation-related lung cancer. However, randomised evidence has shown an association between radiotherapy and lung cancer risk in breast cancer survivors, particularly those treated with mastectomy. Observational evidence suggests that this radiation-related risk is limited to the ipsilateral lung, and increases multiplicatively with any smoking-related risk. The proportional increase in risk appears to be greater in women under 50 years old at exposure, but the trend with age at diagnosis of initial cancer has not been characterised in detail. No direct analyses of trend across calendar periods of diagnosis have been performed and the increasing trend with time since exposure in lung cancer risk has not been investigated specifically for radiation-related lung cancer cases particularly into the third decade. Finally, there is little information on the extent to

which the risk of radiation-related lung cancer may be modified by chemotherapy and hormonal therapy.

The population of individuals diagnosed with cancer as teenagers and young adults is an understudied population within the oncology and general medical literature. The TYA cancer population is distinct, as regards hormonal, socio-economic factors, tumour biology and tumour distribution. Overall 5-year survival is 81% for males and 84% for females, but over the last decade survival has improved less than in childhood cancer. There have only been two studies as yet to focus on cause-specific mortality risk within an entire TYA cancer population. Heart disease risk has been investigated in childhood cancer, breast cancer and Hodgkin lymphoma patients, which found that the cardiac mortality risk was elevated throughout the entire age range, but that the risk is greater in younger patients. There is a need for further analysis of cardiac risk within the TYA cancer population.

This thesis aims to characterise the radiation-related heart disease and lung cancer risk in breast cancer survivors, and to describe the risk of heart disease in the TYA cancer population. This thesis aims to use data from large population-based cohorts to, as far as possible given the information available, address the unanswered questions. The specific aims that this thesis plans to address are:

1. *Provide a thorough methodology-based discussion of the potential pitfalls of observational data that need to be considered carefully during analysis.* Selection effects and other biases are known to be present in both randomised and observational data. However, during analyses of randomised data, these biases should be evenly distributed throughout the treatment groups, meaning that associations between treatment and outcomes are likely to be due to true causation as the treatment allocation was randomised. This is not the case in observational data, and so this thesis aims to describe the impact of these biases in observational data, using randomised data as a 'gold-standard' comparison. In addition, it

aims to provide an alternative method and consequently explain the rational for the analyses presented in the following chapters.

2. *Characterise the radiation-related risks of heart disease and lung cancer -- the largest causes of mortality before recurrence, from causes other than breast cancer – in survivors of breast cancer.* Randomised evidence from individual patient data meta-analyses performed by EBCTCG have demonstrated that radiotherapy for breast cancer reduces the breast cancer recurrence and mortality rate, but this clear benefit can be offset by an increased risk of mortality from causes other than the original breast cancer, namely heart disease and second primary cancers, particularly lung cancer. Previous published studies have begun to characterise these radiation-related risks in observational cohorts, which are representative of the general population. However, few factors have been shown, other than the effect of radiation dose, to determine the magnitude of the risk. Therefore, using the largest observational study to date, this thesis aims to characterise the magnitude of the radiation-related risk of heart disease and lung cancer including the variation by various treatment and patient characteristics.

3. *Characterise the long-term risk of heart disease for the entire spectrum of cancers diagnosed in teenagers and young adults aged 15-39.* To this date, the focus of cancer outcomes research has been on either childhood or specific mature adult cancers. As such, teenagers and young adults have fallen into a gap of medical specialities and research, and are an understudied population. Among childhood cancer survivors, and adult survivors of breast cancer and Hodgkin lymphoma heart disease is known to be the leading non-neoplastic cause of mortality. Therefore, this thesis aims to characterise the long-term risk of heart disease in this understudied TYA cancer population.

CHAPTER 2:
MATERIALS & METHODS

2.1 Materials

This thesis is based on two population-based prospective datasets: the Collaborative Group on Observational Studies of Breast Cancer Survivors (COBS) and the Teenage and Young Adult Cancer Survivors Study (TYACSS). Chapter 3 is a methodological study based on data from the Surveillance and Epidemiology End Results (SEER) cancer registries from the USA. This data is also included in the COBS dataset. All datasets will be explained individually.

In addition to preparing the datasets for analysis and running all the analyses, my personal involvement in cleaning and processing subsets of these cohorts was: the cleaning of updated data supplied by two Nordic cancer registries to COBS; the application of and processing of the updated SEER dataset; and checking the Welsh data in TYACSS. Other cleaning and data processing was carried out by others.

2.1.1 Collaborative Group on Observational Studies of Breast Cancer Survivors

The Collaborative Group on Observational Studies of Breast Cancer Survivors was established in 2007 to generate a large-scale population-based dataset to study several potential adverse health effects of treatment for breast cancer. The collaboration was established by Dr Max Parkin, Professor Sir Richard Peto, Professor Sarah Darby, Dr Paul McGale and Dr Carolyn Taylor, and voting members of the International Association of Cancer Registries and a number of others were invited to collaborate. The aim was to collate information on a relatively small number of essential data items from a large number of cancer registries.

Overall, the dataset includes information from 87 cancer registries in 40 countries worldwide, providing information on more than 2 million women diagnosed during 1935-2008, with follow-up extending to 2011. However, not all registries were able to supply complete information for all endpoints of interest. Therefore, the COBS subsets used for the three studies presented in this thesis are:

- Cardiac mortality study: 1.9 million women from 57 cancer registries in 22 high income countries. Countries were dropped if they supplied data on less than 50 heart disease deaths
- Cardiac incidence study: 669,000 women from 13 cancer registries in 8 countries. Countries were dropped if they supplied data on less than 25 cardiac events
- Lung cancer study: 1.6 million women from 24 cancer registries in 18 countries. Countries were combined into one category if they supplied data on less than 20 deaths or events

Detailed information on the data supplied by each registry is included in Appendix B.

2.1.1.1 Data Collection

Each of the 87 participating cancer registries assembled their own dataset. Follow-up was usually ascertained by cross-matching against national registers. The datasets were anonymised and then submitted to the secretariat in Oxford, where they were checked and collated into a standard pre-determined format. The datafiles were then merged with all registry data to create a file suitable for analysis.

2.1.1.2 Eligibility Criteria

The main eligibility criteria were:

1. Women diagnosed with carcinoma in situ in the breast which was treated with radiotherapy
2. Women diagnosed with invasive breast cancer (regardless of whether they were treated with radiotherapy) and who are not in 1.

For inclusion, individuals needed to be diagnosed with invasive breast cancer or ductal carcinoma in situ as their first cancer diagnosis. Women with bilateral cancer were excluded. Their record had to include a valid follow-up until a specified date and known radiotherapy status.

Both the laterality of the index breast cancer and lung cancer, where applicable, had to be known. Breast cancer diagnosis had to be between the ages of 20 and 79 years old.

Patients were excluded if: they had been previously diagnosed with any other invasive cancer (excluding non-melanoma skin cancer) on or before the date of diagnosis of the index breast cancer; they were known to have emigrated at any time prior to date of index breast cancer diagnosis (even if subsequently re-immigrated); they were known to have immigrated at any time (before or after breast cancer diagnosis); they died on the date of diagnosis of breast cancer, or were diagnosed at autopsy; they were known to have previously been treated with thoracic radiotherapy.

2.1.2 Teenage and Young Adult Cancer Survivor Study

The Teenage and Young Adult Cancer Survivor Study (TYACSS) is a large population-based cohort of individuals diagnosed with cancer aged 15-39 inclusive in England and Wales. The cohort holds information on 5-year survivors diagnosed during 1971-2006 with follow-up to the 28th of February 2014. For inclusion, the individual had to be diagnosed with a malignant tumour, unless it was a tumour of the brain or bladder, in which case both benign and malignant tumours were included. The TYACSS is the largest population-based cohort to date to focus on the TYA cancer population. A total of 233,081 individuals met the inclusion criteria, contributing 3,325,102 person-years at risk. The cohort was ascertained through the Office of National Statistics for England, and the Welsh Cancer Registry. Only an individual's first cancer diagnosed in the study period was considered. Comparison to the British Childhood Cancer Survivor Study (BCCSS) (Hawkins, Lancashire et al. 2008) enabled exclusion of individuals who were previously diagnosed with cancer during childhood (<15 years).

Legal consent to process patient identifiable information was obtained from the Patient Information Advisory Group. Ethical approval (a favourable opinion) was given by the National

Research Ethics Committee (TYACSS NRES: 10/H1102/24 and NIGB: ECC 3-04 (c) / 2010, BCCSS NRES: 10/H1102/86 and NIGB: ECC 2-02 (f) / 2011).

2.1.2.1 Vital Status and Cause of Death Ascertainment

Linkage with the Health and Social Care Information Centre (HSC-IC, previously known as the NHS Information Centre) provided the vital status and embarkations due to emigration for each survivor. For all 5-year survivors known to have died within the study period, the underlying cause of death was obtained from HSC-IC, recorded using the revision of International Classification of Diseases which was applicable to the year of death (revision 9 or 10). The use of both revisions 9 and 10 of the ICD was not likely to impact on the findings presented.

2.1.2.2 Cancer Classification

First primary tumour groupings were based on the widely used TYA cancer classification scheme (Birch, Alston et al. 2002, Barr, Holowaty et al. 2006). This classification comprises ten main diagnostic groups, but was modified to create finer groupings of carcinomas, giving 18 groups in total (see Table 2-1 below).

First Primary Cancer Grouping	Specific Cancer Diagnosis
Breast	Breast
Non-Melanoma Skin Cancer	NM Skin
Testicular	Germ cell gonadal
	Oth spec gonadal tumours (if male)
Cervix	Cervix
Melanoma Skin Cancer	Melanoma & Naevi
Hodgkin lymphoma	Hodg Dis (spec)
	Hodg Dis NOS
Central Nervous System tumour	Pilocytic astrocytoma
	Oth spec astrocytoma
	Glioblastoma/anaplastic astrocytoma
	Astrocytoma NOS
	Oligodendroglioma
	Other specified glioma
	Glioma, NOS
	Ependymoma
	Medulloblastoma
	Supratentorial PNET
	Craniopharyngioma
	Oth Pituitary tumours

Table cont. on next page

	Pineal tumours
	Choroid plexus tumours
	Meningioma
	CNS nerve sheath tumours
	Oth spec CNS
	Uns malig CNS
	Uns benign CNS
	Germ cell intracranial
Non-Hodgkin lymphoma	Spec NHL
	Unspec NHL
	misc lymphoreticular neops NEC
Genitourinary	GU tract
	Kidney
	Bladder
	GU tract (oth)
	Wilms tumour
Thyroid	Thyroid
Gastrointestinal	Colon & rectum
	Stomach
	Liver
	Pancreas
	GI tract (oth)
Soft Tissue Sarcoma	Fibrosarcoma
	Malig fibrous histiocytoma
	Dermatofibrosarcoma
	Rhabdomyosarcoma
	Liposarcoma
	Leiomyosarcoma
	Synovial sarcoma
	Clear cell sarcoma
	Blood vessel tumours
	Nerve sheath tumours
	Alveolar soft part sarcoma
	Other Specified STS
	Unspecified STS
Ovarian	Ovary
	Oth spec gonadal tumours (if female)
	Germ cell gonadal (if female)
Leukaemia	A L Leuk
	A M Leuk
	C M Leuk
	Oth L Leuk
	Oth M Leuk
	Oth Spec Leuk
	Oth Unspec Leuk
Bone tumour	Osteosarcoma
	Chondrosarcoma
	Ewing sarcoma
	Ewing sarcoma NOT bone
	Ewing sarcoma SITE UNSPEC
	Oth bone tumours SPEC

Table cont. on next page

	bone tumours UNSPEC
Other	Unsc malig neops
	Germ cell OTHER
	Breast (Note: These are male)
	Adrenocortical
	Carcinoma - oth
	Neuroblastoma
	Oth paediatr NEC
	Paraganglioma & glomus
	Oth spec neops NEC
	Unspec malig neops NEC
	Not in ICD-9/10, ICDO-T
	Histology different in ICDO 2 & 3
	Incorrect site/type combination
	hist-incorrect behaviour (>=3)
	Oth benign
	Not in Histology classification
Lung	Trachea, bronchus & lung
Head and neck	Nasopharyngeal
	Oth lip/oral cavity/pharynx
	Oth Nasal cavity/middle ear

Table 2-1: Modified cancer classification groups.

2.1.2.3 Data Cleaning and Processing

The data for the TYACSS cohort was obtained in stages, from three sources within England and Wales. Within this process, my role involved checking the cancer-based file supplied by the Welsh Cancer Registry for duplicates and problems before it was sent to HSC-IC for vital status and cause of death information. There were 20,159 cancer registrations, of which 16,000 had an NHS number. Among registrations where no NHS number was present, duplicates were identified by considering combinations of various patient information variables. The values recorded in the dataset were checked against the codebook supplied by ONS. Missing data and invalid dates were checked for and queried with the data supplier. Many were corrected, and records that could not be corrected were excluded.

2.1.3 Surveillance, Epidemiology and End Results

The Surveillance, Epidemiology and End Results database is run by the National Cancer Institute in the USA, and routinely collects cancer data from designated population-based cancer registries. SEER started collating information in 1973, when it covered 10% of the US population. Currently, 17 cancer registries are included in SEER, covering approximately 28% of the US population. Mortality data is provided to SEER by the National Centre for Health Statistics. As with most other cancer registry data, the SEER database does not include detailed treatment data. Surgery type (breast conserving surgery or mastectomy) has been recorded in SEER since 1983. In our analyses, all individuals diagnosed before 1983 were automatically recorded to have received mastectomy.

For inclusion, individuals needed to be diagnosed with localised or regional breast cancer within a SEER geographical region during 1973-2011. Patients who moved out of a SEER region were lost to follow-up. The eligibility and exclusion criteria used for the SEER data is as explained in Section 2.1.1.2. This left 558,871 women eligible for analysis, of which 46% were recorded to have received radiotherapy.

2.2 Classification of Heart Disease

The underlying cause of death was used, and recorded using the International Classification of Disease (ICD). Multiple versions of the ICD codes were in use throughout the study period, and the classification accounted for this. Dr David Cutter formulated a mutually exclusive and exhaustive classification of ICD codes into heart disease categories. This is shown in Table 2-2. The fully extended version for ICD revisions 5 to 10 is in Appendix B.3. The categories 'Ischaemic HD' and 'Arrhythmias' were combined for analyses of radiation-related heart disease in COBS, and the categories 'Valvular HD' and 'Rheumatic Valv. HD' were combined for analyses of the TYACSS.

Cause of Death	ICD-10
All cardiac	I01, I02.0, I05-I09, I11, I13, I20-I25, I27.1-I27.9, I30-I52
Cardiomyopathy/CHF	I01.2, I09.0, I11.0, I13.0, I13.2, I40-I43, I50, I51.4-5, I51.7
Valvular HD	I34-I39
Rheumatic Valv. HD	I01.1, I05-I08, I09.1
Ischaemic HD	I20-I25
Arrhythmias	I44-49
Pericardial	I01.0, I09.2, I30-I32
Others	I01.8-9, I09.8-9, I11.9, I13.1, I13.9, I27.1-I27.9, I33, I51.0-3, I51.6, I51.8-9, I52

Table 2-2: ICD codes for cardiac groups.

2.3 Methods

The COBS and TYACSS cohorts contain required different analytical approaches. Among breast cancer patients, radiotherapy-related risks could be estimated by utilising the fact that the breast is a paired organ. The heart is situated to the left-side of the body, making a comparison of left-sided versus right-sided breast cancer in irradiated women effectively a comparison of higher versus lower radiation dose.

Within the TYACSS, the focus is on a wide distribution of cancer types which required a different approach. Therefore, comparisons were made to the matched general population in order to estimate the excess risk potentially attributable to the cancer. Details of the method by which the cancer population was matched to the general population are included in Section 2.3.2.

All calculations used Stata versions 12 and 13.

2.3.1 Statistical Methodology for COBS Cohort

2.3.1.1 Mortality and Incidence Rate Ratios

Two comparison types were employed throughout the analyses of the COBS data: left-sided versus right-sided breast cancer for the analysis of heart disease; ipsilateral versus contralateral for the analysis of microscopically confirmed lung cancer.

Mortality and incidence rate ratios were estimated using grouped logistic regression by maximum likelihood estimation. The number of deaths and person-years were calculated conditional on defined strata. The stratification was based on the cross-classification of four explanatory variables: calendar year of diagnosis (5-year groups), age at diagnosis (5-year groups), country of treatment and years since diagnosis (5-year groups). Each woman's contribution to the person-years are risk ran from the date of breast cancer diagnosis to the earliest of death, loss to follow-up, 85th birthday, or end of follow-up period (varied for each registry).

In order to remove the dependence on a baseline category in the regression, a further weighted-average adjustment was performed (where appropriate) on the multivariable model with the four explanatory variables. The variables used in the multivariable model were: time since breast cancer diagnosis, country of breast cancer diagnosis, age of breast cancer diagnosis and calendar year of breast cancer diagnosis. The following chapters will indicate if the rate ratios were calculated using this additional weighted-average adjustment. Thus, the rate ratio for an explanatory variable was the average of adjusted rate ratios over all combinations of the categories of the other three explanatory variables, weighted by the corresponding person-years. Formally, the averaged value for category t of the explanatory variable time since diagnosis, after adjusting for all categories of the other three explanatory variables α_m, β_n and γ_p was:

$$e^{\tilde{\tau}_t} = \theta e^{\hat{\tau}_t + \hat{\mu}}$$

Where:

$$\theta = \sum_{m=1}^{M} \sum_{n=1}^{N} \sum_{p=1}^{P} w_{mnp} e^{\hat{\alpha}_m + \hat{\beta}_n + \hat{\gamma}_p}$$

With $w_{mnp} = \frac{P_{.mnp}}{P_{....}}$

The variance of the rate ratio was then calculated using Taylor expansion to produce a linear combination of the estimates of the full model with their respective variances and

covariance. The approximate standard error on the log scale was then used with the exact point estimate of the adjusted rate ratio to calculate the 95% confidence interval.

Tests for trend and heterogeneity were performed using the likelihood ratio test and based on the chi-squared distribution. Significance tests were two-sided.

See Appendix B for an extended explanation of this statistical methodology.

2.3.1.2 Cumulative mortality

The cumulative mortality risk in irradiated women was calculated by transforming the relative risk ratios into absolute rates. For each age group, the relative size of the absolute rates was set equal to the relative size of the estimated mortality ratio. Thus, the estimated mortality ratio was assumed to be the increase in rate in the exposed group compared to the unexposed group (the general population). The exposure was set to be laterality: either of the index breast cancer, or the concordance of the breast and lung cancer. A detailed explanation is included in Appendix B. The mortality ratio estimates used to produce the cumulative mortality risk curve were estimated using grouped logistic regression with an interaction term between the age at diagnosis and time since diagnosis. This allowed estimation of the age-specific cumulative mortality with respect to the corresponding follow-up period.

The death counts used for the population rates were obtained from the World Health Organisation[5], and the population counts were from the UN[6] (both accessed 3rd December 2012). For Belgium and Denmark, the 2006 death rates were applied to the 2010 population estimates. For France, Greece, Italy and Luxembourg, the 2009 death rates were applied.

[5] http://www.who.int/healthinfo/morttables/en/
[6] http://esa.un.org/unpd/wpp/Excel-Data/population.htm

2.3.2 Statistical Methodology for TYACSS Cohort

Each individual's contribution to the person-years at risk began at the date of 5-year survival and ended at the earliest of 28th of February 2014, death or loss to follow-up (for example due to embarkation). The cause of death for cancer survivors was ascertained from national sources, using the underlying cause of death on the death certificate, therefore the cause of death for both the cancer population and general population were allocated in the same way.

Standardised mortality ratios (SMRs) and absolute excess rates (AERs) were calculated using standard cohort techniques (Breslow and Day 1987). SMRs were calculated as the number of deaths observed divided by the numbers expected derived from age (5-year groups), sex, and calendar-year (1-year groups) specific death rates for England and Wales combined. AERs were calculated as the numbers of deaths observed minus the number expected from the national population per 10,000 person-years at risk.

Tests for trend and heterogeneity were performed using likelihood-ratio tests within Poisson regression models. Statistical significance was defined as $2p<0.05$.

Multivariable Poisson regression models for the SMRs and AERs were used to evaluate the simultaneous effect of demographic and cancer-related factors. If the results from univariable modelling were similar to the multivariable model, then such robust findings were reported in terms of SMRs and AERs. If the univariable results were not similar, then the multivariable results were reported in terms of relative risks or excess morality ratios. The factors of interest were: sex, age at cancer diagnosis (5-year groups), calendar year of diagnosis (10-year groups), time since diagnosis (5-year groups), attained age (20-39, 40-49, 50-59 and 60+ years) and first primary cancer type. To avoid collinearity between attained age and years since diagnosis ($r=0.73$, $2p<0.0001$) only one of these variables was included in any multivariable model at a time.

Cumulative risk of mortality, taking account of competing risk of death from any cause other than heart disease, was estimated for the for first primary cancer groups with at least 100 cardiac deaths and a significant overall SMR (Coviello and Boggess 2004).

CHAPTER 3:
METHODOLOGICAL DISCUSSION OF COMPARISONS USED TO INFER THE EFFECT OF RADIATION

3.1 Introduction

Increasingly scarce resources in the US for the conduct of randomised controlled trials (Institute of Medicine 2010, Chakma, Sun et al. 2014) have led to growing interest in the use of observational datasets and comparative effectiveness research to determine the impact of cancer treatments. Comparative effectiveness research is designed to provide reliable information on comparisons of existing health care interventions in patients representative of the general population, and observational sources of data may be particularly valuable in illuminating the impact of treatment in real-world settings (Korn and Freidlin 2012, Lyman and Levine 2012, Meyer, Wheeler et al. 2014). However, determining causation in the context of observational studies is challenging. Selection biases can arise from the selection of more aggressive treatments for patients with adverse disease characteristics or favourable comorbidity profiles. Therefore, associations may arise between treatment and outcomes which are in fact due to confounding rather than true causal mechanisms. This is in contrast to a randomised trial where associations are more likely to reflect true causation. Giordano and colleagues (Giordano, Kuo et al. 2008) examined Surveillance Epidemiology and End Results (SEER)-Medicare data in 2008 to "question the reliability of using mortality endpoints to assess treatment efficacy in non-randomised data". Their study focused on patients with prostate and colon cancer, and found that several analyses of treatment-related effects produced improbable results which conflicted directly with the findings of randomised trials in those diseases. It is important to investigate whether similar problems exist when analysing mortality outcomes associated with radiotherapy for breast cancer. Breast cancer is the most commonly diagnosed cancer among women in the developed world, and radiotherapy is used in the adjuvant setting for the vast majority of women following breast conserving surgery (BCS) and a substantial proportion of node-positive women following mastectomy. Jagsi and colleagues found that among women with strong indications for adjuvant radiotherapy, 95.4% were irradiated after breast conserving surgery and 77.6% after mastectomy (Jagsi, Abrahamse et al. 2010). Strong indications for

radiotherapy were defined using consensus guidelines and evidence that had been published by 2005. Strong indications for radiotherapy after BCS were defined as all other patients than "patients older than 70 years undergoing breast conserving surgery for stage I, estrogen receptor-positive tumours". After mastectomy, strong indications for radiotherapy were categorised as "those with N2 or greater disease, T4 disease, or T3N1 disease".

Observational data relating to breast radiotherapy is available from the SEER and SEER-Medicare cohorts. As an initial step in determining the temporal pattern and scope of studies using these data, a systematic review was undertaken, and the number of papers and methods used noted. Randomised data have been presented in individual patient data meta-analyses by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (Early Breast Cancer Trialists' Collaborative Group 2000, Early Breast Cancer Trialists' Collaborative Group 2005, Early Breast Cancer Trialists' Collaborative Group 2011, Early Breast Cancer Trialists' Collaborative Group 2014). This chapter sought to utilise these two sources of data to investigate whether mortality outcomes in the SEER observational data are subject to bias, using EBCTCG randomised evidence as a gold standard source for comparison. In addition, the impact of adjustment for known potential confounding factors, such as age and tumour characteristics, could be determined.

For a number of mortality outcomes, selection biases present in observational breast cancer radiotherapy analyses can be circumvented by comparing mortality rates by breast cancer laterality (i.e. left-sided versus right-sided breast cancer) (Vandenbroucke 2004). This method is particularly useful for outcomes relating to organs situated to one side of the body or bilateral organs. The position of the heart towards the left-side of the body results in the heart usually receiving a higher radiation dose during treatment for left-sided breast cancer as compared to right-sided breast cancer, likewise for the ipsilateral lung compared to the contralateral lung. Thus, a comparison of cardiac outcomes using left-sided versus right-sided breast cancer is

effectively a comparison of higher versus lower cardiac dose. This laterality comparison will be presented and compared to the gold standard randomised results. There are however many outcomes of interest for which this technique is not an appropriate method for determining the effect of radiotherapy.

3.2 Aim

The aim of this chapter was to answer the question: does a comparison of irradiated and unirradiated women give the correct answers in observational data when investigating the effects of radiotherapy?

3.3 Materials and Methods

A subset of the materials described in Chapter 2 will be used for this methodological discussion, and they are detailed below. In addition, the details of the systematic review are presented in the following section.

3.3.1 Systematic Review of Observational Studies

Studies were considered for the review if they analysed disease control, toxicity, or second malignancy after radiotherapy for breast cancer using the SEER or SEER-Medicare linked databases. A primary result was one where the comparison of radiotherapy versus not was presented as a main outcome, and conclusions were drawn from these results. A secondary result was one where the comparison was used, in either a univariable or multivariable regression model, and the result was presented, but no conclusions were drawn by the authors relating to that comparison. EMBASE (up to 22nd May) and MEDLINE (up to May week 2 2014) were searched, and two additional searches in PubMed were performed on 23/05/2014. See Table 3-1 for details of the search strategies. After removing duplicates, full text articles (where available) were examined. Where the full articles were not available, the abstract was screened.

References were categorised into one of the following categories:

a) full articles comparing left-sided versus right-sided breast cancer as a main result

For articles that did not present left-sided versus right-sided as a primary result were categorised as:

b) full articles comparing radiotherapy versus no radiotherapy (RT+ vs RT-) as a primary result
c) full articles comparing RT+ vs RT- as a secondary result, e.g. with analyses of urban versus rural areas as a main result
d) conference abstracts comparing RT+ vs RT- as a primary result
e) conference abstracts comparing RT+ vs RT- as a secondary result.

Database	Search Order	Search Terms
EMBASE		1. radiotherapy*.mp †
		2. radiation.mp or exp radiation/
		3. irradiat*.mp
		4. brachytherapy*.mp
		5. exp radiotherapy/
		6. 1 or 2 or 3 or 4 or 5
		7. SEER.mp
		8. (Surveillance Epidemiology and End Results).mp.
		9. 7 or 8
		10. 6 and 9
MEDLINE		1. radiotherapy*.mp §
		2. exp Radiation/
		3. radiation.mp
		4. brachytherapy*.mp
		5. exp Radiotherapy/
		6. 1 or 2 or 3 or 4 or 5
		7. SEER.mp
		8. (Surveillance Epidemiology and End Results).mp.
		9. 7 or 8
		10. 6 and 9
PubMed (n=192)	-	((breast cancer) AND radiotherapy) AND SEER
PubMed (n=738)	-	(radiotherapy) AND SEER

† mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword

§ mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier

Table 3-1: Search strategy for the systematic review of studies that used the SEER public-use data set to analyse disease control, toxicity or heart disease and second malignancy associated with radiotherapy for breast cancer.

3.3.2 Randomised Evidence: EBCTCG Meta-Analysis

The latest cycle of the EBCTCG meta-analyses of individual patient data from randomised controlled trials was taken as the gold-standard. The most recent meta-analyses were based on individual patient data for 8,135 women taking part in 22 randomised trials of radiotherapy among women treated with mastectomy and axillary surgery started during 1964 to 1986 (Early Breast Cancer Trialists' Collaborative Group 2014). Prior to this, a meta-analysis of 10,801 women

enrolled in 17 randomised trials started during 1976 – 1999 of radiotherapy versus not after breast conserving surgery was published (Early Breast Cancer Trialists' Collaborative Group 2011).

Breast cancer mortality and all-cause mortality log rank estimates were taken from Web-figure 30 (Early Breast Cancer Trialists' Collaborative Group 2014) for node-positive women given a mastectomy and from Web-figures 3, 12a, 12b and 12c (Early Breast Cancer Trialists' Collaborative Group 2011) for all women given breast conserving surgery.

Mortality ratios, with corresponding 95% confidence intervals, were estimated from the log rank O-E estimates and variances, where O-E is the (O)bserved minus (E)xpected number of deaths in the treatment-allocated arm[7]. Analyses were stratified by trial, individual follow-up year, age at randomisation and pathological nodal status.

3.3.3 Observational Evidence: SEER Cohort

Cause-specific mortality information was obtained from the SEER public-use data set on all women registered with local or regional breast cancer during 1973-2008. Women diagnosed with breast cancer as their first cancer when aged 20-79 years were included, unless their cancer was bilateral. All records had to include a valid follow-up and known status of radiotherapy and breast cancer laterality. Deaths were classified based on the underlying cause on the death certificate.

In this analysis of SEER data, radiotherapy refers to adjuvant radiotherapy administered after either breast conserving surgery or mastectomy. However, the recording procedures have evolved over time. Prior to 1998, radiotherapy was recorded only if it was received during the first four months after surgery. From 1998, radiotherapy was recorded if it was received as part of the planned first course of treatment, whenever it was administered. A number of studies have demonstrated under-ascertainment of radiotherapy receipt in SEER, and variation in

[7] http://www.ctsu.ox.ac.uk/research/meta-trials/ebctcg/section-5-statistical-methods

ascertainment even after 1998 (Malin, Kahn et al. 2002, Yu, Gross et al. 2009, Jagsi, Abrahamse et al. 2010, Jagsi, Abrahamse et al. 2012, Walker, Giordano et al. 2013).

In calculating death rates, each woman's contribution to the person-years at risk ran from the date of breast cancer diagnosis to the earliest of: death, loss to follow-up, end of study period (1st January 2009) or 85th birthday. Mortality ratios were estimated using Poisson regression with stratification by available possible confounders. These included the following patient, disease, and treatment characteristics: calendar year of cancer diagnosis, time since diagnosis, age at cancer diagnosis (all in 5-year groups), race / ethnicity, tumour size, tumour grade, surgery type, number of involved nodes, axillary clearance, clinical nodal status (from 2004 onwards), ER status and disease stage. Prior to 1990, there was limited information recorded on tumour characteristics, for example for women diagnosed in 1973, 89% were recorded with an unknown grade, and 90% an unknown tumour size. Therefore, when the stratification included the tumour characteristics the cohort was restricted to 1990+.

3.4 Results

The mortality ratio, irradiated versus unirradiated, is a measure of the association between mortality and the treatment exposure, which in this case is radiotherapy. As such, a mortality ratio value greater than 1 indicates an increased risk of death following radiotherapy, whereas a ratio value less than 1 demonstrates a decreased risk of death following radiotherapy.

3.4.1 Systematic Review of Studies Published Using SEER and SEER-Medicare

Out of a total of 4,358 articles screened, 67 articles which were published during 1993 to 2014 were eligible (Figure 3-1). The distribution of eligible articles by main outcome reported varied for the five groups (groups a) – e) described in Section 3.3.1). 28 were full articles and used a RT+ vs RT- comparison as a primary result. Out of these 28 full articles that were eligible, 10 used overall survival as the main outcome measure, 11 articles presented mortality or

incidence of second cancers, and only one analysed heart disease as the main outcome. Only 7 of the 67 articles presented the comparison of left-sided and right-sided breast cancer patients. All but one of these 7 articles used a main outcome of heart disease. 20 of the 67 articles were conference abstracts, with 18 of these including a comparison of radiotherapy versus not (RT+ vs RT-) as a primary result. These articles are listed in Appendix Tables C-1 to C-3, and summarised in Table 3-2. The studies that presented a RT+ vs RT- comparison varied in the extent to which they attempted to control for selection biases and other confounding factors and the extent to which they recognised this as a limitation in the interpretation of their findings.

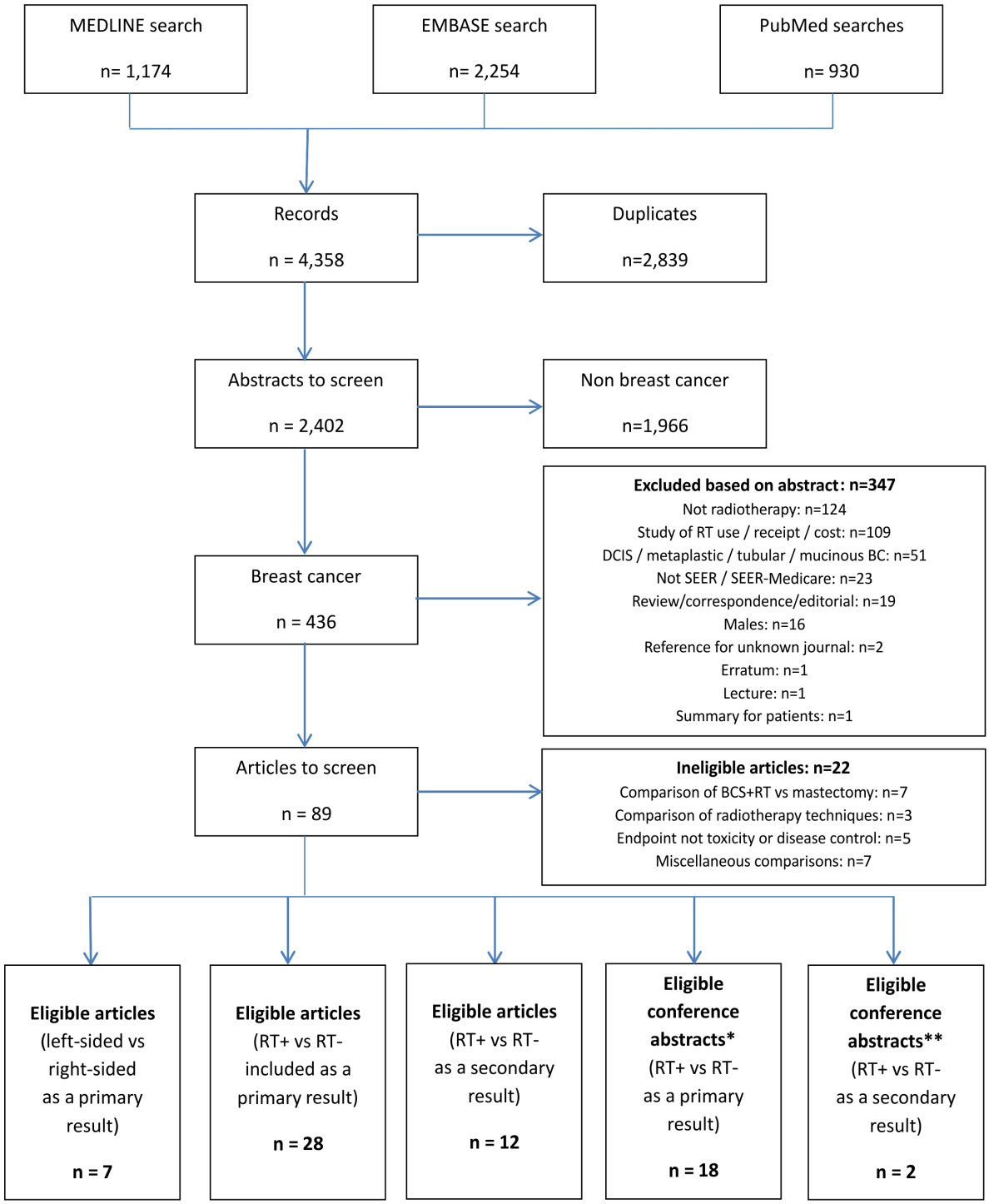


Figure 3-1: Diagram of the study selection process for the systematic review of studies that used the SEER public-use data set to analyse disease control, toxicity or heart disease and second malignancy associated with radiotherapy for breast cancer.

Outcome	Type of comparison		
	Radiotherapy vs not		Left-sided versus right-sided breast cancer
	Primary result	Secondary result	Primary or secondary
Overall survival			
Any cause	22	8	0
Breast cancer			
Survival	7	4	1
Subsequent mastectomy	2	0	0
Cause specific survival			
Any non-breast cancer	2	1	0
Heart disease	3	0	6
Hypothyroidism	1	0	0
Second cancers			
Any	12	1	2
Total	**28 articles + 16 abstracts**	**12 articles + 1 abstract**	**7 articles**

Table 3-2: Summary of review of 67 studies screened from 2,402 articles using SEER data to analyse disease control, toxicity, or second malignancy after radiotherapy for breast cancer.

3.4.2 Randomised Trials Results

The mortality ratios, radiotherapy versus not, calculated using the EBCTCG data, are shown in Table 3-3. There were reductions in both breast cancer mortality and all-cause mortality for women randomised to radiotherapy with a rate ratio (RR) of 0.83 (95% CI 0.78-0.89) and RR=0.91 (95% CI 0.86-0.96) respectively. These proportional reductions were similar in magnitude in the breast conserving surgery (BCS) and mastectomy groups for both all cause and breast cancer mortality. Considering deaths other than breast cancer, in BCS patients RR=1.08 (95% CI 0.96-1.21) and in mastectomy patients RR= 1.17 (95% CI 0.91-1.50). The

number of deaths, women and the log-rank values that were used in this analysis are shown in Appendix Table C-4.

Cause of death	Ratio of annual death rates, RT versus No RT* (95% confidence interval)				
	Breast conserving surgery (10,801 women in 17 trials)	Mastectomy and axillary dissection (3,131 node-positive women in 14 trials)	2p for difference†	All women	2p for effect of RT‡
Breast cancer	0.82 (0.75-0.90)	0.84 (0.76-0.94)	0.75	0.83 (0.78-0.89)	<0.0001
Other causes	1.08 (0.96-1.21)	1.17 (0.91-1.50)	0.55	1.09 (0.99-1.21)	0.09
All causes	0.92 (0.85-0.99)	0.89 (0.81-0.97)	0.64	0.91 (0.86-0.96)	0.0007

* Stratified by trial, individual year of follow-up, age at randomisation (<40, 40-49, 50-59, 60-69, 70+ years), and nodal status (breast conserving surgery: negative/positive, mastectomy: 1-3 positive nodes/4+ positive nodes/number of positive nodes unknown).

† 2-sided significance level for difference between effect of radiotherapy following breast-conserving surgery compared to its effect following mastectomy and axillary dissection.

‡ 2-sided significance level for effect of radiotherapy in all randomised women.

§ Results for individual causes are not available separately for women receiving breast conserving surgery and mastectomy.

Table 3-3: Randomised evidence: death rate ratios in 13,932 women with early breast cancer randomised to receive adjuvant radiotherapy (RT) or not (No RT). Refer to Appendix Table C-4 for corresponding values.

Considering deaths from causes other than breast cancer, the rate ratios were increased in both the breast conserving surgery and the mastectomy groups. These increases were not statistically significant, but additional information on mortality in women randomised to radiotherapy compared with women randomised to no radiotherapy was also available for other groups of women (Early Breast Cancer Trialists' Collaborative Group 2005). Information on causes of death other than from breast cancer in all trials of radiotherapy versus no radiotherapy in early breast cancer are available from an earlier EBCTCG paper and are summarised in Table 3-4. The excess of non-breast-cancer mortality seen in the irradiated patients was largely due to heart disease (RR=1.27 95% CI 1.12-1.44) and lung cancer (RR=1.78 95% CI 1.30-2.46).

Cause of death	Ratio of annual death rates, RT versus No RT* (95% confidence interval)				
	Breast conserving surgery (10,801 women in 17 trials)	Mastectomy and axillary dissection (3,131 node-positive women in 14 trials)	2p for difference†	All women	2p for effect of RT‡
Lung cancer§	-	-	-	1.78 (1.30-2.46)	0.0004
Heart disease	-	-	-	1.27 (1.12-1.44)	0.0001
Other specified causes	-	-	-	1.00 (0.91-1.11)	0.94
Unspecified cause, not breast cancer	-	-	-	1.05 (0.90-1.23)	0.54

* Stratified by trial, individual year of follow-up, age at randomisation (<40, 40-49, 50-59, 60-69, 70+ years), and nodal status (breast conserving surgery: negative/positive, mastectomy: 1-3 positive nodes/4+ positive nodes/number of positive nodes unknown).

† 2-sided significance level for difference between effect of radiotherapy following breast-conserving surgery compared to its effect following mastectomy and axillary dissection.

‡ 2-sided significance level for effect of radiotherapy in all randomised women.

§ Results for individual causes are not available separately for women receiving breast conserving surgery and mastectomy. Estimates for these ratios were obtained from an earlier EBCTCG publication (Early Breast Cancer Trialists' Collaborative Group 2005)

Table 3-4: Randomised evidence: death rate ratios for all causes other than breast cancer in women with early breast cancer randomised to receive adjuvant radiotherapy (RT) or not (No RT).

3.4.3 Observational Study Results

3.4.3.1 Radiotherapy versus Not Comparison

Using data from the SEER cancer registry (see Appendix Table C-5 for patient characteristics) mortality was compared in irradiated and unirradiated women (Table 3-5). Among patients who underwent mastectomy, the all-cause mortality ratio was 1.62 (95% CI 1.60-1.65), compared to a ratio of 0.63 (95% CI 0.62-0.65) among BCS patients (2p for difference <0.0001) where the analysis was stratified using patient characteristics (basic stratification). Tumour characteristics were reliably available only for women diagnosed with breast cancer in 1990 or later. When the analysis was repeated using an additional stratification taking the tumour characteristics into account, very similar results were obtained (BCS RR= 0.63 (95% CI 0.61-0.65) and mastectomy RR=1.62 (95% CI 1.59-1.66)).

Breast cancer and other causes of death were also considered separately. The breast cancer mortality ratios estimated using stratification by both patient and treatment characteristics were 2.11 (95% CI 2.05-2.17) for mastectomy patients and 0.63 (95% CI 0.61-0.66) for BCS patients. Using both types of stratification there was a highly significant difference by surgery type for breast cancer mortality. Generally, there was highly significant differences between the mortality ratios for women give BCS and mastectomy for all outcomes except lung cancer. Focusing on some of the specific causes of death, using the basic stratification only, radiotherapy was associated with a 37% increased heart disease mortality risk after mastectomy, but a reduction in heart disease mortality after BCS (RR=0.56 95% CI 0.53-0.60). This pattern was mirrored for the outcome of accidents and violence, with mortality ratios of 1.06 (95% CI 0.90-1.24) and 0.68 (95% CI 0.56-0.82) for mastectomy and BCS, respectively. The numbers and person-years that contributed to this analysis are shown in Appendix Tables C-6 and C-7.

Certified cause of death	Ratio of annual death rates, RT versus No RT (95% confidence interval)					
	Basic stratification only*			Basic stratification and additional stratification†, 1990+		
	Breast conserving surgery 197,727 RT/ 57,322 No RT‡	**Mastectomy** 59,249 RT/ 244,573 No RT	***2p for difference*** **§**	**Breast conserving surgery** 186,571 RT/ 54,146 No RT	**Mastectomy** 40,745 RT/ 151,381 No RT	***2p for difference*** **§**
Breast cancer	0.64 (0.62, 0.66)	1.97 (1.94, 2.01)	*<0.0001*	0.63 (0.61-0.66)	2.11 (2.05-2.17)	<0.0001
Other deaths	0.63 (0.61-0.65)	1.21 (1.18-1.24)	*<0.0001*	0.63 (0.61-0.66)	0.98 (0.93-1.02)	<0.0001
Lung cancer ¶	0.86 (0.75-0.99)	1.27 (1.13-1.43)	*<0.0001*	0.84 (0.72-0.97)	0.85 (0.69-1.06)	0.88
Other cancers	0.78 (0.73-0.84)	1.29 (1.22-1.36)	*<0.0001*	0.78 (0.73-0.85)	1.26 (1.15-1.37)	<0.0001
Heart disease	0.56 (0.53, 0.60)	1.37 (1.31, 1.43)	*<0.0001*	0.55 (0.51-0.59)	1.01 (0.92-1.10)	<0.0001
Other diseases	0.59 (0.56-0.62)	1.03 (0.99-1.08)	*<0.0001*	0.59 (0.56-0.63)	0.84 (0.79-0.91)	<0.0001
Accidents & violence	0.68 (0.56-0.82)	1.06 (0.90-1.24)	*<0.0001*	0.69 (0.56-0.85)	1.01 (0.78-1.29)	0.03
All causes **	0.63 (0.62-0.65)	1.62 (1.60-1.65)	*<0.0001*	0.63 (0.61-0.65)	1.62 (1.59-1.66)	<0.0001

* Basic stratification: age (<40, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79 and calendar year of cancer diagnosis (1973-77, 1978-82, 1983-87, 1988-92, 1993-97, 1998-02, 2003-08), years since cancer diagnosis (0-4, 5-9, 10-14, 15-19, 20+), race (black, white & other/unknown).

† Additional stratification: stage (localised/regional), tumour size (T1 (<2cm) / T2 (2-5cm) / T3 (5+cm) / unknown), number of involved nodes (exact number of nodes examined by the pathologist that were found to be positive (0 / 1-3 / 4-9 / 10+ / unknown or not specified / NA / not stated) and from 2004 use the AJCC clinical nodal stage (N0 / N1 (1-3 nodes) / N2 (4-9 nodes) / N3 (10+ nodes) / not applicable / unknown)), grade (low/intermediate/high/unknown), estrogen receptor status (positive/negative/unknown), quadrant (inner / outer / other), axillary clearance (breast conserving surgery (BCS) with axillary clearance (AC) / BCS without AC / mastectomy with AC / mastectomy without AC / other).

‡ Numbers of women recorded as receiving radiotherapy (RT) or as not receiving radiotherapy (No RT).

§ 2-sided significance level for difference between effect of radiotherapy following breast-conserving surgery compared to its effect following mastectomy and axillary dissection.

¶ Includes only deaths from women with microscopically confirmed lung cancer, identified by cross-matching of recorded deaths to SEER data file of lung cancer registrations.

** Includes deaths with unknown cause.

Table 3-5: Observational evidence: death rate ratios, radiotherapy versus not, in 558,871 women registered with breast cancer in the SEER public-use data set .

3.4.3.2 Left-sided versus Right-sided Breast Cancer Mortality Comparison

For all women combined in the SEER data, the breast cancer mortality ratio, left-sided versus right-sided, was 1.01 (95% CI 1.00-1.03), with no difference by surgery type (2p=0.11), see Table 3-6. Neither was there a significant difference in breast cancer mortality by surgery type in women recorded as receiving or not receiving radiotherapy. The proportional effect due to laterality for breast cancer mortality was similar in magnitude in the breast conserving surgery (BCS) and mastectomy groups.

Considering causes other than breast cancer in women not recorded as receiving radiotherapy, there were no significant differences by surgery type, for either all causes together, or for heart disease, lung cancer and all causes except breast cancer, heart disease and lung cancer separately. For women recorded as having received radiotherapy, there were highly significant differences by surgery for heart disease and lung cancer specifically. The mortality ratio (left-sided versus right-sided breast cancer) for all causes excluding breast cancer was 1.08 (95% CI 1.03-1.13) for mastectomy patients and 0.99 (95% CI 0.96-1.03) for BCS patients (Table 3-6). There was a significant 26% left-sided excess of heart disease deaths for mastectomy patients, the corresponding mortality ratio for BCS patients was 0.97 (95% CI 0.91-1.04). Significant heterogeneity existed between surgery types (2p<0.0001). The overall lung cancer mortality ratio for irradiated women was 1.30 (95% CI 1.16-1.45) using a comparison of ipsilateral and contralateral lung cancer.

There was no evidence of any heterogeneity between surgery types for women recorded as not having received radiotherapy, or any evidence of a significant left-sided excess.

Extent of surgery	Certified cause of death				
	Breast cancer	**All causes except breast cancer**	**Heart disease**	**All causes except breast cancer, heart disease and lung cancer**	**Lung cancer***
	Ratio of annual death rates (95% confidence interval) †				
	Left-sided versus right-sided				**Ipsilateral vs contralateral**
			Recorded as receiving radiotherapy		
BCS	1.04 (1.00-1.08)	0.99 (0.96-1.03)	0.97 (0.91-1.04)	1.00 (0.96-1.04)	1.20 (1.06-1.37)
Mastectomy	1.02 (0.99-1.05)	1.08 (1.03-1.13)	1.26 (1.16-1.36)	1.01 (0.95-1.07)	1.63 (1.31-2.04)
2p for difference	*0.43*	*0.002*	*<0.0001*	*0.74*	*0.02*
All surgery	1.03 (1.00-1.05)	1.02 (1.00-1.05)	1.08 (1.03-1.14)	1.01 (0.97-1.03)	1.30 (1.16-1.45)
			Not recorded as receiving radiotherapy		
BCS	1.03 (0.97-1.09)	1.01 (0.96-1.07)	1.05 (0.95-1.16)	1.00 (0.94-1.07)	0.95 (0.74-1.22)
Mastectomy	1.01 (0.99-1.03)	1.01 (0.99-1.03)	1.02 (0.99-1.06)	1.01 (0.99-1.03)	0.97 (0.88-1.07)
2p for difference	*0.46*	*0.93*	*0.55*	*0.87*	*0.87*
All surgery	1.01 (0.99-1.03)	1.01 (0.99-1.03)	1.02 (0.99, 1.06)	1.01 (0.99, 1.02)	0.97 (0.89-1.06)
			All women		
BCS	1.04 (1.00-1.07)	1.00 (0.97-1.03)	1.00 (0.95-1.06)	1.00 (0.97-1.03)	1.06 (0.97-1.15)
Mastectomy	1.01 (0.99-1.02)	1.02 (1.00-1.04)	1.05 (1.02-1.09)	1.01 (0.99-1.03)	1.15 (1.02-1.29)
2p for difference	*0.11*	*0.17*	*0.11*	*0.61*	*0.26*
All surgery	1.01 (1.00-1.03)	1.02 (1.00-1.03)	1.04 (1.01-1.07)	1.01 (0.99-1.02)	1.09 (1.02-1.14)

* Includes only deaths from women with microscopically confirmed lung cancer, identified by cross-matching of recorded deaths to SEER data file of lung cancer registrations.

† Death rate ratios stratified by: age (<40, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79 and calendar year of cancer diagnosis (1973-77, 1978-82, 1983-87, 1988-92, 1993-97, 1998-02, 2003-08), years since cancer diagnosis (0-4, 5-9, 10-14, 15-19, 20+) and race (black, white & other/unknown).

Table 3-6: Observational evidence: death rate ratios, left-sided versus right-sided, in 558,871 women registered with breast cancer in the SEER public-use data set.

3.5 Discussion

In this study, mortality outcomes after radiotherapy were investigated using two large-scale sources of evidence regarding breast cancer patients, finding strikingly dissimilar results between the analysis of data from randomised trials compiled by the EBCTCG

meta-analyses and the analysis of observational data in the SEER registries. The EBCTCG meta-analysis, which provides an unconfounded comparison of irradiated and unirradiated patients, clearly demonstrated that radiotherapy results in significantly improved overall and breast cancer-specific mortality, irrespective of surgery type. In contrast, analyses of the SEER registry data suggested that after breast conserving surgery (BCS) radiotherapy appeared to reduce breast cancer mortality but increase it after mastectomy. Controlling for known confounders, namely stage, tumour size, number of involved nodes, axillary clearance, clinical nodal stage, grade and ER (estrogen receptor) status had little effect. One specific example was that the analyses of SEER suggested that radiotherapy prevented accidental deaths and violence after breast conserving surgery, but not after mastectomy. This is unlikely to be a true association, but rather a reflection of the type of woman who is selected to receive radiotherapy.

It is well-recognised in clinical practice that patients and physicians select treatments very carefully. In the management of breast cancer, guidelines recommend the delivery of adjuvant radiotherapy to most patients after BCS. Even among elderly women, who are now known to attain a small absolute benefit from adjuvant radiotherapy following BCS, high rates of receipt occur in the U.S, with 76.5% of Medicare beneficiaries receiving radiotherapy as shown in a recent study by Soulos and colleagues (Soulos, Yu et al. 2012).The small number of patients who did not receive radiotherapy after BCS are likely to have unmeasured comorbidities or other risk factors that increased their risk of mortality compared to the majority who receive treatment. This may appear to accentuate any beneficial impact of treatment when evaluating associations in observational data. By contrast, following mastectomy, radiotherapy is indicated only for patients with adverse disease characteristics, such as nodal involvement (Recht, Edge et al. 2001, Early Breast Cancer Trialists' Collaborative Group 2014). It is important to note that the recent meta-analysis by EBCTCG found that radiotherapy reduced both recurrence and breast cancer mortality in women with one to three positive lymph nodes (Early Breast Cancer Trialists'

Collaborative Group 2014). This finding will not have influenced the treatment decisions of the women in this SEER study population, yet it may have an influence on the selection effects present in future observational studies of this type. This can lead to a spurious underestimation of the benefits of radiotherapy (or, as the current findings demonstrate, it may suggest the opposite effect from what has been observed in the randomised trials). Although the general nature of this sort of selection bias tends to be well appreciated, the current study provides a particularly important demonstration of the dramatically different results that can follow from analyses of the randomised trials versus that of data in the SEER registries. Such selection may explain the SEER results shown in Table 3-5 of radiotherapy versus not where it appears that radiotherapy doubles the risk of breast cancer mortality after mastectomy, but halves it after breast conserving surgery. This highlights the fact that despite the great awareness amongst clinicians of the predictive and prognostic factors for treatment, some of which may be confounders, there are many unknown factors that also confound the apparent effect of radiotherapy in the observational setting, and these cannot be fully controlled for. Misclassification in the recording of radiotherapy may also have contributed to this. Figure 3-2 shows the number of women recorded as both receiving radiotherapy and not receiving radiotherapy by calendar year of diagnosis. It demonstrates a clear jump in the number of women recorded to have received radiotherapy after the change in the SEER Program Coding and Staging Manual in 1998. Before 1998, adjuvant therapies were only recorded if they were administered within four months of the surgery. This meant that if a poorer prognosis patient also received adjuvant chemotherapy, their radiotherapy treatment may have been delayed. After 1998, all adjuvant treatment was recorded if it was part of the planned first course of treatment. This suggests that there may have been substantial misclassification.

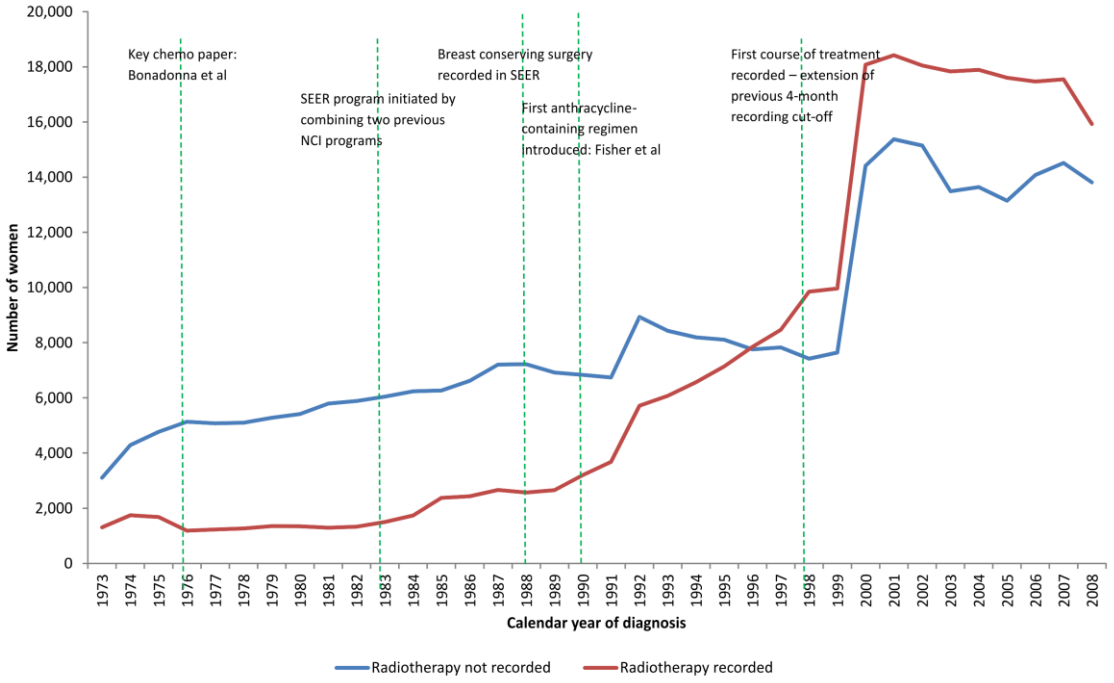


Figure 3-2: Number of women recorded to have received radiotherapy in SEER by calendar year of diagnosis.

Giordano et al previously demonstrated similar concerns using the linked SEER-Medicare dataset to evaluate outcomes in prostate and colon cancer (Giordano, Kuo et al. 2008). Three examples were presented which clearly highlighted the problems of treatment selection. All three examples produced improbable results compared to the clinical trial evidence available. None of the improbable results were reduced through controlling for known confounders, for example comorbidity, or through the use of propensity scores. The conclusions drawn from these results are similar to those in the current work, which harnessed the opportunity to compare observational findings to the particularly large dataset of randomised evidence that exists in breast cancer thanks to the collaboration of the EBCTCG.

The systematic review showed there are numerous studies which analysed disease control, toxicity, or second malignancy associated with radiotherapy for breast cancer using the SEER observational dataset. More than 80% of the articles used a comparison of irradiated and unirradiated women to draw conclusions on overall survival and second malignancy risk

associated with radiotherapy. Given the results presented in this chapter, some of these articles may be misleading.

Although randomised controlled trials are the gold standard, several reasons have led researchers to consider observational data to investigate certain treatment-related effects (Bekelman, Shah et al. 2011). First, in general, only a limited number of women have been randomised to treatments in the setting of controlled trials, resulting in a limited number of events available for analysis. Observational data, particularly SEER, holds information on a large number of women. Therefore, the corresponding large number of events allows analyses that may not be possible in randomised controlled trials, specifically investigation of rare events. SEER also lends itself very well to studies of late effects due to the extended follow-up, which is not usually feasible in the randomised setting due to cost constraints. Observational studies allow investigation of proven treatment modalities, which would be unethical to randomly withhold from a patient. Finally, women selected for randomised trials tend to be healthy, with less comorbidity that the general population. The SEER data allows investigation of a cohort that should be representative of the general population. These concerns have led researchers to complement analyses of efficacy in randomised trials with considerations of comparative effectiveness in actual practice (Bekelman, Shah et al. 2011, Korn and Freidlin 2012, Lyman and Levine 2012, Meyer, Wheeler et al. 2014). Still, as the current results show, despite the promise of observational analysis, caution must be employed when analysing observational data to ensure that biases are adequately recognised and addressed. A recent review by a panel of experts in health services research discussed the use of large scale observational data in radiation oncology (Jagsi, Bekelman et al. 2014). The conclusions drawn regarding the strengths and limitations of observational data particularly with regards to determining causality, including the effect of patient selection, were complementary to those presented in this chapter.

3.5.1 Strengths and Limitations

Breast cancer studies are in a unique position due to the availability of evidence from the EBCTCG who provide a comprehensive, reliable report on all treatment types every five years. The main strength of this chapter was the use of a large-scale dataset of high-quality randomised evidence as a gold-standard comparator for the observational results. This demonstrated very clearly the issues caused by patient selection and other potential sources of confounding, along with the potential magnitude of this problem, even after controlling for measured confounding factors present in the SEER data.

This chapter also has potential limitations. The SEER registry data alone was used as the source of observational data. SEER data have a number of limitations that make it particularly difficult to control for selection bias and other sources of confounding, including lack of detailed treatment information; lack of information on comorbidities and socio-economic measures; problems in death ascertainment (Devis and Rooney 1999) and under-ascertainment of treatment (Malin, Kahn et al. 2002, Yu, Gross et al. 2009, Jagsi, Abrahamse et al. 2010, Jagsi, Abrahamse et al. 2012, Walker, Giordano et al. 2013). Other registries may contain more robust information on confounding factors not measured in SEER and more accurate and detailed information on treatment receipt. Studies using those observational datasets may be able to reduce the effects of selection biases observed in the current study. Still, as noted above, these findings are very similar to those of Giordano et al. who considered the more detailed information available in the linked SEER-Medicare dataset. This suggests that caution is appropriate even when a greater array of potential confounding factors have been measured and included in analysis.

3.6 Conclusions

Three main conclusions can be drawn from this study. Firstly, when investigating mortality from the original cancer, and its association with treatment, evidence from randomised

trials should always be used where available. Secondly, when analysing treatment-related toxicities, selection biases can be problematic. For some endpoints, alternative comparisons exist and could be employed when using SEER registry data, for example a comparison of heart disease outcomes in women irradiated for left- versus right-sided breast cancer. Wherever possible, such creative approaches to address the inherent limitations of observational analyses are critical to consider. Finally, when evaluating rare late effects for which sufficient randomised evidence does not exist and for which alternative non-confounded comparisons are impossible, analyses that compare treated and untreated patients and where selection biases are likely to exist must be interpreted with considerable caution. Manuscripts reporting such analyses should consider and discuss the direction and size of the effect of these biases.

Awareness of the selection effects and the corresponding spurious results informed the choice of analysis methods for the following chapters. The laterality comparison was used throughout the analyses of the COBS cohort, using a comparison of left-sided and right-sided breast cancer patients for the study of heart disease, and ipsilateral and contralateral lung cancer. During treatment for cancer diagnosed in teenagers and young adults, physicians tend not to select patients for treatment as they give patients the maximum treatment possible. Due to the young age of the patients, the benefits of treatment far outweigh the risk of late treatment-related toxicities. Therefore, selection effects were less problematic in the TYACSS cohort than in the breast cancer cohort, but they were still considered prior to the analyses.

CHAPTER 4:
CARDIAC MORTALITY RISK FOLLOWING BREAST CANCER RADIOTHERAPY

4.1 Introduction

Radiotherapy can reduce the risk of breast cancer recurrence and of death from breast cancer, but it often involves some incidental irradiation of the heart. Long-term follow-up of trials in which women with early stage breast cancer were randomised to either radiotherapy or the same surgery but not radiotherapy has shown that radiotherapy can increase the risk of death from heart disease (Cuzick, Stewart et al. 1994, Early Breast Cancer Trialists' Collaborative Group 2005), thereby reducing the extent to which overall survival is improved by radiotherapy and reducing the quality of life for some breast cancer survivors. A number of observational cohort studies have also demonstrated that this incidental irradiation resulted in an increased risk of heart disease (Darby, McGale et al. 2005, McGale, Darby et al. 2011, Darby, Ewertz et al. 2013, Henson, McGale et al. 2013). As discussed in the previous chapter, randomised evidence is taken to be the gold standard, as associations between treatment and outcomes are more likely to reflect true causation when treatment is allocated at random. However, only a limited number of women were randomised into trials of radiotherapy versus not, and most used treatment regimens are now outdated. This, alongside the need to study heart disease risk in all patients with breast cancer rather than those selected for trial entry has increasingly led researchers to use population-based observational cohorts to explore radiation-related late effects of treatment to complement the randomised evidence (Jagsi, Bekelman et al. 2014).

Due to the selection biases, and other biases that cannot be controlled (Chapter 3) observational epidemiological studies comparing the risk of heart disease in breast cancer patients who have received different treatments cannot usually be relied on to provide valid estimates of the effect of different treatments on the heart. However, for the particular case of breast cancer, the opportunity to make valid inferences arose because the positioning of the heart means that it usually receives a higher radiation dose from treatment for left-sided breast cancer than for right-sided breast cancer. Up until recently, the laterality of breast cancer has

had little influence in selecting who should receive radiotherapy (Vandenbroucke 2004). A systematic review of studies published during 2003 to 2013 (Dr Carolyn Taylor provisional work, personal communication, November 2014) demonstrated that the mean heart dose received was 4.8 Gy in women treated for left-sided breast cancer, and 1.6 Gy for right-sided radiotherapy. This suggests that, despite improving treatment techniques, a substantial difference in mean heart dose by breast cancer laterality remains. Thus, a comparison of mortality from heart disease in irradiated woman with left-sided and right-sided breast cancer is an effective way of investigating the risk of heart disease associated with radiotherapy for women treated.

Comparisons of cardiac incidence and mortality in women who have been irradiated for left-sided and right-sided breast cancer have produced results that are consistent with the randomised trials and have provided insight into radiation-related cardiac risks following breast cancer radiotherapy. The mortality risk of radiation-related heart disease has been investigated using a laterality comparison in 16 observational studies (summarised in Table 1-2 of Chapter 1). The largest study used information recorded on 558,871 women in the SEER public-use dataset, USA, and found a significant 8% left-sided excess among irradiated women (Henson, McGale et al. 2013). However, only the risk of all heart disease combined (as opposed to specific cardiac diagnoses) can be investigated in SEER as data are not available for specific ICD-codes. All studies, except one (Bouchardy, Rapiti et al. 2009), found an increased risk of heart disease mortality among women treated for left-sided breast cancer, compared to right-sided. Each of these relevant studies used data from a single source, and some studies had a modest population size, thus the radiation-related heart disease risk has yet to be investigated on a 'big data' scale, particularly combining data from multiple sources and countries. In addition, there is only limited data at present regarding factors, other than the cardiac radiation dose (Darby, Ewertz et al. 2013), which influence the risk of radiation-related heart disease. Individual patient information

was, therefore, collated from cancer registries round the world to provide further insight on this issue.

4.2 Aim

This study aimed to characterise the long-term cardiac mortality risk associated with radiotherapy for breast cancer, in the largest, as yet, collaborative population-based cohort of 22 countries worldwide. It also aimed to investigate the variation in radiation-related risk by key patient, tumour and treatment characteristics.

4.3 Results

4.3.1 Characteristics of study population

A total of 1,934,248 women from 57 cancer registries in 22 countries were included in this study contributing 14,853,410 person-years during 1935-2008 (Table 4-1). The percentage of women recorded as receiving radiotherapy was slightly smaller for women with left-sided cancer than for women with right-sided cancer (52.6 per cent left-sided versus 52.8 per cent right-sided, 2p for difference: 0.003). For other factors the percentage of women recorded as receiving radiotherapy varied, sometimes substantially — for example over 70 per cent of women who had breast-conserving surgery (BCS) had radiotherapy compared with less than 30 per cent of women who had mastectomy. Despite this, similar proportions of women with left-sided and right-sided breast cancer were recorded as receiving radiotherapy (50% for both left- and right-sided). This was consistent for all categories of the patient characteristics suggesting that breast cancer laterality did not influence the decision to irradiate a patient. A total of 55,264 deaths from heart disease was reported.

	Number of women		Percentage recorded as irradiated		Number of cardiac deaths	
	Left-sided	Right-sided	Left-sided	Right-sided	Left-sided	Right-sided
Calendar year of diagnosis						
< 1960	16,297	15,067	47.5	47.4	1,791	1,571
1960 - 69	31,744	29,554	60.6	60.3	1,856	1,588
1970 - 79	86,778	80,753	50.2	50.2	5,729	5,071
1980 - 89	176,543	164,497	46.7	46.8	8,774	7,732
1990 - 99	317,616	298,183	53.0	53.1	8,070	7,602
2000+	367,307	349,909	55.1	55.5	2,839	2,641
Age at diagnosis (years)						
< 40	67,579	66,078	55.1	55.4	355	277
40 - 49	204,149	195,363	55.6	55.5	1,954	1,720
50 - 59	267,957	252,008	56.0	56.2	4,674	3,949
60 - 69	261,607	244,036	53.1	53.3	9,688	8,976
70 - 79	194,991	180,476	43.0	43.3	12,388	11,283
Stage						
DCIS *	67,950	63,824	38.1	38.3	1,122	1,016
Local	378,266	360,074	50.0	50.4	12,867	11,758
Regional	244,231	229,963	54.6	54.6	7,245	6,539
Metastatic	42,946	39,771	48.1	47.9	742	669
Unknown	158,487	147,148	50.8	51.1	3,146	2,840
Not recorded†	104,405	97,183	70.8	71.1	3,937	3,383
Surgery						
BCS ‡	262,831	252,280	72.8	73.0	4,949	4,688
Mastectomy	249,487	236,322	26.9	27.1	8,884	8,158
None	27,895	25,489	38.1	38.5	551	496
Unknown	371,511	344,979	52.1	52.2	11,272	9,871
Not recorded †	84,561	78,893	72.0	72.2	3,403	2,992
Chemotherapy						
Yes	115,195	107,882	63.8	63.9	699	669
No	355,681	329,821	52.7	53.1	9,796	8,740
Unknown	509,216	485,000	49.3	49.5	18,344	16,617
Not recorded †	16,193	15,260	72.2	72.0	220	179
Hormonal therapy						
Yes	164,624	152,995	62.8	63.2	2,960	2,683
No	289,196	268,949	50.7	51.1	7,466	6,690
Unknown	534,290	508,712	50.1	50.3	18,475	16,713
Not recorded †	8,175	7,307	69.5	69.4	158	119

table cont. on next page

* Ductal carcinoma in situ

† Data not provided by registry, including the period before common use of therapy.

‡ Breast-conserving surgery

Table continued

	Number of women		Percentage recorded as irradiated		Number of cardiac deaths	
	Left-sided	Right-sided	Left-sided	Right-sided	Left-sided	Right-sided
Race/ethnicity						
White	469,630	446,365	47.6	47.9	17,332	15,804
Black	34,502	32,348	43.0	42.9	1,428	1,262
Asian/Pacific	29,906	28,628	45.3	45.9	492	517
Other	3,451	3,354	42.8	45.3	144	100
Unknown	137,995	128,460	52.4	52.5	2,308	2,073
Not recorded †	320,801	298,808	61.7	62.0	7,355	6,449
Region						
Europe: Britain & Ireland						
UK	178,307	165,677	54.3	54.5	3,286	2,899
Ireland	7,078	6,516	44.8	45.2	53	61
Europe: Nordic countries						
Denmark	52,642	49,238	58.2	58.5	3,006	2,672
Finland	39,553	36,641	60.2	60.2	2,835	2,475
Norway	10,402	9,908	47.1	47.9	98	89
Sweden	24,831	23,229	59.0	59.8	889	864
Europe: Other countries						
Austria	6,050	5,558	58.3	56.8	117	106
Estonia	5,794	5,249	44.3	45.6	376	346
France	3,102	2,915	74.0	74.6	108	84
Germany	123,000	113,846	56.7	56.9	1,209	1,074
Italy	20,140	19,564	52.8	52.7	293	262
Lithuania	5,560	5,252	43.5	44.7	97	95
Netherlands	13,330	12,090	71.0	71.1	119	116
Slovakia	14,836	13,303	64.9	65.3	41	32
Slovenia	4,518	4,345	41.8	42.9	77	58
Spain	3,061	2,794	80.0	80.6	25	32
Switzerland	3,618	3,358	49.2	50.4	59	46
North America						
Canada	54,526	51,585	80.1	80.4	1,213	1,098
USA	397,624	380,424	43.8	44.2	14,594	13,335
Other regions						
Australia	24,340	22,653	57.1	57.9	460	385
Israel	2,476	2,351	31.6	30.6	60	48
Japan	1,497	1,467	37.7	37.5	44	28
Total	**996,285**	**937,963**	**52.6**	**52.8**	**29,059**	**26,205**

* Ductal carcinoma in situ
† Data not provided by registry, including the period before common use of therapy.
‡ Breast-conserving surgery

Table 4-1: Patient characteristics of cardiac mortality study by laterality of the breast cancer (left- or right-sided).

4.3.2 Cardiac mortality by radiotherapy use

Mortality ratios were initially estimated using a comparison of radiotherapy versus no radiotherapy, as a check following the findings of Chapter 3 (Figure 4-1). For all women combined, the heart disease death rate was similar in irradiated and unirradiated women (mortality ratio, radiotherapy versus not: 0.99 95% CI 0.97-1.01). This ratio differed substantially between women who were given breast-conserving surgery (BCS) and women who were given mastectomy (2p for difference < 0.0001). Specifically, the overall value included a substantial deficit in cardiac mortality among women given BCS and radiotherapy compared with women given BCS without radiotherapy, and a substantial excess among women given post-mastectomy radiotherapy compared with women given mastectomy but not radiotherapy (BCS: 0.70 95% CI 0.67-0.73; mastectomy: 1.24 95% CI 1.19-1.30, 2p for difference: 0.0003). The difference was present both overall and for the Nordic countries, Britain and Ireland, other European countries, Canada, and the United States when these areas were considered separately (see Figure 4-2).

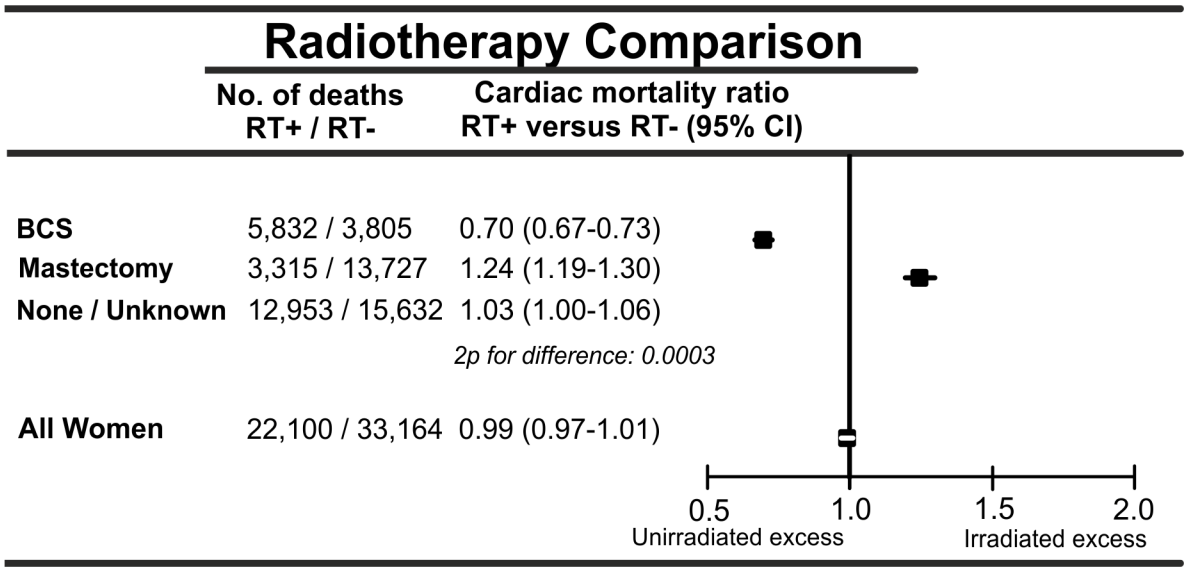


Figure 4-1: Cardiac mortality in women who were recorded as receiving radiotherapy (RT+) versus women who were not recorded as receiving radiotherapy (RT-) subdivided by surgery type.

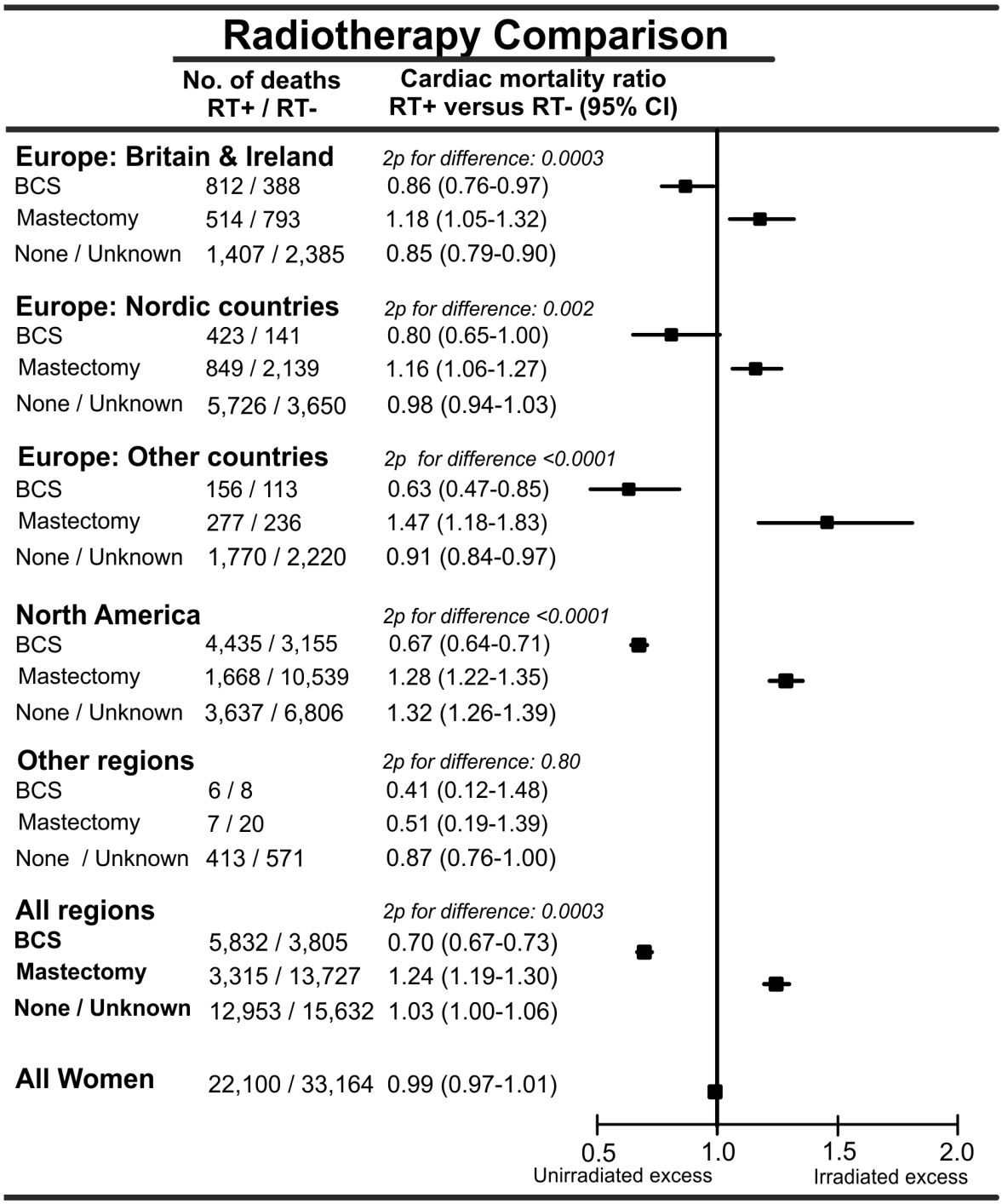


Figure 4-2: Cardiac mortality in women who were recorded as receiving radiotherapy (RT+) versus women who were not recorded as receiving radiotherapy (RT-) subdivided by geographic region and surgery type.

4.3.3 Cardiac mortality by breast cancer laterality

When all women were considered together, heart disease mortality was higher in women with left-sided cancer than in women with right-sided cancer (rate ratio, left versus right: 1.04 95% CI 1.02-1.06, 2<0.0001, Figure 4-3). The rate ratios, left versus right, did not differ significantly between all women given BCS and all women given mastectomy (1.00 95% CI 0.96-1.04 and 1.02 95% CI 0.99-1.05, 2p for difference 0.50). Note that the surgery type was unknown or no surgery was performed for 52% of the women who died from heart disease. Neither was the difference between women given BCS and women given mastectomy significant when women who were recorded as receiving radiotherapy and those who were not were considered separately (2p for difference: 0.14 and 0.79 respectively, see Figure 4-3). This held true for all of the geographical regions (see Appendix Figure D-1).

For women not recorded as receiving radiotherapy, there was no excess mortality from heart disease following treatment for left-sided breast cancer. However, the cardiac mortality ratio (left-sided versus right-sided breast cancer) for women recorded as receiving radiotherapy was 1.07 (95% CI 1.04-1.14). This means that there was a significant 7% increase in the mortality rate from all types of heart disease combined following left-sided breast cancer as compared to right-sided breast cancer. There was a significant difference between the mortality ratio among irradiated and unirradiated women (2p=0.003), suggesting a radiation-related effect.

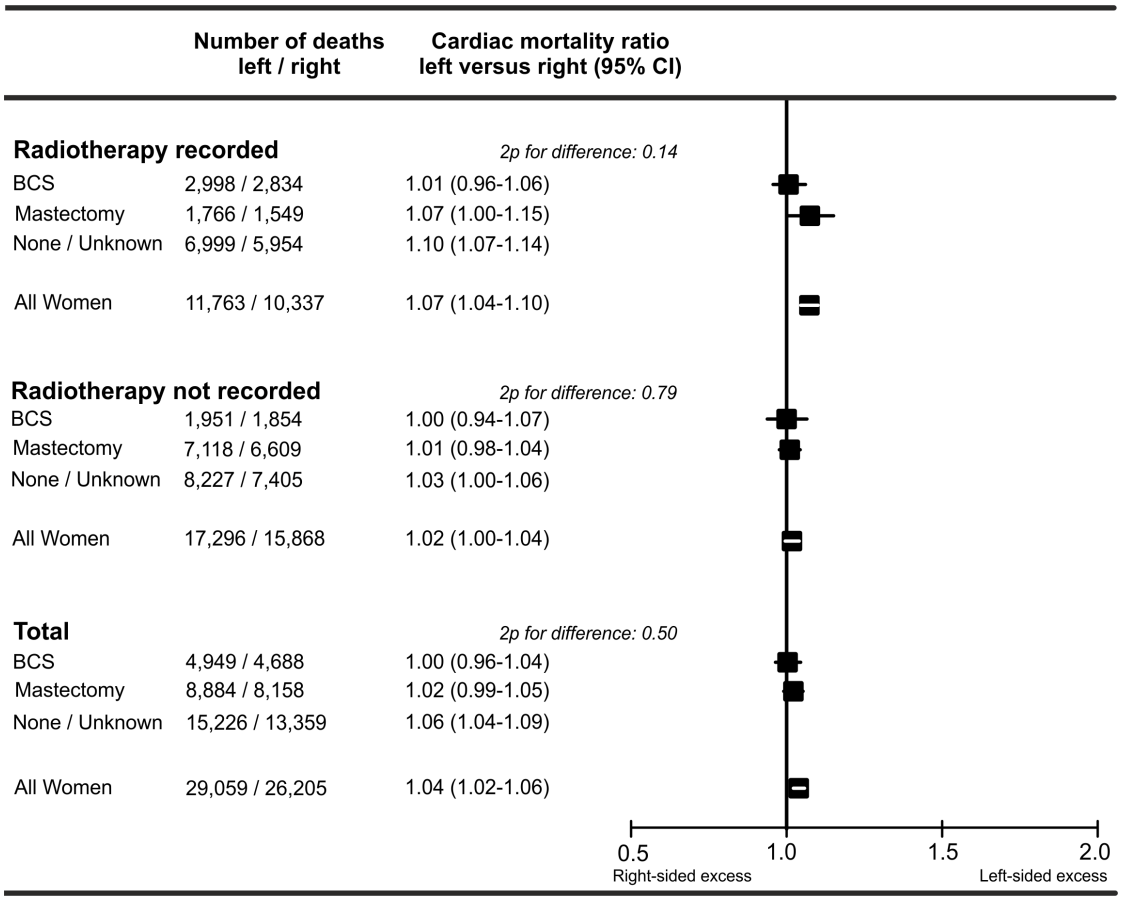


Figure 4-3: Cardiac mortality in women with left-sided breast cancer versus women with right-sided breast cancer subdivided by type of surgery and whether or not the woman was recorded as receiving radiotherapy.

4.3.4 Mortality from different types of heart disease

Among irradiated women, there were significant left-sided excesses when ischaemic and other heart disease deaths were analysed separately. The mortality ratios, left versus right, for ischaemic heart disease deaths and other heart disease deaths were 1.09 (95% CI 1.05-1.13) and 1.06 (95% CI 1.02-1.10), respectively (Figure 4-4). When specific types of heart disease other than ischaemic heart disease were considered, there was a significant left-sided excess of deaths due to non-rheumatic valvular disease (1.19 95% CI 1.00-1.40) and a left-sided excess also existed for arrhythmia (1.08 95% CI 0.94-1.24), heart failure (1.06 95% CI 0.97-1.16) and pericardial disease (1.19, 95% 0.65-2.16).

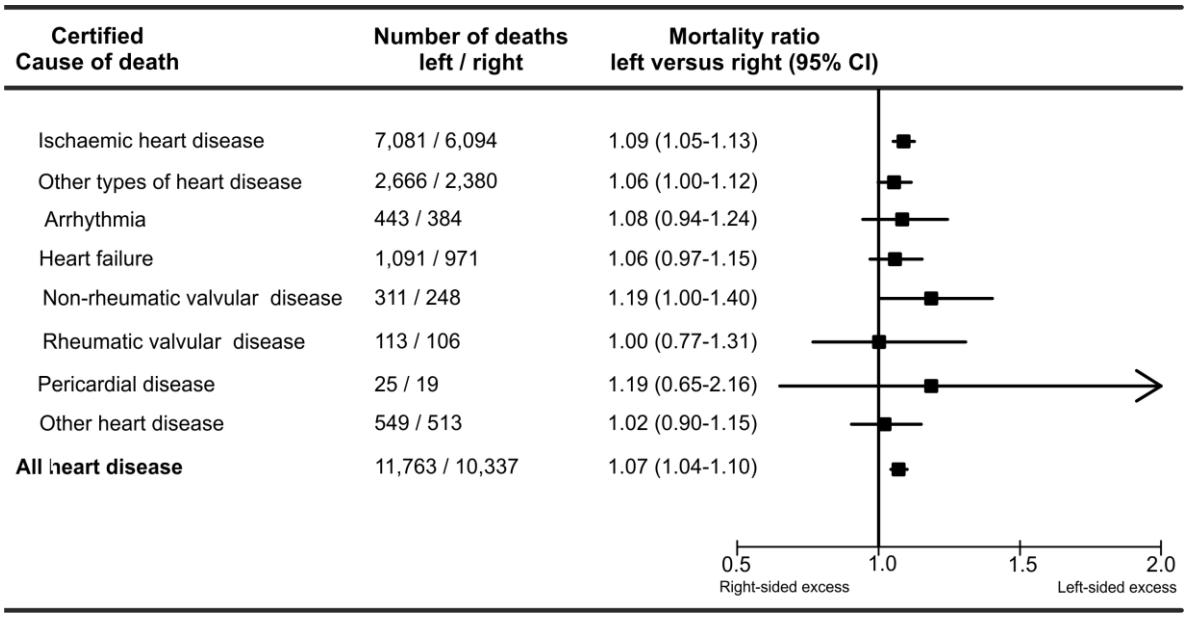


Figure 4-4: Cardiac mortality in irradiated women with left-sided breast cancer versus women with right-sided breast cancer subdivided by type of heart disease.

4.3.5 Variation between different geographical regions

When the registries were grouped into 6 geographical regions, the cardiac mortality ratios, left versus right, for irradiated women were similar across all regions (Britain & Ireland: 1.11, Nordic countries: 1.06, Other European countries: 1.08, North America: 1.06, Other regions: 1.06, 2p for heterogeneity: 0.86, Figure 4-5). When the registries were grouped into individual countries, more variability existed between the rate ratios, as expected, but there was no significant heterogeneity between countries within any of the regions, or between all countries considered together (2p for heterogeneity between 22 countries: 0.72). When deaths attributed to ischaemic heart disease and to other types of heart disease were considered separately patterns were similar (see Appendix Figure D-2).

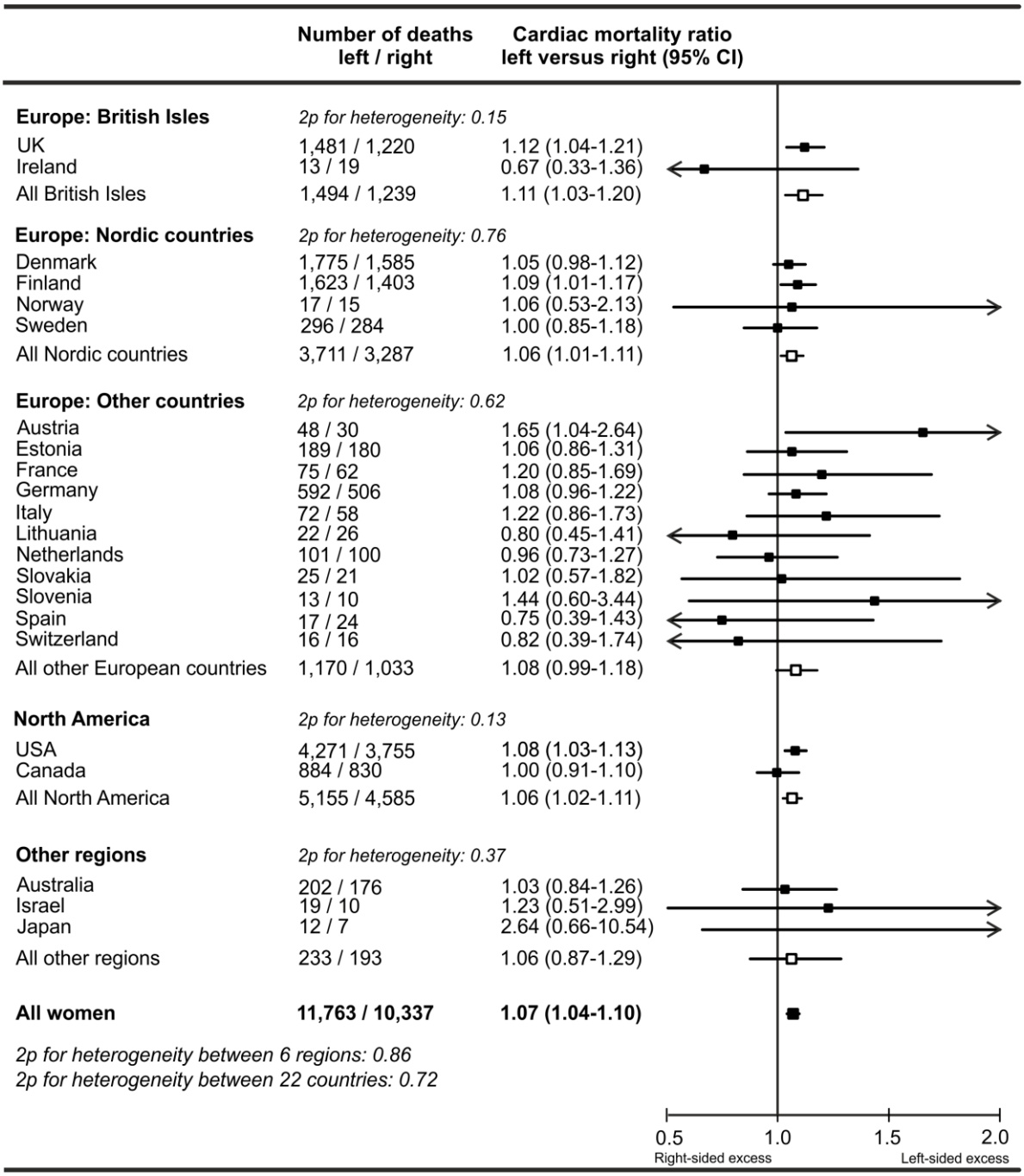


Figure 4-5: Cardiac mortality in irradiated women with left-sided breast cancer versus irradiated women with right-sided breast cancer subdivided by country.

4.3.6 Variation across age at cancer diagnosis by laterality in women given radiotherapy

There was a highly significant decreasing trend (2p<0.0001) with increasing age at cancer diagnosis in the cardiac mortality ratios. The cardiac mortality ratio, left-sided versus right-sided, was 1.37 (95% CI 1.10-1.70), 1.16 (95% CI 1.06-1.27), 1.20 (95% CI 1.13-1.28),

1.05 (95% CI 1.00-1.10) and 1.01 (95% CI 0.97-1.06), respectively, for ages <40, 40-49, 50-59, 60-69 and 70-79 years at breast cancer diagnosis (Figure 4-6). This was strong evidence that the proportional left-sided cardiac mortality excess was higher in women who were younger when they were diagnosed with breast cancer.

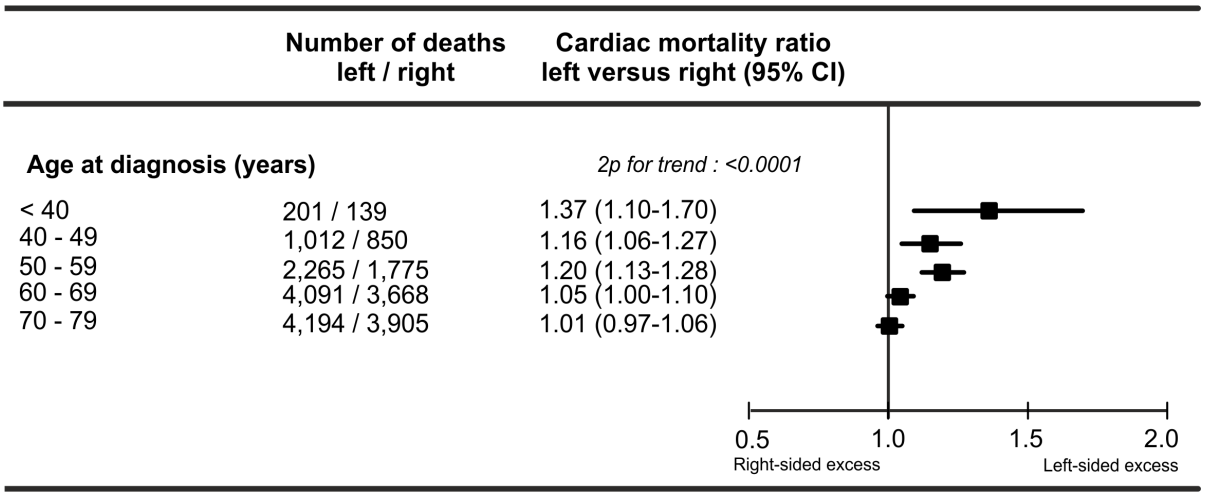


Figure 4-6: Cardiac mortality in irradiated women with left-sided breast cancer versus irradiated women with right-sided breast cancer subdivided by age at breast cancer diagnosis.

The proportional mortality risk for ischaemic heart disease and other types of heart disease was also greater for younger women (Figure 4-7). In addition, a significant trend of decreasing mortality ratio with increasing age at cancer diagnosis was shown for ischaemic heart disease (2p trend: 0.002) but not, all other heart disease (2p trend: 0.42).

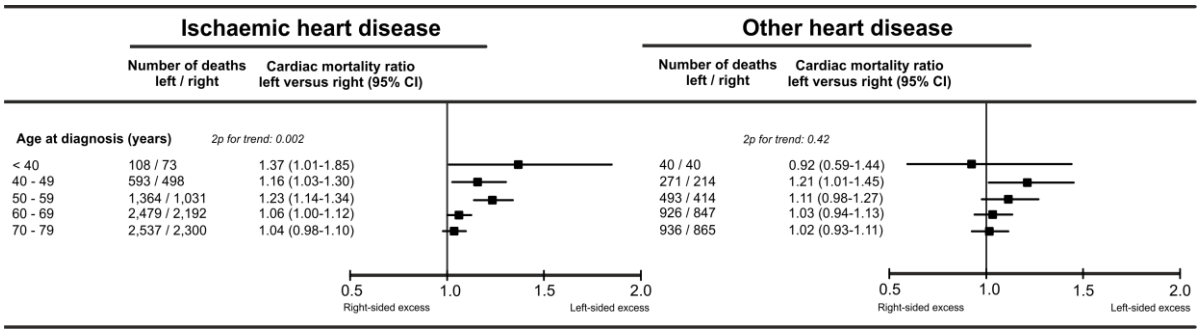


Figure 4-7: Mortality from ischaemic heart disease and other types of heart disease in irradiated women with left-sided breast cancer versus irradiated women with right-sided breast cancer subdivided by age at breast cancer diagnosis.

The variation in the absolute risk of radiation-related cardiac mortality by age at cancer diagnosis was also investigated using cumulative mortality up to age 80 (Figure 4-8). The reference population used to represent the irradiated right-sided breast cancer was the most recent values available at analysis (2010) in the mortality tables for the 15 westernmost countries of the European Union. The death counts were obtained from WHO[8] and the population counts from the UN[9]. Using these counts, the cumulative mortality was calculated as described by Darby and colleagues and assumed to represent the women diagnosed with right-sided breast cancer (referred to as the reference population from now on) (Darby, Ewertz et al. 2013). The rate ratios for each age group of cancer diagnosis were applied to the cumulative mortality of the reference population, taking into account the variation with time since diagnosis. At all ages of cancer diagnosis, the cumulative mortality was low for the first ten years, then increased gradually up until approximately age 70, after which it increased sharply. The greatest absolute difference between left-sided and right-sided patients in cumulative mortality at all ages occurred in women diagnosed aged 35. Considering the irradiated left-sided breast cancer patients diagnosed aged 35, 5.4% of population had died of heart disease by age 80, compared to 4.4% of right-sided patients. The absolute difference in cumulative risk by laterality was smaller for women

[8] http://www.who.int/healthinfo/morttables/en/
[9] http://esa.un.org/unpd/wpp/Excel-Data/population.htm

diagnosed at older ages, but the cumulative mortality reached 5% for women diagnosed with left-sided breast cancer aged 45 and 55 years. See Appendix D for values used for this graph.

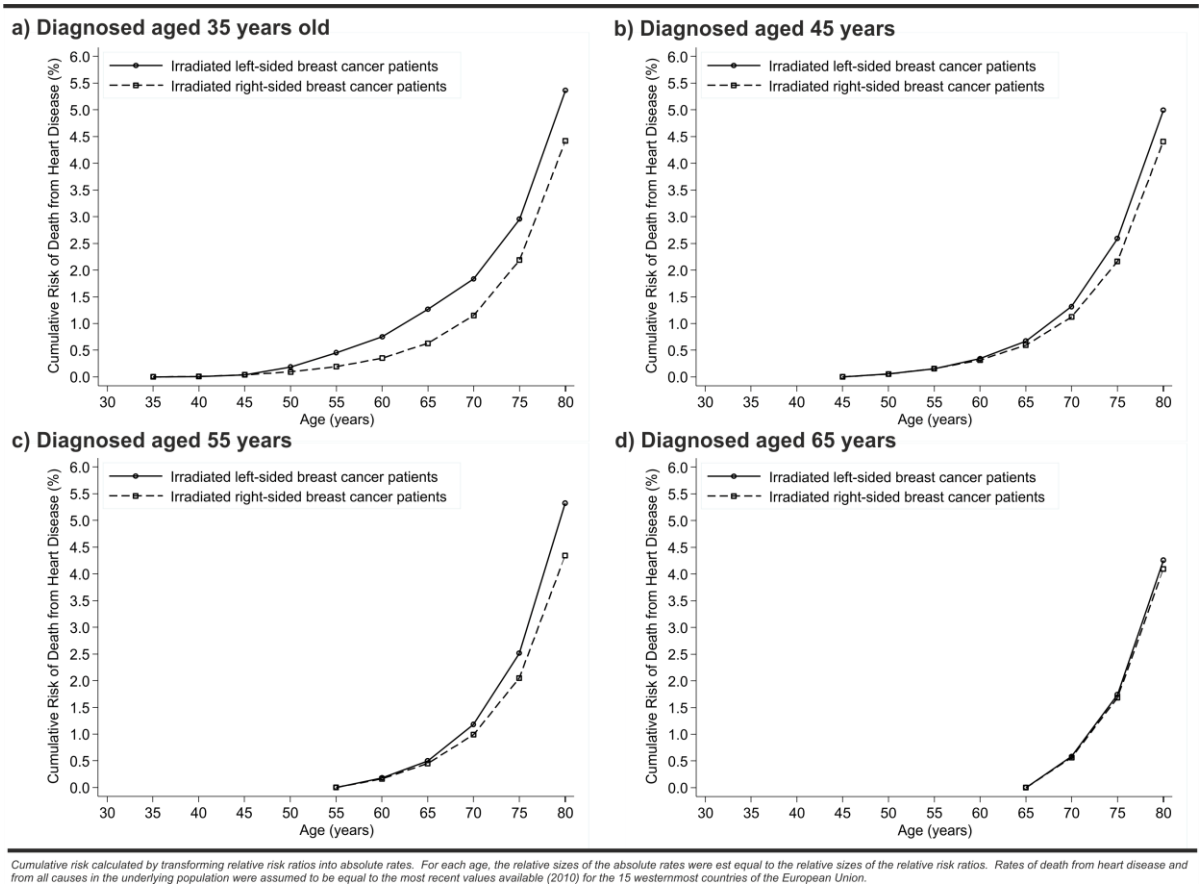


Figure 4-8: Cumulative mortality of all heart disease combined in irradiated women subdivided by age of cancer diagnosis.

4.3.7 Variation with calendar period of diagnosis and years since radiotherapy by laterality in women given radiotherapy

A decreasing trend in the cardiac mortality ratio, left-sided versus right-sided, by calendar year of cancer diagnosis ($2p<0.0001$) was found among irradiated women (Figure 4-9). Also, there were significant trends with increasing time since breast cancer diagnosis in the mortality ratios, left versus right, for all heart disease. The left-sided excess for all types of heart disease combined was still present at 25+ years (1.21 95% CI 1.10-1.33).

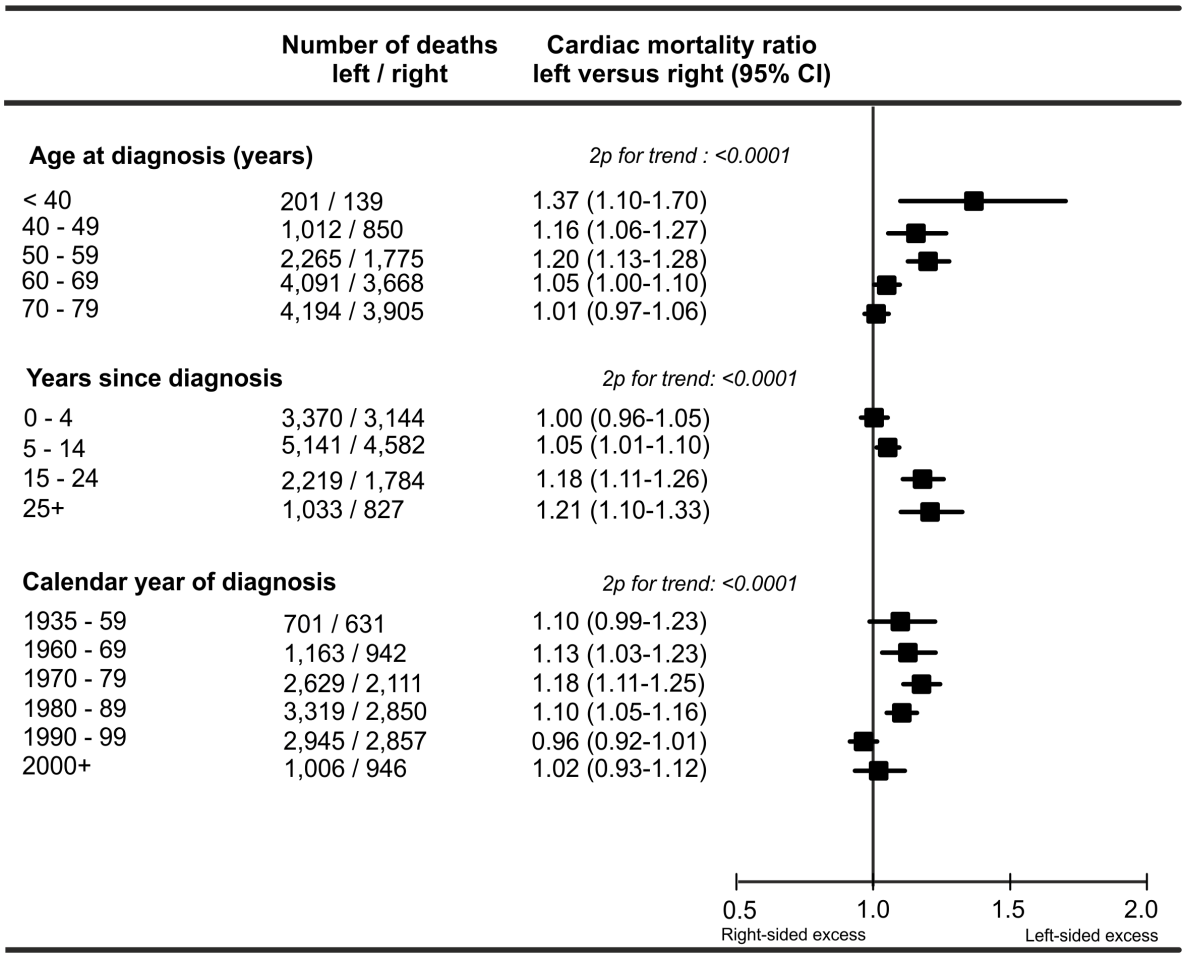


Figure 4-9: Cardiac mortality in irradiated women with left-sided cancer versus irradiated women with right-sided breast cancer subdivided by years since breast cancer diagnosis, age at breast cancer diagnosis and calendar year of breast cancer diagnosis.

4.3.8 Interaction with chemotherapy and hormonal therapy

Information on whether chemotherapy and hormonal therapy were used, and on stage of breast cancer, type of surgery, and race was available for some registries. However, for some registries it was available only for recent years, and for others it was not available at all. Rate ratios for irradiated women with left-sided versus right-sided breast cancer were calculated separately according to different levels of these factors using the information available. There was no significant difference in the cardiac mortality ratio, left versus right, according to whether or not chemotherapy or hormonal therapy was used and no significant heterogeneity according to stage of breast cancer, type of surgery or race (Figure 4-10).

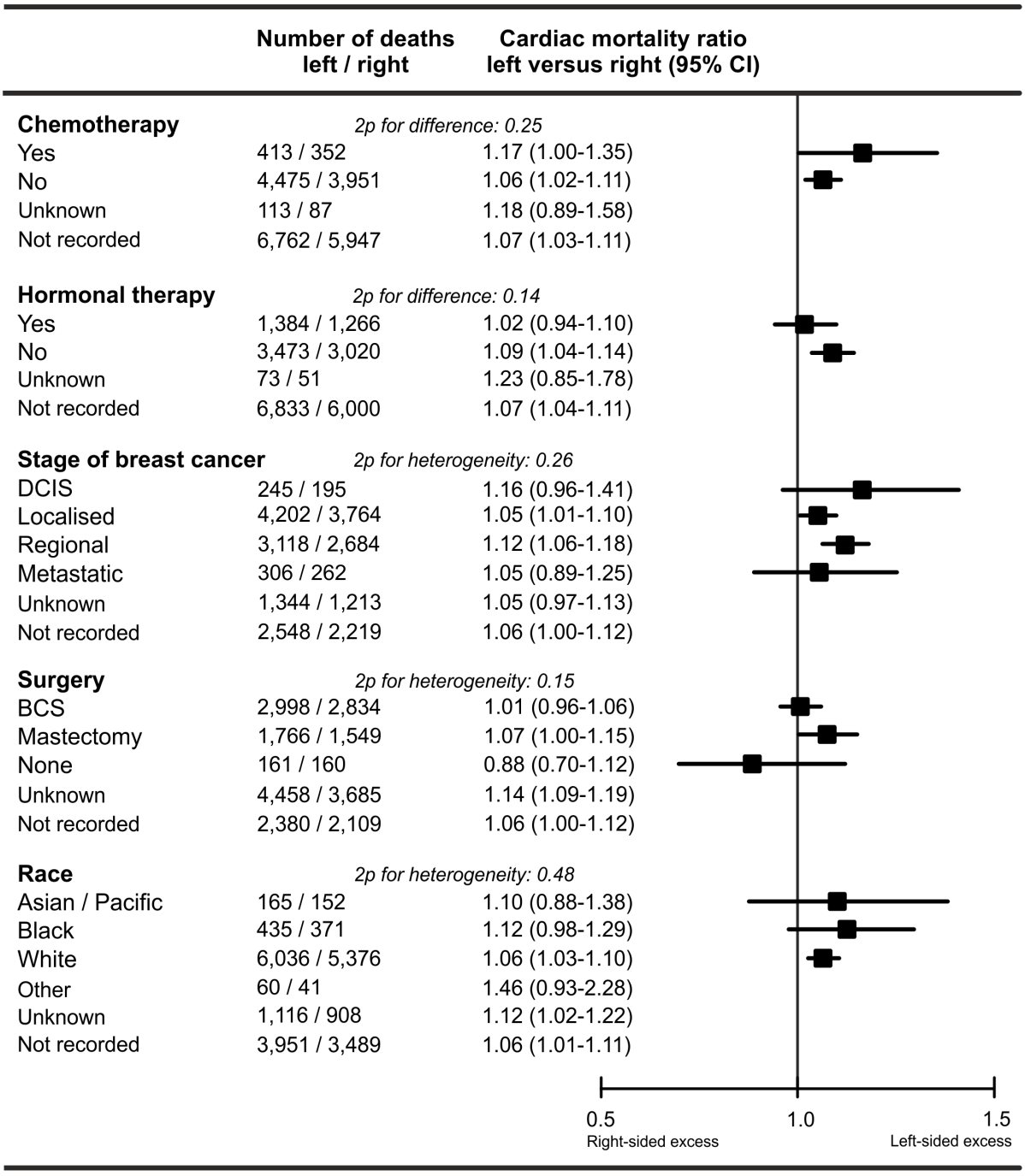


Figure 4-10: Cardiac mortality in irradiated women with left-sided breast cancer versus irradiated women with right-sided breast subdivided by various treatment and tumour factors.

4.3.9 Investigation of possible confounding and subdivision by age groups

Survivors of breast cancer who were younger when they are diagnosed with cancer are likely to live longer than women who were older. Therefore, there may be some confounding between age at cancer diagnosis and years since cancer diagnosis in Figure 4-6. However, when

age at cancer diagnosis was adjusted for the effect of time since cancer diagnosis (as well as calendar year and country see Figure 4-11), strong evidence of a trend remained (2p for trend: 0.005). In contrast, when time since cancer diagnosis was corrected for the effect of age at cancer diagnosis (and calendar year and country), the trend with time since cancer diagnosis was no longer significant (2p for trend: 0.15).

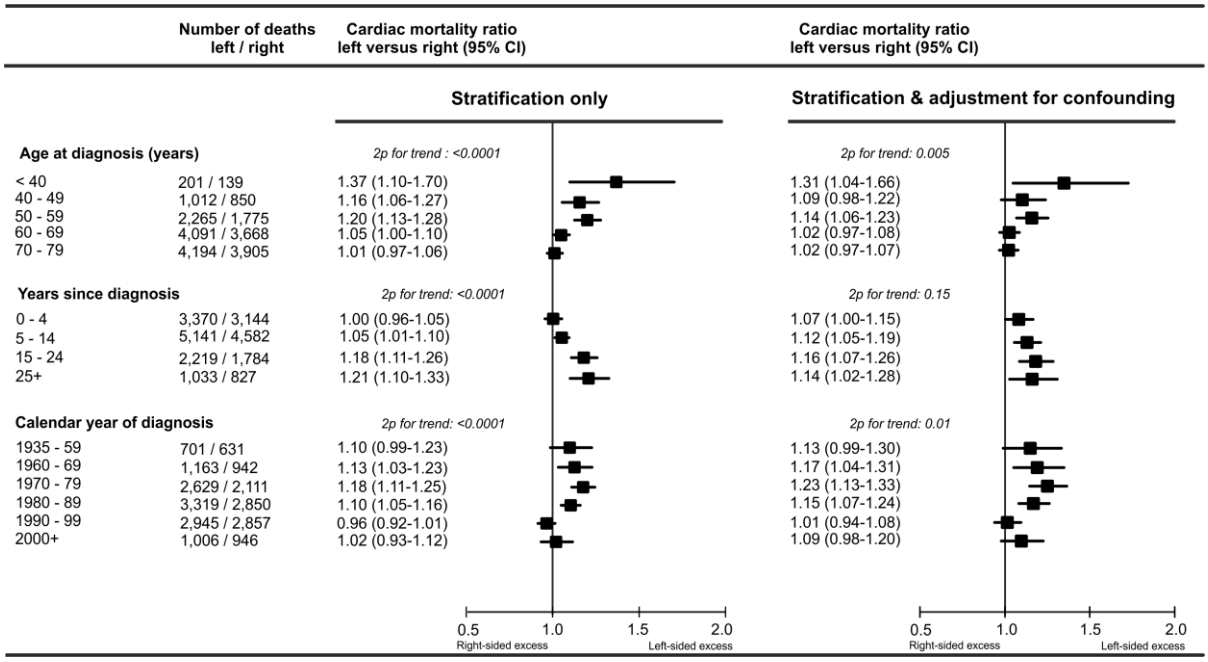


Figure 4-11: Cardiac mortality in irradiated women with left-sided cancer versus irradiated women with right-sided breast cancer subdivided by years since breast cancer diagnosis, age at breast cancer diagnosis and calendar year of breast cancer diagnosis calculated using both the univariable model, and the model with additional adjustment for confounding.

In order to fully understand the results by age at cancer diagnosis, separate analyses were run subdivided by age at cancer diagnosis: by women who were aged <60 and 60+ years at cancer diagnosis (Figure 4-12). Among irradiated women who were aged <60 when diagnosed with cancer, the mortality ratio, left versus right, for all time-periods considered together was 1.19 (95% CI 1.13-1.25, 2p<0.0001) and a significant increasing trend with time since cancer diagnosis existed (2p:0.001), with mortality ratios taking values 1.00, 1.16 and 1.27 in periods 0-4, 5-14, and 15+. In addition there was little evidence that the mortality ratios, left versus right,

were lower in more recent years among women diagnosed with cancer at ages <60 (1.19, 1.22, and 1.14 for women diagnosed <1970, 1970-89, and 1990+, 2p trend: 0.65).

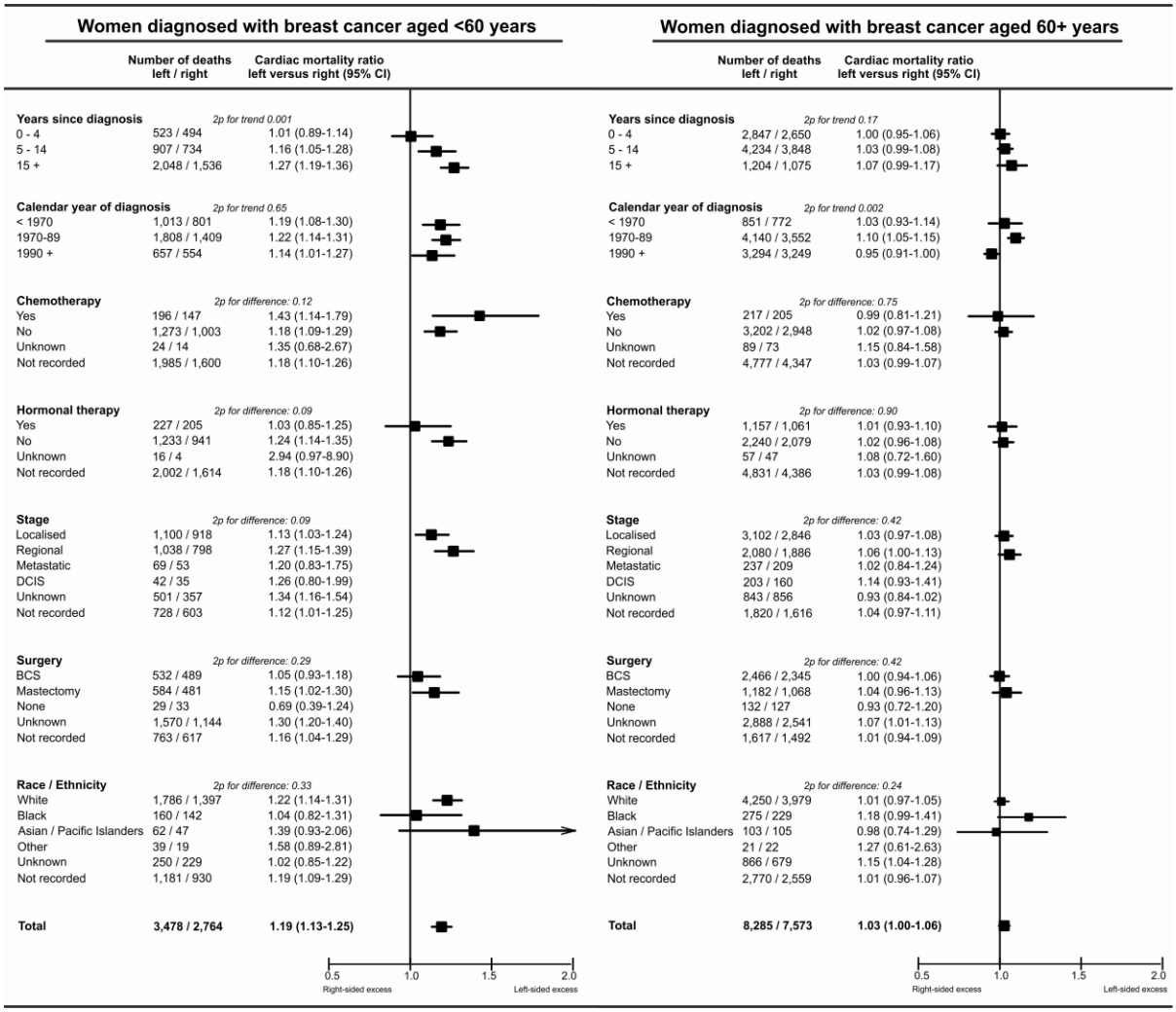


Figure 4-12: Cardiac mortality in irradiated women with left-sided breast cancer versus irradiated women with right-sided breast cancer subdivided by age at cancer diagnosis (<60, 60+ years) and various factors.

The cardiac mortality ratio, left-sided versus right-sided, was higher for women who had chemotherapy as well as radiotherapy (1.43 95% CI 1.14-1.79), compared to those with radiotherapy but no chemotherapy (1.18 95% CI1.09 1.28) among women aged <60 years although the difference did not reach statistical significance (2p=0.12). There were no significant differences according to use of hormonal therapy (2p for difference: 0.10), stage of cancer (2p for difference: 0.09), or type of surgery (2p: for difference: 0.29). These findings were confirmed by a model including adjustment for confounding, see Appendix Table D-1.

For women diagnosed with breast cancer when aged 60+ years and recorded to have received radiotherapy, the overall mortality ratio, left versus right, was 1.03 (95% CI 1.00-1.06, 2p: 0.05) and it was lower for women who had been diagnosed with cancer more recently (2p trend: 0.002). There was little evidence of any left-sided increase for women diagnosed with cancer in the most recent calendar period (0.95 95% CI 0.91-1.00) and there were no significant differences, trends or heterogeneity with any other factors.

4.4 Discussion

4.4.1 Overall findings

Randomised trials have clearly shown that radiotherapy for early breast cancer resulted in an increased risk of heart disease. However, this has yet to be investigated in an observational cohort on the same scale as the COBS cohort presented in this thesis. Thus, this study presents results from the largest cohort of breast cancer survivors to date, in terms of survivors, person-years and cardiac deaths. The most striking finding, which has not yet been demonstrated so clearly, is that of the trend with age at cancer diagnosis, with larger increases for women aged <60 years at cancer diagnosis. This will be thoroughly discussed in Section 4.4.2. Among irradiated women the mortality ratio, left-sided versus right-sided, for all heart diseases combined was estimated to be 1.07 (95% CI 1.04-1.10, 2p<0.0001). There was significant heterogeneity between the irradiated and unirradiated group, suggesting that the excess of cardiac mortality in these breast cancer survivors is a radiation-related effect. This supports previous observational studies that have demonstrated a radiation-related risk of mortality from heart disease in women treated for left-sided breast cancer (Nixon, Manola et al. 1998, Darby, McGale et al. 2005, Harris, Correa et al. 2006, Marhin, Wai et al. 2007, Gutt, Correa et al. 2008, Bouchardy, Rapiti et al. 2009, Bouillon, Haddy et al. 2011, Henson, McGale et al. 2013). These studies found left-sided excesses in the range 3% to 67%, and the variation in estimates can be largely attributed to differences in study population, for example country of treatment, calendar

period, number of women included in the study and average follow-up. One Swiss study of node-negative breast cancer patients with a modest follow-up (average of 7.7 years) demonstrated a non-significant right-sided excess, but the population-size was modest resulting in wide confidence intervals (Bouchardy, Rapiti et al. 2009). The authors suggested that shielding of the heart during treatment for left-sided breast, and the resulting reduced mean heart dose, may have contributed to the weakened association between laterality and cardiovascular mortality. However, it is also likely due to the low numbers of events combined with limited follow-up, and little emphasis should be placed on it. Therefore, the left-sided excess for all heart disease combined found in this study is consistent with the published literature.

No significant heterogeneity was present across either countries or continents of cancer diagnosis. This suggests that the radiation-related risk of heart disease among breast cancer survivors is relevant for all countries worldwide, and not only limited to a few countries. Consideration of this risk during treatment planning and patient follow-up is necessary everywhere.

The excess of cardiac mortality was largely due to deaths from ischaemic heart disease (IHD), which accounted for 60% of the total cardiac deaths among irradiated women. IHD was the main cardiac subgroup with a significant left-sided excess of 9%. A significant left-sided excess among irradiated women was also demonstrated for death from non-rheumatic valvular disease, with an estimate of 1.19 (95% CI 1.00-1.40). No study, as yet, has shown an excess of radiation-related non-rheumatic valvular disease mortality. All other cardiac groups – congestive heart failure, valvular disease, arrhythmia, pericardial disease and other cardiac diseases – had a left-sided excess of deaths, yet none of them reached statistical significance. The nature of this large cohort allowed estimation of stable proportional estimates, allowing subdivision into specific causes of cardiac mortality. A number of studies have demonstrated significantly increased radiation-related mortality from specific cardiac diagnoses, namely fatal myocardial

infarction and ischaemic heart disease, using a comparison of left-sided and right-sided breast cancer patients (Rutqvist and Johansson 1990, Paszat, Mackillop et al. 1998, Paszat, Mackillop et al. 1999, Darby, McGale et al. 2003, Darby, McGale et al. 2005, Giordano, Kuo et al. 2005, Borger, Hooning et al. 2007, Paszat, Vallis et al. 2007). The range of mortality ratios were 1.06 to 1.99 and 1.07 to 2.10 for IHD and fatal MI, respectively. The largest cohort to investigate mortality was based on 27,283 women recorded by the SEER program in the USA during 1973-1989, with a mortality ratio of 1.16 (95% CI 1.07-1.26) (Giordano, Kuo et al. 2005). This is very similar to the results presented in this study, yet there was only 9.5 years of follow-up.

4.4.2 Heart disease mortality by age of cancer diagnosis

No study has yet demonstrated so clearly the association between cardiac mortality ratio and age at cancer diagnosis. This association with age at cancer diagnosis was present when all heart disease was combined, and also for ischaemic heart disease. Alongside the highly significant trend with age, it was also demonstrated that for all factors under consideration (years since diagnosis, calendar year, chemotherapy, hormonal therapy, stage, surgery and race) a left-sided excess was present at all levels for women diagnosed before age 60. In contrast, among women diagnosed with cancer after age 60, there was no overall left-sided excess nor variation with the factors listed above. This suggested that the association suggested between radiotherapy and subsequent heart disease is mainly among younger women. This finding did not appear to be confounded by length of follow-up, as demonstrated in the Appendix.

The only study to investigate the trend in mortality ratios with age in 10-year groups was an analysis of the SEER registry, which found a non-significant trend in heart disease mortality ratios ($p=0.40$) (Darby, McGale et al. 2005). The proportional risk was greatest in women treated for breast cancer aged 20-49 years, with a significant 54% left-sided excess, and a 28% non-significant left-sided excess in women irradiated age 70-79 years. The association between age at cancer diagnosis and radiation-related heart disease has been presented in a number of

other studies, two of which found no significant trend with age (Vallis, Pintilie et al. 2002, Bouillon, Haddy et al. 2011). Three other studies used the subdivision of <60 years with 60+ years (Paszat, Mackillop et al. 1999, Marhin, Wai et al. 2007, Paszat, Vallis et al. 2007). All three studies found an increased risk of cardiac mortality in women treated at ages 60+, which was not seen in women treated before the age of 60. The two studies by Paszat et al found a significantly increased risk in the older women, yet the cardiac endpoint studies was fatal acute MI. This was in contrast to the results of this COBS study. As an additional check, an analysis of MI deaths produced mortality ratios, left-sided versus right-sided, of 1.25 (95% CI 1.14-1.37, 2p<0.0001) and 1.11 (95% CI 1.04-1.18, 2p=0.0007) for ages <60 years and 60+ years, respectively (data not shown). The reason for these conflicting results with respect to the <60 and 60+ mortality ratios is not clear. It may be due to the increasing use of cardiotoxic anthracyclines in younger women in recent years, which may be interacting with radiotherapy (see next section). More broadly, it may also be due to, for example, the treatment regimens received by the patients, or the general health and lifestyles of the women included (namely the prevalence of traditional cardiovascular risk factors). However, as none of this information was available for this study, or the three published studies, it was impossible to check whether any of these factors varied by laterality and would therefore influence the results. These factors would only be problematic in these analyses if the distribution varied in left-sided and right-sided women, therefore confounding the laterality comparison.

4.4.3 Risk of heart disease mortality in relation to chemotherapy

No study has yet investigated the association between radiotherapy and chemotherapy in an observational cohort of breast cancer survivors using a laterality comparison. In the COBS cohort, there was information on chemotherapy receipt for 47% of the cohort. Among women recorded to have recorded radiotherapy and chemotherapy, there was a significant left-sided 17% excess. In comparison, women only recorded to have radiotherapy had a significant 6%

left-sided excess. This difference was not significant, yet among women diagnosed with breast cancer before age 60, the difference was starker, with 43% left-sided excess among women who received both treatments, and 18% for women who received radiotherapy only. Despite these findings not reaching statistical significance, this may be suggestive that there may be an association or interaction between the two types of treatment, particularly in younger women. This was in agreement with the published literature, which stated that the mechanisms of radiation and chemotherapy induced damage are very different (Shapiro and Recht 2001, Bovelli, Plataniotis et al. 2010, Cutter, Taylor et al. 2010) suggesting that the two treatments may be additive in terms of cardiac mortality risk. One study has used a laterality comparison to investigate the association between chemotherapy and radiation-related heart disease, but found no impact of chemotherapy on cardiovascular mortality after adjusting for radiotherapy (Bouillon, Haddy et al. 2011). However, meta-analyses of randomised trials have demonstrated that chemotherapy increases the risk of heart disease, with a rate ratio of polychemotherapy versus not of 1.21 (95% CI 0.93-1.59, p=0.16) for all heart disease (Early Breast Cancer Trialists' Collaborative Group 2005), which would suggest that an association between the two treatment types in terms of cardiac risk would be likely. Further research is needed on the risk associated with the suggested interaction between chemotherapy and radiotherapy. Any particular increase among a certain age group may provide evidence towards increased monitoring and surveillance over a long-term period after their cancer diagnosis in that population.

4.4.4 Absolute burden of cardiac mortality in the study population

The focus so far has been on relative measures of mortality risk, using a comparison of left-sided and right-sided breast cancer patients. However, it is important to put the relative risk in context using absolute measures. This was achieved through cumulative mortality measures, which demonstrated that the cumulative absolute risk of death from heart disease over the entire follow-up period was less than 5.5% for left-sided patients, and less than 4.5% for right-sided

breast cancer patients. This was true for women diagnosed between 35 and 65 years old. These absolute measures were in agreement with the published literature (Darby, Ewertz et al. 2013). Thus, despite significantly increased relative risks, the absolute risks for all women combined remained low. This is reassuring, yet it does not reduce the importance of minimising the risk of radiation-related late effects.

When considering the absolute burden of cardiac mortality, it is important to note that mortality rates for cardiovascular disease have decreased substantially over the last decade. A recent overview of cardiovascular disease (including stroke) in Europe demonstrated this decreasing rate over the past ten years, and its wide variation between countries (Nichols, Townsend et al. 2014). This wide variation resulted in differing magnitudes of change across the countries. For example, in the UK and Germany, the two European countries with the greatest number of breast cancer survivors in the COBS study, the 10-year change in mortality rate of coronary heart disease among males was -48% and -39%, respectively, and among females was -51% and -43%, respectively.

4.4.5 Dose and changes in radiotherapy techniques

Radiation-related heart disease risk varies with both patient and treatment factors. The variation by patient characteristics has been clearly demonstrated by this study, and the overall variation by the three main treatment types (radiotherapy, chemotherapy and hormonal therapy) has also been shown. It is known that over the past few decades the radiotherapy targets and techniques have changed. Therefore, the maximum radiation dose received by the heart in patients treated today, on average, is smaller. This study did demonstrate a raised mortality risk in women treated after the year 2000, and a significant left-sided excess was present among younger women particularly those treated after 1990+. This may be partially attributed to the increasing use of modern techniques, for example intensity modulated radiation therapy (IMRT), in which a larger volume of the heart receives a lower radiation dose, but the total mean dose is

greater than that received by tangential fields (Intensity Modulated Radiation Therapy Collaborative Working Group 2001, Veldeman, Madani et al. 2008, Staffurth 2010). IMRT changes the intensity of radiation in different part of a single beam during treatment, which allows areas within the target to be treated to different dose levels. It is, as yet, unclear the effect of this cardiac dose over an extended period of follow-up.

Individual treatment information would allow the mean heart dose to be estimated, providing there was information on the prescribed dose, the target, and the techniques used. However, this information was not available for the women in this study, as the aim was to study large numbers of women, and as a result only basic patient and treatment information was available. However, the irradiation of the internal mammary chain (IMC) is a large determinant in the mean radiation heart dose received by a patient. The reported use of IMC fields in radiotherapy regimens can be found for some countries using Pattern of Care Studies, which aim to retrospectively document national irradiation practices during a specific period, and allow the investigation of regional differences and deviations from standard protocols. These studies have shown that the use of IMC irradiation varies widely and significantly across Europe, the United States and Canada (Taghian, Jagsi et al. 2004). It was found that, in 2001, European treatment centres were more likely to use IMC irradiation compared with North America ($p<0.01$). It has been shown that the use of IMC radiotherapy has declined in the United States, with 62% of women receiving IMC radiation in the 1980s but only in 1% of women in the 1990s (Solin, Fowble et al. 1990, Shank, Moughan et al. 2000). This decline in the use of IMC radiotherapy was also present in Austria, with 62% of patients receiving internal mammary node irradiation in 1985 and 7.5% in 2001 (Mayer, Handl-Zeller et al. 2007). But, the percentage of women receiving IMC radiation was greater in Austria in 2001 than in the USA in the 1990s, highlighting the variation in treatment between countries. In the Netherlands, a non-significant excess of heart disease was shown after right-sided breast cancer as compared to left-sided breast cancer. The short internal

mammary chain field used in the Netherlands in the 1970s and 1980s was positioned high on the patient's chest, meaning that all of the heart was outside the radiation field. This meant that the heart radiation dose was only 0.7Gy for left-sided and 0.5Gy for right-sided breast cancer, partially explaining this right-sided excess (Taylor 2008). It seems likely that IMC irradiation is going to be given more often in the future (Early Breast Cancer Trialists' Collaborative Group 2014).

4.4.6 Radiotherapy comparison, selection effects and potential misclassification

An illustration of the biases resulting from the selection of patients to treatment was presented in Chapter 3. In brief, the standard protocol in good prognosis patients is to use radiotherapy after breast conserving surgery, but not after mastectomy. Post-mastectomy radiotherapy is only indicated in patients with node involvement (Early Breast Cancer Trialists' Collaborative Group 2014), and therefore with a poorer prognosis. Therefore, in observational data, a comparison of irradiated and unirradiated women is simply a comparison of the type of women selected for treatment, not the effect of the treatment itself. This was shown clearly in Figure 4-1 and Figure 4-2, in which it appeared that radiotherapy was protective against heart disease mortality in women treated with breast conserving surgery, but harmful post-mastectomy. This is clearly not plausible as radiotherapy is known from randomised evidence to increase the risk of heart disease irrespective of the type of surgery. An alternative analysis method is to use a comparison of left-sided and right-sided breast cancer patients, as presented in this chapter. This laterality comparison is valid if similar proportions of women received radiotherapy for both left-sided and right-sided cancer, which was shown to be true in Table 4-1. It is important to note that the laterality comparison relies on the fact that the mean heart dose is different during treatment for left- and right-sided cancer.

In women not recorded to have received radiotherapy, there was a borderline significant left-sided excess of cardiac mortality. This was unexpected, as there should be no non-treatment related difference in the risk of heart disease by breast cancer laterality. However, misclassification of radiotherapy is known to be problematic, and studies have demonstrated that radiotherapy is under-ascertained in the SEER registry, which is the largest registry to supply data to COBS (Jagsi, Abrahamse et al. 2012). In SEER, until 1998, radiotherapy was only recorded if it was administered in the first four months following surgery. This resulted in a proportion of women not having their radiotherapy recorded, particularly if they received chemotherapy. For a number of the registries that supplied data to COBS, there are caveats in their recording procedures for radiotherapy, which may have resulted in the misclassification of irradiated women to unirradiated. Details of these caveats are tabulated in Appendix, see Table B-1. Not all registries supplied details on their recording procedure, meaning that the potential for misclassification of radiotherapy may be applicable to registries other than those listed. The main recording procedure which could have increased radiotherapy misclassification was the use of a time-period within which radiotherapy receipt would be recorded. Thus, some of the women in the unirradiated category may have actually received radiotherapy, and may account for the slightly raised mortality ratio in unirradiated women.

4.4.7 Strengths and limitations of study

The main strength of this study is the large study size, which is the largest observational study on radiation-related heart disease in breast cancer patients as yet. This has provided the power to demonstrate clear progressive trends in patient characteristics that have previously not been shown so clearly. In addition, all of the recorded factors that could influence the association between radiotherapy and cardiac mortality were investigated thoroughly.

The study is limited by lack of detailed information, particularly specific treatment information. There is potentially a large variation in the treatment received by patients in

different countries, but as detailed dosimetry information wasn't supplied this could not have been investigated. However, the aim of the collaboration was to collect information on a large number of women: a 'broad brush' approach in which only a limited amount of information was available for each woman. A purpose of cohort analyses is to identify associations which can be more fully investigated within nested case-control studies. Thus, these limitations were expected when the study was designed, and do not negate the relevance of this type of approach.

4.4.8 Conclusion

This study of 1.9 million women diagnosed with breast cancer in 22 countries worldwide found a significant excess of cardiac mortality in women irradiated for left-sided breast cancer, which was mainly due to ischaemic heart disease. The proportional increase was highest for younger women, and clear trends by calendar year and time since diagnosis were shown for women aged <60 at cancer diagnosis. It also appears that the risks from modern radiotherapy were lower than in earlier years. The late adverse effects of radiation-treatment used today are unknown, however results from past regimens and knowledge of current radiation dose received provides evidence of future potential risks. In combination with other results, it can be used by clinicians to improve care and quality of life for cancer survivors, as by knowing who is most at risk for adverse effects you can adjust their treatment accordingly in order to reduce adverse effects. Therefore, it is clear that breast cancer radiotherapy can cause appreciable increases in heart disease in younger women with left-sided cancer, especially if chemotherapy is also given. Measures to reduce the risk, such as breathing adapted radiotherapy (Nissen and Appelt 2013) or the use of less cardiotoxic chemotherapies may be appropriate for some women.

CHAPTER 5:
INCIDENT CARDIAC RISK FOLLOWING BREAST CANCER RADIOTHERAPY

5.1 Introduction

As shown in the previous chapter, radiotherapy significantly increases the risk of death from heart disease in women treated for left-sided breast cancer as compared to right-sided breast cancer: by 7% (RR = 1.07 95% CI 1.04-1.10) in a large collaborative population-based cohort. This left-sided excess continued into the third decade, and was proportionally higher for younger women. However, investigation of mortality does not provide a complete illustration of the potential risk. Advances in medical treatments have resulted in improved survival from cardiac diagnoses, meaning mortality measures should be supplemented with incidence analyses to capture the potentially less serious cardiac diagnoses that may not have resulted in death. Thus, a complete exploration of the potential risk can be achieved by a complementary incidence analysis, in which all events, both fatal and non-fatal, are investigated. It also allows investigation of multiple events experienced by a patient which permits a more complete understanding of their survivorship experience.

Cardiac incidence following treatment for breast cancer has been investigated in a number of studies using a laterality comparison (Rutqvist, Liedberg et al. 1998, Vallis, Pintilie et al. 2002, Patt, Goodwin et al. 2005, Harris, Correa et al. 2006, Borger, Hooning et al. 2007, Correa, Litt et al. 2007, Doyle, Neugut et al. 2007, Hooning, Botma et al. 2007, Jagsi, Griffith et al. 2007, Paszat, Vallis et al. 2007, Pinder, Duan et al. 2007, McGale, Darby et al. 2011, Darby, Ewertz et al. 2013). Of the published studies, the overall incidence ratio estimates varied greatly. This is partially due to a variation in the definitions of the cardiac endpoints used, but also cohort size, diagnosis periods, average follow-up and other relevant patient and treatment characteristics. Four of these studies had information on more than 10,000 women, with the largest study investigating all heart disease combined as well as specific cardiac diagnoses among 70,000 women treated in Denmark and Sweden (McGale, Darby et al. 2011). Thus, no published work

has yet investigated cardiac incidence using a population on the same scale as the COBS collaborative cohort presented in this thesis.

5.2 Aim

This study aimed to provide a comprehensive investigation of radiation-related incident heart disease in the largest population-based observational cohort to date among women treated for breast cancer. Specific aims included the presentation of a detailed subdivision of cardiac, and the variation in radiation-related risk by both patient and treatment.

5.3 Results

Not all registries supplied non-fatal information to the collaboration, and a registry was included in the analysis if it contributed at least 20 cardiac events in women recorded to have received radiotherapy. As such, 18 registries from 8 countries worldwide were eligible, and four of these registries only provided information on unirradiated women. Thus, a total of 670,850 women diagnosed with breast cancer during 1953 to 2007 were eligible for this analysis, contributing 6,386,597 person-years.

Within the study period, 88,960 cardiac events (fatal or non-fatal) were recorded among both irradiated and unirradiated women. Just under half of the women were recorded to have received radiotherapy, with 47.0% and 47.4% of left-sided and right-sided women irradiated, respectively. The proportion of women irradiated remained similar across left-sided and right-sided women for all of the age groups, calendar periods and countries of interest (Table 5-1). Three quarters of the population were diagnosed with breast cancer after age 60. This is driven by the fact that the majority (65%) of cardiac events were diagnosed in women aged 65+ years who were recorded by the Medicare database in the US.

	Number of women		Percentage recorded as irradiated		Number of cardiac events
	Left-sided	Right-sided	Left-sided	Right-sided	
Time since diagnosis (years)					
0 – 4	109,704	103,036	50.8	51.3	16,707
5 – 14	164,921	156,534	50.1	50.3	44,055
15 – 24	55,971	53,005	35.7	35.6	21,353
25+	14,176	13,503	27.6	28.7	6,845
Age at diagnosis					
<50	56,115	53,904	54.2	54.2	7,131
50 - 59	81,830	77,271	50.4	50.7	15,459
60 - 69	113,983	107,715	47.3	47.7	31,889
70 - 79	92,844	87,188	39.4	39.8	34,481
Calendar year of diagnosis					
1953 - 1969	2,595	2,379	77.2	76.3	1,920
1970 - 1989	90,944	85,321	36.1	35.9	37,392
1990 - 1999	120,294	11,3451	47.3	47.4	32,333
2000 - 2007	130,939	124,927	53.8	54.6	17,315
Country					
Australia	24,340	22,653	57.1	57.9	2,994
Denmark	29,679	27,984	49.2	49.8	9,336
Finland	39,553	36,641	60.2	60.2	11,343
Italy	4,825	4,809	52.4	52.4	426
Netherlands	3,707	3,394	87.3	87.8	983
Spain	943	875	94.4	95.1	25
Sweden	18,276	17,133	60.8	61.3	4,523
UK	11,671	10,815	59.4	59.5	1,109
USA	211,640	201,665	40.2	40.7	58,221
Total	**344,772**	**326,078**	**47.0**	**47.4**	**88,960**

Table 5-1: Patient characteristics of incident cardiac study by laterality of breast cancer.

5.3.1 Analysis of first cardiac event (after breast cancer diagnosis) only

5.3.1.1 Incidence of all heart disease combined and specific cardiac diagnoses

Among women recorded not to have received radiotherapy, the incidence ratio, left-sided versus right-sided breast cancer, for all heart disease combined was 1.03 (95% CI 1.01-1.04). In contrast, for women recorded as receiving radiotherapy, the incidence

ratio for all heart disease was 1.08 (95% CI 1.06-1.10) (Figure 5-1). The heterogeneity between these two incidence ratios suggested a radiation-related effect (2p for radiotherapy heterogeneity: 0.0002).

A left-sided excess of cardiac incidence was present for all of the main cardiac diagnoses: ischaemic heart disease (IHD), valvular heart disease, arrhythmia, pericarditis, heart failure / cardiomyopathy, and other / ill-defined heart disease. This left-sided excess reached statistical significance for IHD, valvular heart disease and pericarditis, with incidence ratios of 1.11 (95% CI 1.07-1.14), 1.32 (95% CI 1.19-1.47) and 1.50 (95% CI 1.27-1.78). The incidence ratio was significantly raised for the three subgroups of IHD (acute myocardial infarction, angina, and all other IHD) and for aortic valvular disease, multiple/unspecified valvular disease and acute pericarditis. The highest incidence ratio was for acute pericarditis, with a two-fold significant excess among left-sided compared to right-sided breast cancer patients. All other subcategories of cardiac diagnoses combined, were found to have a left-sided excess, but it did not reach statistical significance.

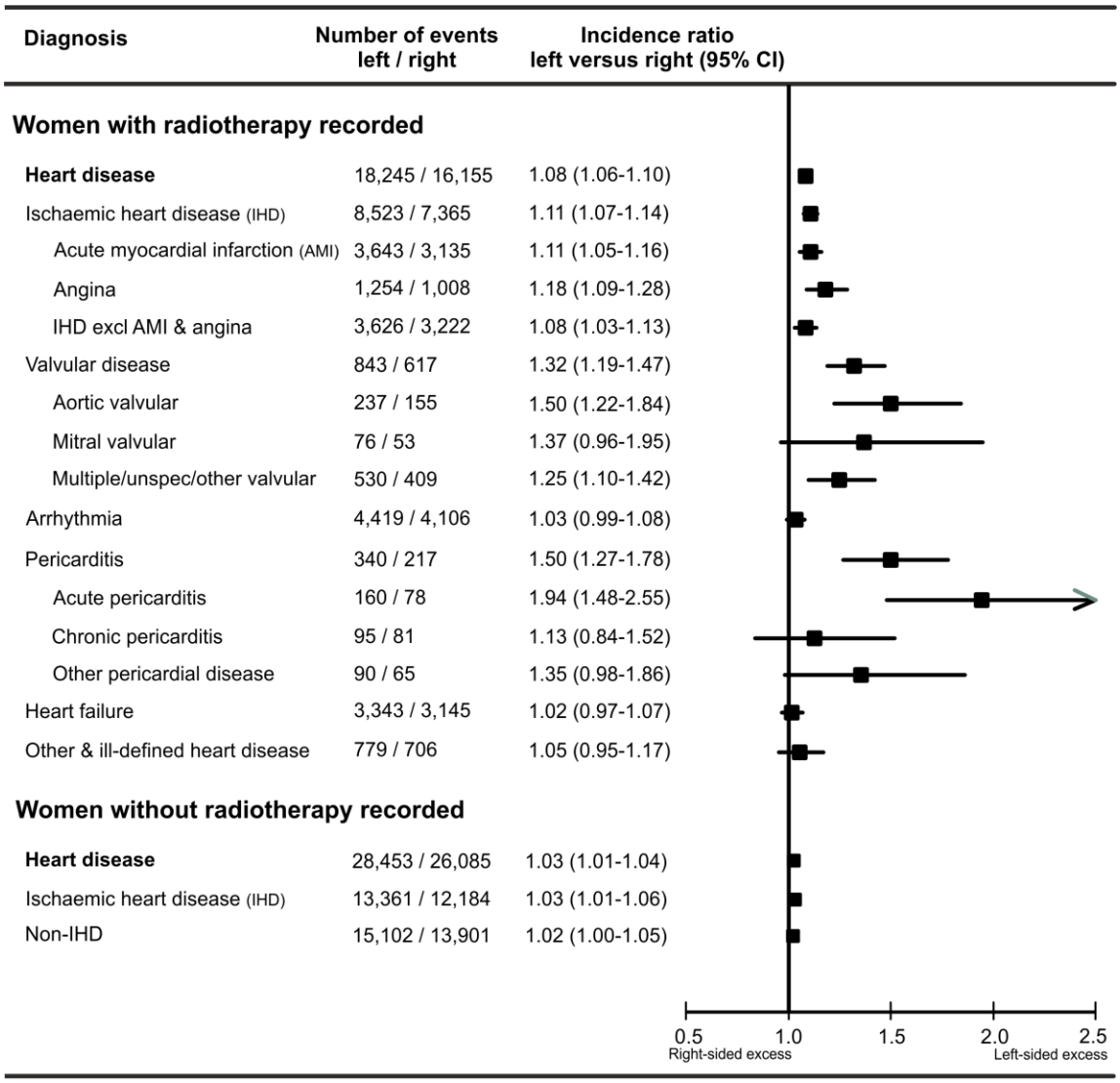


Figure 5-1: Cardiac incidence ratios, left-sided versus right-sided breast cancer, calculated using a univariable model for specific subgroups of cardiac diagnoses.

To fully understand the relationship between the univariable and multivariable results, the incidence ratios, left-sided versus right-sided, were calculated for the largest country and largest age group, in terms of numbers of events, separately. These subgroups groups were the USA and ages 70-79 years (across all countries), see Figure 5-2. These subgroups would have the greatest influence (weighting) in the multivariable analysis. Among irradiated women, the incidence ratio for all heart disease combined was lower for women diagnosed in USA alone, and women diagnosed aged 70-79 years alone, as compared to the results for all women combined shown in Figure 5-1. This held true for all specific cardiac diagnoses and sub-groups.

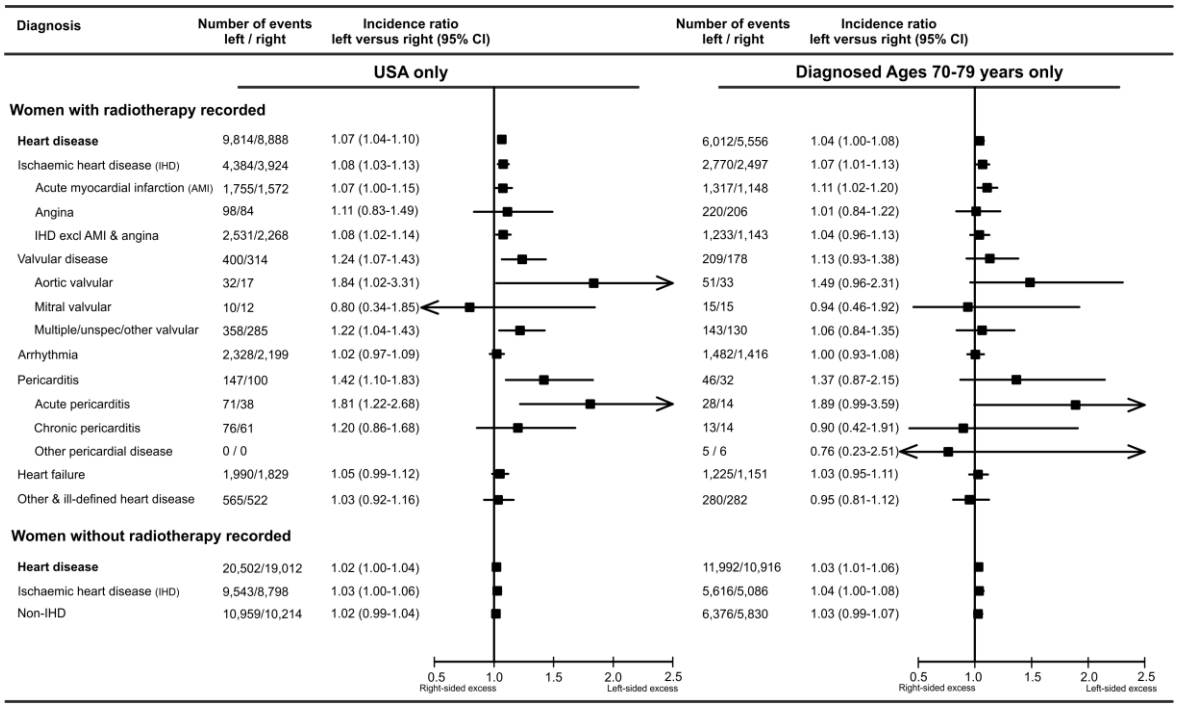


Figure 5-2: Cardiac incidence ratios, left-sided versus right-sided breast cancer, calculated using a univariable model for specific subgroups of cardiac diagnoses - for USA and ages 70-79 years only.

After an additional person-years weighted average (based on a multivariable model) was applied, the incidence ratio, left-sided versus right-sided, for all heart disease combined was 1.04 (95% CI 1.01-1.07). There was a significant left-sided excess for IHD and valvular heart disease, but it was no longer significant for pericarditis (Figure 5-3). There was a significant 12% left-sided excess compared to right-sided of acute myocardial infarction, based on a total of 6,778 events. The highest left-sided excess was for aortic valvular disease, with a significant 71% left-sided excess which was based on only 392 events.

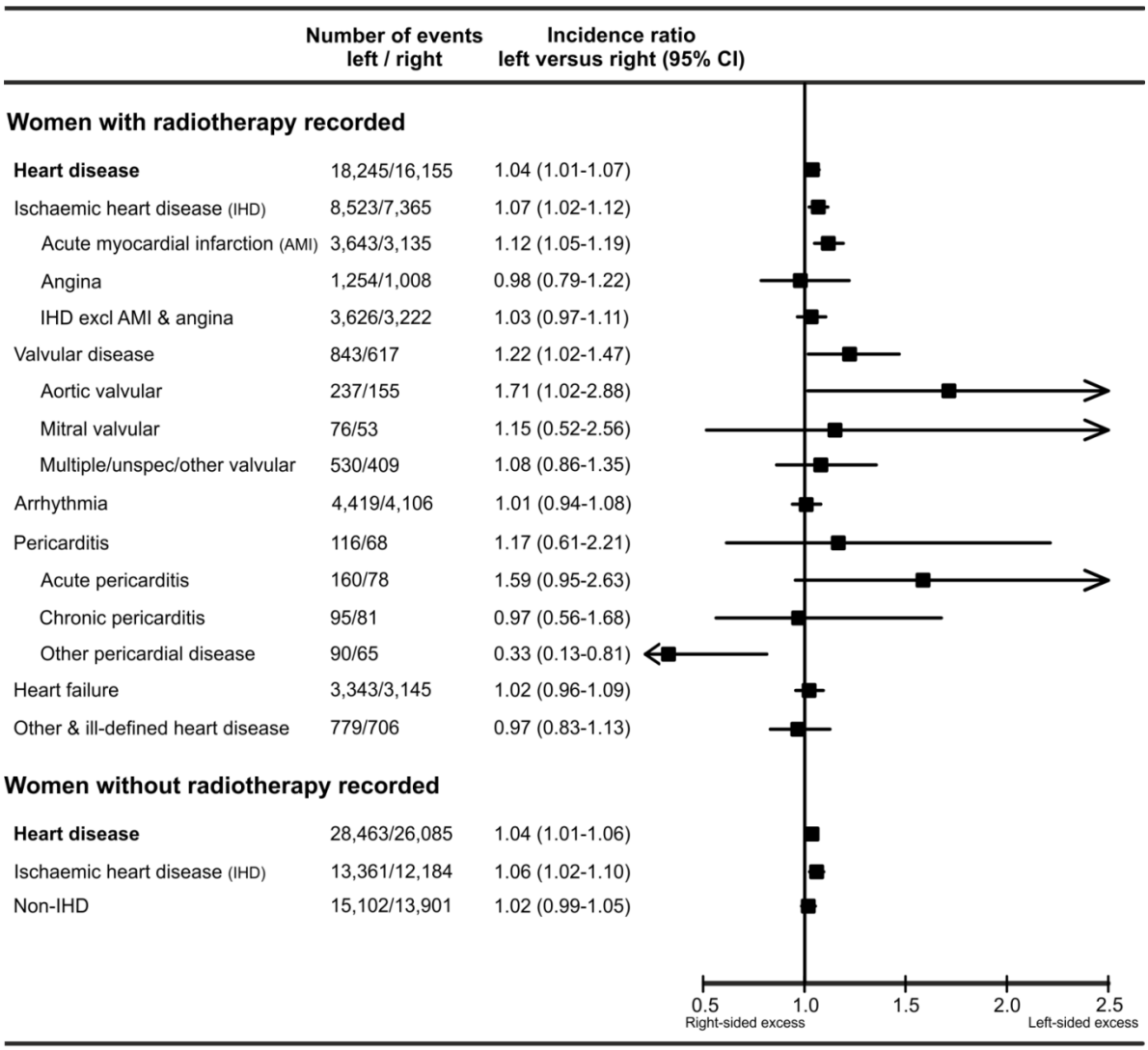


Figure 5-3: Cardiac incidence ratios, left-sided versus right-sided breast cancer, for specific subgroups of cardiac diagnosis, calculated using a multivariable model and additional person-years weighting.

5.3.1.2 Variation in incidence of all heart disease combined subdivided by patient characteristics

A significant linear trend was found for irradiated women by years since diagnosis (2p: 0.004), age (2p: 0.009) and calendar year of diagnosis (2p: 0.05), and there was significant heterogeneity in the incidence ratios by country (2p: 0.05) (Figure 5-4). These were calculated using univariable models with a baseline group of years since: 0-4 years, age: <40 years old, calendar period: 1953 to 1969 and country: UK. The incidence ratios increased with increasing years since diagnosis, with the greatest proportional excess in left-sided women at 25+ years since cancer diagnosis (1.15 95% CI 1.06-1.24). Younger women were at the greatest

proportional risk, with a significant 17% left-sided excess and decreasing trend with increasing age at diagnosis. Women treated more recently were at a lower proportional risk compared to those treated in the 1970s, with a significant decreasing linear trend (2p=0.05). However, a significant left-sided excess existed for women treated during 2000-2007 with an incidence ratio, left-sided versus right-sided, of 1.07 (95% CI 1.02-1.12). Significant heterogeneity existed between countries, with all countries except Spain demonstrating an incidence ratio greater than 1. The left-sided excess was significantly elevated for Australia, Finland, the UK and USA. No heterogeneity was present across the countries when Spain was removed from the test (2p=0.11).

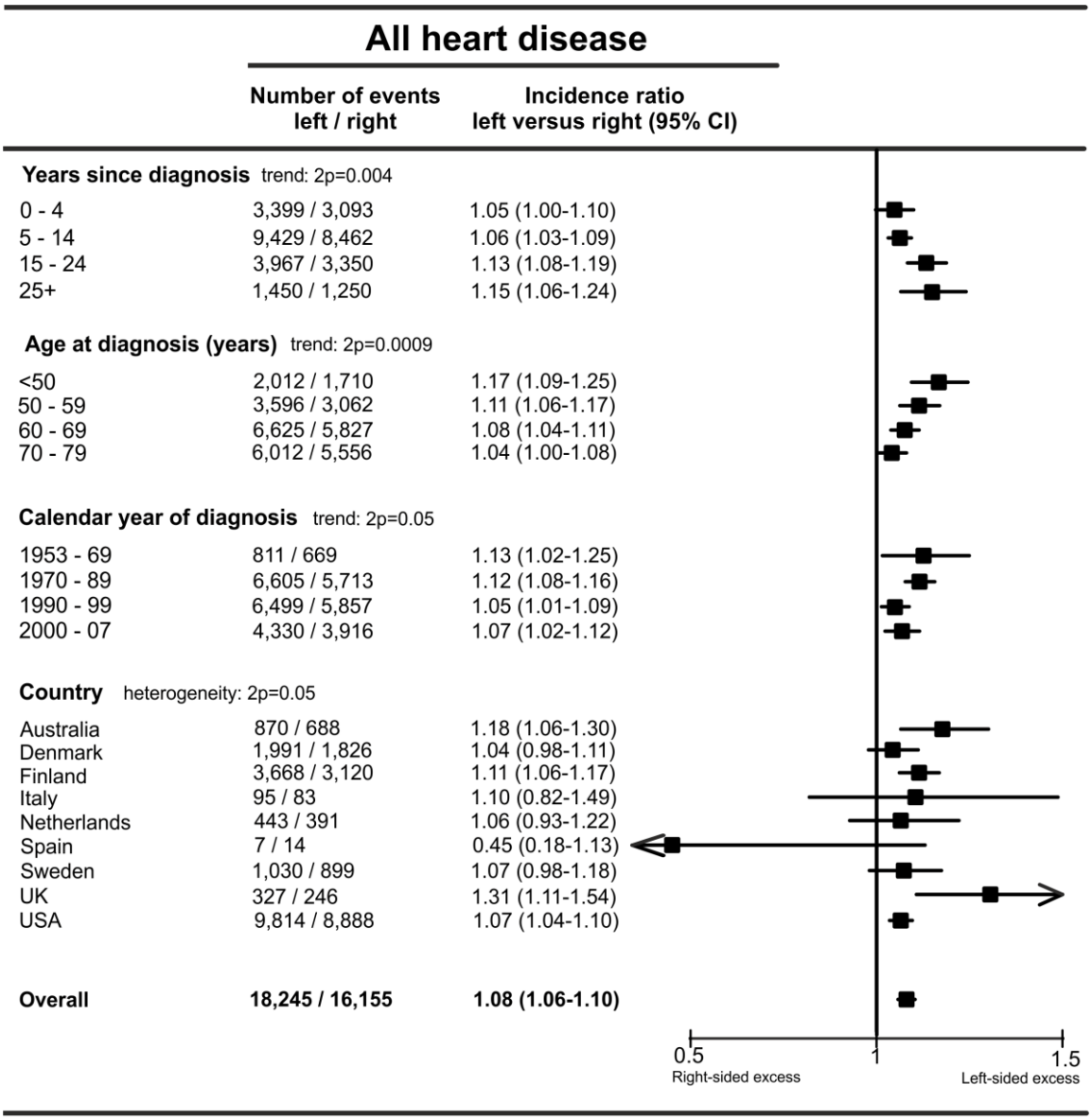


Figure 5-4: Cardiac incidence ratios, left-sided versus right-sided breast cancer, estimated using a univariable model subdivided by years since diagnosis, age, calendar year and country of treatment.

Removal of the dependence on a baseline through the use of a multivariable model and weighted average resulted in a significant decreasing trend with age at diagnosis (2p=0.03), significant heterogeneity between countries (2p=0.03), but not a significant trend with either time since diagnosis (2p=0.11) or calendar year (2p=0.94). The incidence ratio was 1.14 (95% CI 1.05-1.23) for women diagnosed before the age of 50 years, and the rate ratios decreased with increasing age at diagnosis. However, the left-sided excess remained significant in women treated during their 70s. The left-sided excess remained significant in Australia, Finland, the UK and the USA, with the greatest excess of 34% in women treated in America.

Despite a non-significant linear trend with increasing years since diagnosis, there was a suggestion that the proportional increase was greatest after the second decade since treatment and continued after 25 years. The incidence ratios, left-sided versus right-sided, were 1.15 (95% CI 1.09-1.21) and 1.11 (95% CI 1.02-1.22) for 15-24 years and 25+ years from diagnosis, respectively. There was no consistent trend in the incidence ratio for each calendar period of diagnosis, but, notably of interest, the ratio remained significantly elevated in women diagnosed more recently, taking a value of 1.10 (95% CI 1.05-1.16) for women treated during 2000 to 2007.

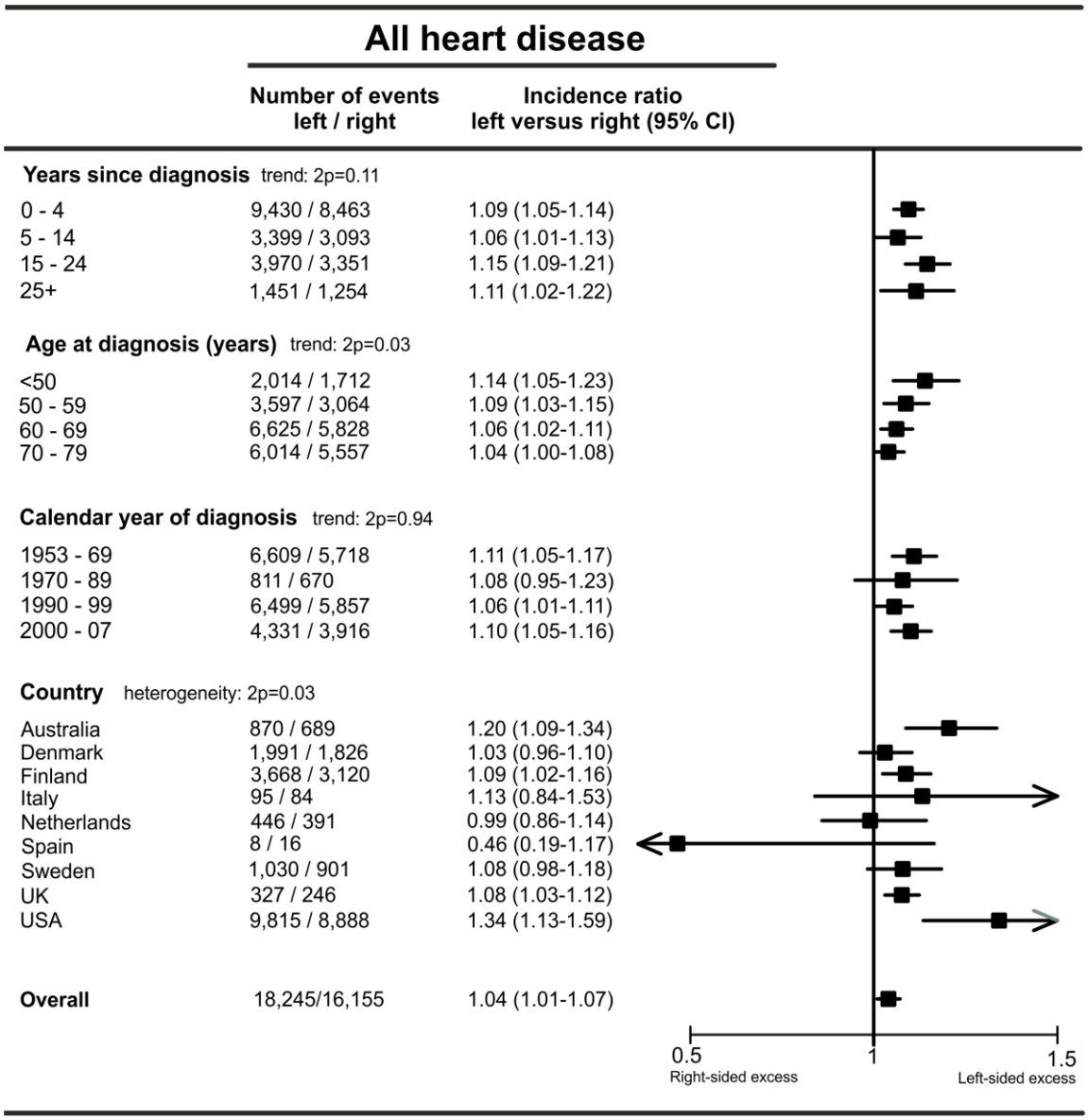


Figure 5-5: Cardiac incidence ratios, left-sided versus right-sided breast cancer, subdivided by years since diagnosis, age, calendar year and country of treatment calculated using a multivariable model and additional person-years weighting.

5.3.1.3 Variation in incidence of specific categories of heart disease subdivided patient characteristics

Despite a relatively low number of pericarditis events, there was a significant increasing trend (2p=0.007) in pericarditis incidence ratios, left-sided versus right-sided, with increasing years since cancer diagnosis (Figure 5-6). The incidence ratio at 15-24 years since diagnosis was 3.03 (95% CI 1.81-5.07), which decreased slightly to 2.55 (95% CI 0.91-7.15) at 25+ years since diagnosis. For IHD, valvular heart disease and other & ill-defined heart disease, the trends in

years since diagnosis, age and calendar year of diagnosis were similar to the findings for all heart disease combined as shown in Figure 5-5, but they did not reach statistical significance. There was no apparent trend for heart failure or arrhythmia. For IHD, valvular heart disease and pericarditis, there was a left-sided excess (not always statistically significant) for all categories of age, calendar year and time since diagnosis.

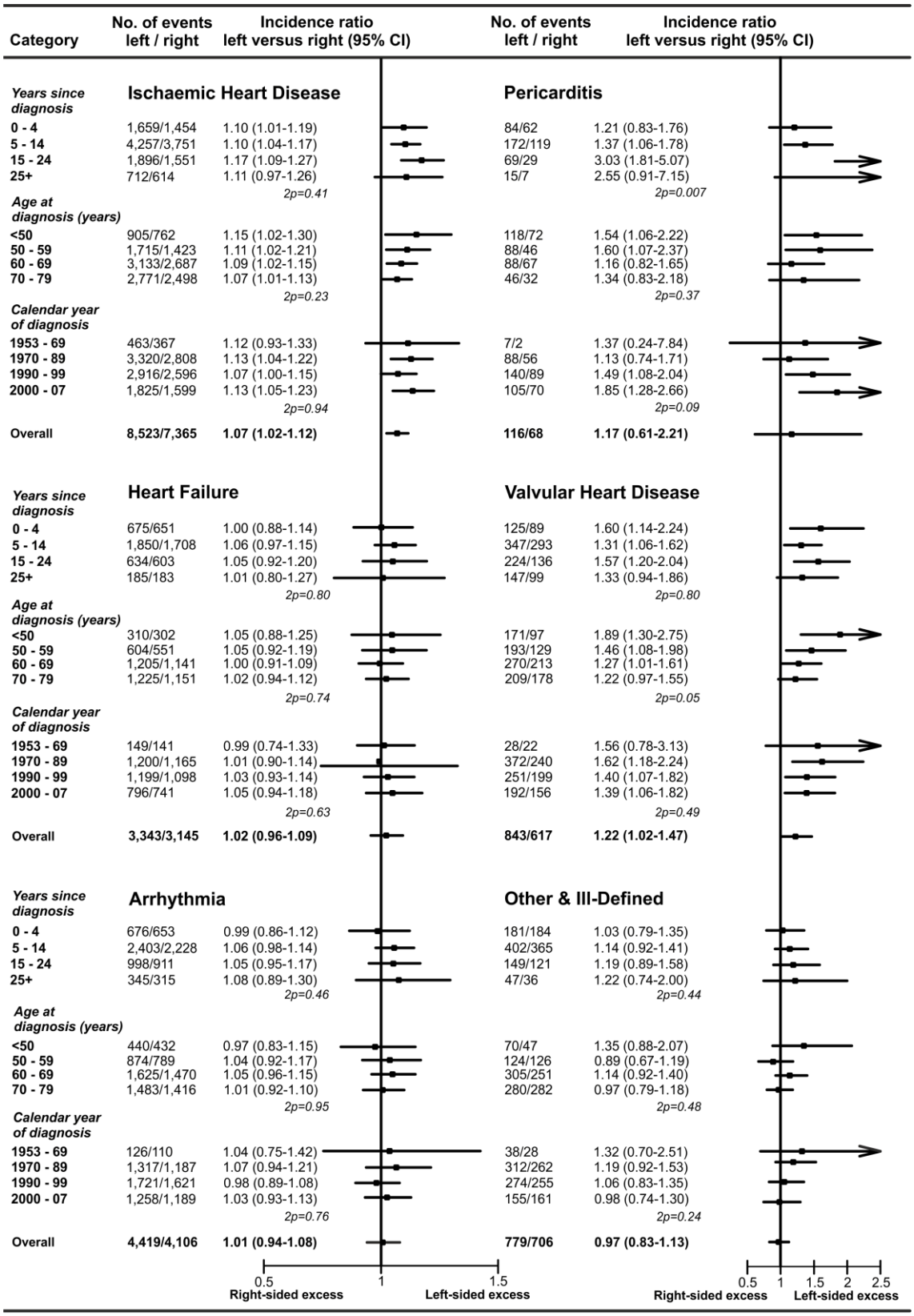


Figure 5-6: Incidence ratios for specific heart disease categories, left-sided versus right-sided breast cancer, subdivided by years since diagnosis, age, calendar year and country of treatment calculated using a multivariable model and additional person-years weighting.

5.3.1.4 Variation in incidence of all heart disease combined by treatment and tumour characteristics

Among women recorded to have received radiotherapy, the cardiac incidence ratio, left-sided versus right-sided, was 1.19 (95% CI 1.08-1.31) for women who received chemotherapy, and 1.08 (95% CI 1.05-1.13) who did not receive chemotherapy (Table 5-2). These two incidence ratios were borderline heterogeneous (2p=0.07) suggesting a potential treatment interaction. No heterogeneity existed between known categories of hormonal therapy, stage of breast cancer, surgery type or race in irradiated women.

		Events		Cardiac incidence	Heterogeneity test *	
		Left	Right	ratio (95% CI)	χ^2 (df)	p-value
Chemo-therapy received	Yes	865	803	1.19 (1.08-1.31)	3.27 (1)	0.07
	No	6,235	5,433	1.08 (1.05-1.13)		
	Unknown	26	28	0.89 (0.51-1.55)		
	Not recorded †	10,991	9,867	1.07 (1.04-1.10)		
Hormonal therapy received	Yes	1,856	1,584	1.10 (1.03-1.18)	0.00 (1)	0.96
	No	5,544	4,834	1.10 (1.05-1.14)		
	Unknown	75	75	0.77 (0.55-1.08)		
	Not recorded	10,743	9,637	1.07 (1.04-1.10)		
Stage of breast cancer	DCIS ‡	927	765	1.16 (1.06-1.28)	4.19 (3)	0.24
	Localised	9,574	8,567	1.07 (1.04-1.10)		
	Regional	6,080	5,382	1.10 (1.06-1.14)		
	Metastatic	556	462	1.16 (1.02-1.31)		
	Unknown	1,013	910	0.99 (0.91-1.09)		
Surgery	BCS §	7,599	6,871	1.06 (1.02-1.09)	0.99 (2)	0.61
	Mastectomy	4,251	3,814	1.08 (1.04-1.13)		
	None	185	166	1.02 (0.82-1.27)		
	Unknown	6,170	5,267	1.12 (1.08-1.16)		
Race	Asian / Pacific	395	388	1.02 (0.89-1.18)	2.55 (3)	0.47
	Black	882	764	1.15 (1.04-1.26)		
	White	11,912	10,723	1.06 (1.04-1.09)		
	Other	27	31	0.96 (0.56-1.65)		
	Unknown	643	485	1.20 (1.07-1.35)		
	Not recorded	4,361	3,748	1.10 (1.05-1.15)		

* Between known categories
† Variable not provided by registry, or period was before common use of therapy
‡ Ductal carcinoma in situ
§ Breast conserving surgery

Table 5-2: Cardiac incidence ratios, left-sided versus right-sided breast cancer, in irradiated women subdivided by chemotherapy and hormonal therapy receipt, stage of breast cancer, surgery type and race.

This suggested chemotherapy-radiotherapy interaction was investigated further by analysing specific cardiac events (Table 5-3). The incidence ratios, left-sided versus right-sided, were calculated for women who received both chemotherapy and radiotherapy, only one of chemotherapy or radiotherapy, and neither treatment. Without radiotherapy, there should be no difference in incident events by laterality, but the difference in incidence ratios between whether chemotherapy was received in irradiated women could suggest an interaction. Significant heterogeneity (2p=0.05) was present across the IHD incidence ratios by treatment received taking values of 1.23 (95% CI 1.06-1.44), 1.14 (95% CI 1.08-1.20), 1.07 (95% CI 0.87-1.32) and 1.05 (95% CI 0.99-1.10) for women treated with radiotherapy and chemotherapy, radiotherapy alone, chemotherapy alone, and neither treatment, respectively. The increased proportional incidence in women who received both treatments was, again, suggestive of a possible interaction. Significant heterogeneity by treatment received (2p=0.05) was also present across the incidence ratios of heart failure, but the greatest proportional increase was in women who received chemotherapy alone (1.29 95% CI 0.94-1.76). The difference in subgroups was borderline significant (2p=0.07) when all cardiac diagnoses were combined.

Event	Radiotherapy received	Chemotherapy received	Number of events Left / Right	Incidence ratio (95% CI) left vs right
All heart disease	Yes	Yes	965 / 803	1.19 (1.08-1.31)
		No	6,492/5,671	1.08 (1.05-1.12)
	No	Yes	513 / 452	1.05 (0.93-1.20)
		No	6,514 / 5,782	1.05 (1.01-1.08)
				2p for het: 0.07
IHD	Yes	Yes	393 / 320	1.23 (1.06-1.44)
		No	3,254 / 2,694	1.14 (1.08-1.20)
	No	Yes	201 / 178	1.07 (0.87-1.32)
		No	3,150 / 2,799	1.05 (0.99-1.10)
				2p for het: 0.05
Arrhythmia	Yes	Yes	251 / 237	1.05 (0.88-1.26)
		No	1,596 / 1,477	1.02 (0.95-1.10)
	No	Yes	154 / 143	1.02 (0.81-1.29)
		No	1,709 / 1,502	1.06 (0.99-1.14)
				2p for het: 0.93
Cardiomyopathy / Congestive heart failure	Yes	Yes	167 / 136	1.21 (0.96-1.53)
		No	1,031 / 1,050	0.93 (0.85-1.01)
	No	Yes	103 / 72	1.29 (0.94-1.76)
		No	1,131 / 1,075	0.97 (0.89-1.06)
				2p for het: 0.05

Table 5-3: Cardiac incidence ratios, left-sided versus right-sided, subdivided by radiotherapy and chemotherapy status for all heart disease combined and specific cardiac diagnoses.

Another important factor, prior heart disease, was then investigated among women recorded to have received radiotherapy. Among irradiated women there was no heterogeneity by prior heart disease for all heart disease combined (2p=0.28), IHD (2p=0.64), arrhythmias (2p=0.90) or heart failure (2p=0.47) (Table 5-4). Similarly, there was no heterogeneity for prior IHD, or prior MI.

		Events		Incidence ratio (95% CI)	Heterogeneity test *	
		Left	Right		χ^2 (df)	p-value
		All heart disease				
Prior heart disease	Yes	1,315	1,257	1.02 (0.95-1.11)	1.19 (1)	0.28
	No	3,854	3,410	1.08 (1.03-1.13)		
	Not recorded	13,033	11,455	1.09 (1.06-1.12)		
Prior IHD	Yes	514	508	1.01 (0.89-1.14)	0.79 (1)	0.37
	No	2,716	2,437	1.06 (1.00-1.12)		
	Not recorded	15,439	13,633	1.09 (1.06-1.11)		
Prior MI	Yes	65	63	1.08 (0.74-1.57)	0.01 (1)	0.92
	No	12,353	11,115	1.07 (1.04-1.09)		
	Not recorded	5,358	4,500	1.13 (1.09-1.18)		
		IHD (first event)				
Prior heart disease	Yes	595	537	1.12 (0.99-1.26)	0.22 (1)	0.64
	No	1,729	1,729	1.16 (1.08-1.24)		
	Not recorded	6,181	6,181	1.09 (1.06-1.14)		
Prior IHD	Yes	44	39	1.26 (0.79-2.03)	0.00 (1)	0.96
	No	1,165	952	1.15 (1.06-1.26)		
	Not recorded	7,297	6,358	1.10 (1.06-1.14)		
Prior MI	Yes	309	283	1.11 (0.94-1.30)	2.04 (1)	0.15
	No	5,574	4,848	1.10 (1.06-1.14)		
	Not recorded	2,626	2,215	1.12 (1.06-1.19)		
		Arrhythmia (first event)				
Prior heart disease	Yes	342	330	0.98 (0.84-1.14)	0.01 (1)	0.90
	No	1,039	1,018	0.97 (0.89-1.06)		
	Not recorded	3,023	2,747	1.06 (1.00-1.11)		
Prior IHD	Yes	6	11	0.45 (0.16-1.29)	2.21 (1)	0.14
	No	793	790	0.95 (0.86-1.05)		
	Not recorded	3,617	3,303	1.05 (1.00-1.10)		
Prior MI	Yes	85	96	0.80 (0.59-1.08)	2.04 (1)	0.15
	No	3,274	3,122	1.01 (0.96-1.06)		
	Not recorded	1,058	884	1.14 (1.05-1.25)		
		Heart failure / cardiomyopathy (first event)				
Prior heart disease	Yes	248	273	0.88 (0.74-1.05)	0.53 (1)	0.47
	No	675	676	0.95 (0.86-1.06)		
	Not recorded	2,419	2,188	1.06 (1.00-1.12)		
Prior IHD	Yes	11	10	1.25 (0.49-3.20)	1.16 (1)	0.28
	No	444	468	0.90 (0.79-1.03)		
	Not recorded	2,887	2,664	1.04 (0.97-1.07)		
Prior MI	Yes	77	93	0.86 (0.63-1.17)	0.46 (1)	0.50
	No	2,248	2,116	1.02 (0.96-1.08)		
	Not recorded	1,016	930	1.03 (0.95-1.13)		

* Between known categories

Table 5-4: Cardiac incidence ratio, left-sided versus right-sided breast cancer, in irradiated women subdivided by prior heart disease, prior IHD and prior MI for cardiac endpoints with at least 100 cardiac events in irradiated women with left-sided breast cancer.

5.3.2 Analysis of any cardiac event

Specific cardiac diagnoses were not treated as mutually exclusive, i.e., one woman could contribute to both an IHD and valvular event. The first event after breast cancer diagnosis of each specific cardiac diagnosis was considered.

As in the first event only analysis using a univariable model, a significant left-sided excess was found for IHD, valvular disease and pericarditis, taking values of 9%, 22% and 45% respectively (Figure 5-7). The incidence ratio, left-sided versus right-sided, was also significantly increased for arrhythmia (1.05 95% CI 1.01-1.09). All subgroups of IHD presented a significant left-sided excess, as did aortic valvular disease, multiple / other valvular disease, and acute pericarditis. The incidence ratio for acute pericarditis was substantially greater than in the first event only analysis, with a significant 50% increased incidence among left-sided breast cancer patients.

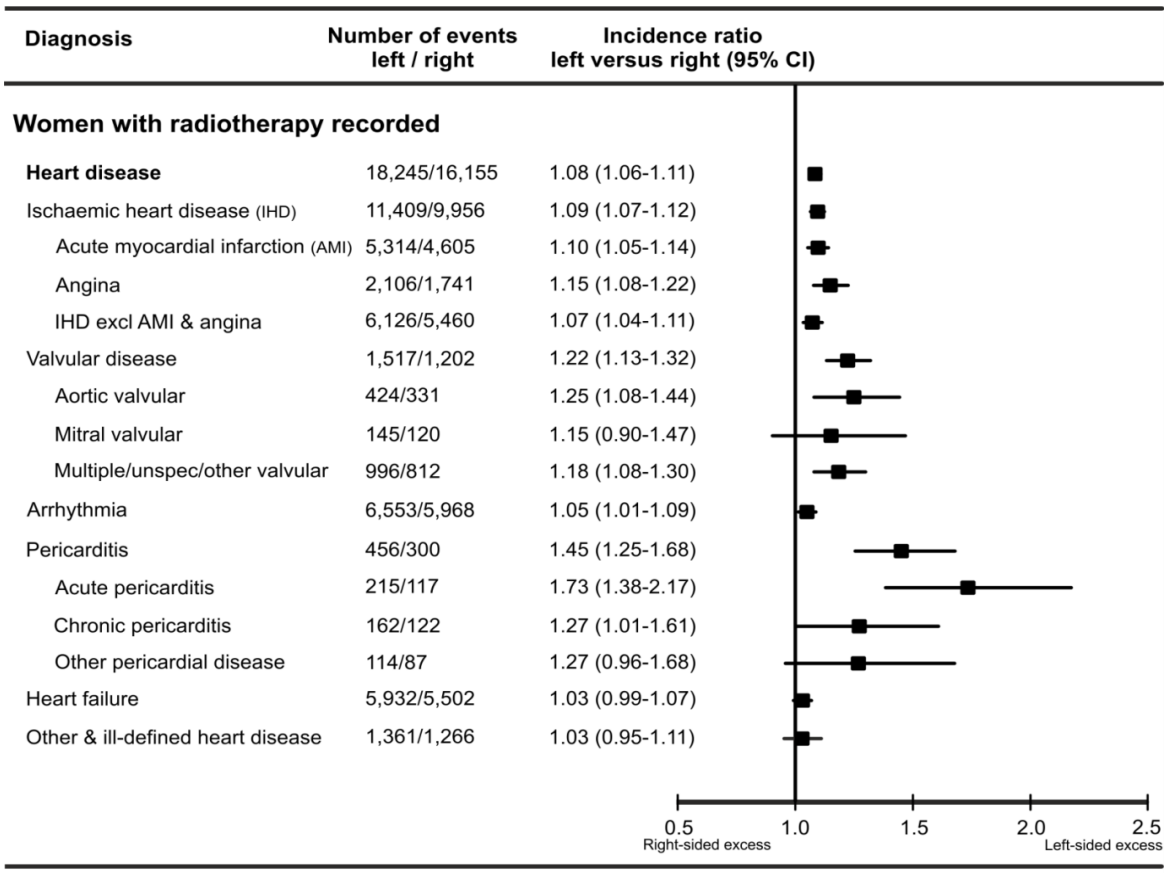


Figure 5-7: Heart disease as any event incidence ratio, left-sided versus right-sided breast cancer, calculated using a univariable model for specific subgroups of cardiac diagnoses.

Incidence ratios for all cardiac subgroups were calculated using a multivariable model with an additional person-years weighted average, see Figure 5-8. The results were similar to those estimated using a univariable model (Figure 5-7), with a significant left-sided excess present for IHD, valvular disease, arrhythmia and pericarditis. However, the incidence ratio for chronic pericarditis was significantly increased with an estimate of 1.67 (95% CI 1.14-2.46). The incidence ratios for acute myocardial infarction, aortic valvular disease and acute pericarditis were also significantly increased. All other known endpoints, except mitral valvular disease, demonstrated a left-sided excess in irradiated women.

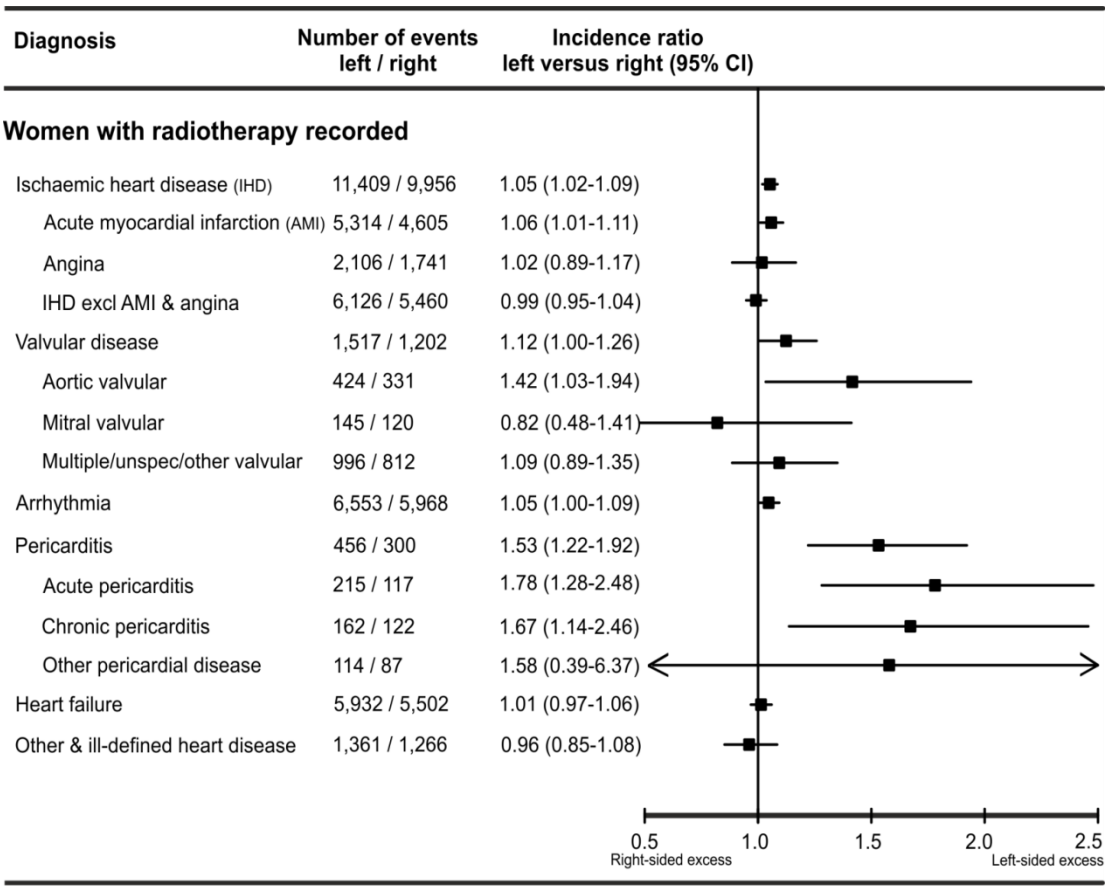


Figure 5-8: Heart disease as any event incidence ratio, left-sided versus right-sided breast cancer, for specific subgroups of cardiac diagnosis, calculated using a multivariable model and additional person-years weighting.

5.4 Discussion

5.4.1 Overall findings

In this chapter, results from the largest population-based study as yet to investigate the incidence of radiation-related heart disease were presented. Women treated with radiotherapy for left-sided breast cancer were 8% more likely to experience a subsequent cardiac event (fatal or non-fatal) than women treated for right-sided breast cancer during 1953 to 2007. This significant left-sided excess was largely due to significant excesses in ischaemic heart disease, valvular heart disease and pericarditis, with ischaemic heart disease contributing the greatest number of events (46% of first cardiac diagnoses).

A number of studies have demonstrated a significantly increased radiation-related incidence of heart disease in left-sided breast cancer patients (Harris, Correa et al. 2006, Borger, Hooning et al. 2007, Jagsi, Griffith et al. 2007, McGale, Darby et al. 2011, Darby, Ewertz et al. 2013). The largest of these is a study of 72,134 women treated in Denmark and Sweden during 1976-2006 (McGale, Darby et al. 2011). The registries analysed in the work by McGale and colleagues also contributed data to the COBS collaboration presented in this thesis, and the number of women from Denmark and Sweden accounted for 8.6% and 4.2%, respectively, of the women analysed for this chapter. In the published study by McGale et al, a significant left-sided excess of events of IHD, MI, angina, pericarditis and valvular heart disease was shown among irradiated women. The greatest excess was found for acute pericarditis, followed by aortic valvular disease. This was in-keeping with the results of this study, in which the incidence ratio, left versus right, was of 1.94 (95% CI 1.48-2.55) and 1.50 (95% CI 1.22-1.84) for acute pericarditis and aortic valvular disease, respectively, which were slightly lower than the incidence ratios of 2.16 (95% CI 1.10-4.26) and 1.70 (95% CI 1.14-2.53) for Denmark and Sweden alone (McGale, Darby et al. 2011). Radiation-related pericarditis, as discussed by McGale et al, has been previously demonstrated experimentally and in Hodgkin lymphoma patients. The findings presented here have now also demonstrated increased radiation-related pericarditis in breast cancer patients. In addition, this COBS study demonstrated an increasing trend in the proportional risk of pericarditis with increasing time since cancer treatment.

Despite a lack of complete understanding of the pathology of radiation-induced valvular heart disease, its existence has been demonstrated in a number of cases (Cutter, Taylor et al. 2010). McGale et al (2011) questioned whether their elevated risk of valvular disease was an effect of radiation itself, or in fact a result of radiation-induced IHD. Two other studies have investigated valvular heart disease incidence after breast cancer radiotherapy with inconsistent results. A study of 1,600 women treated with breast conserving surgery with 16 years of

following up found a 53% significant left-sided excess for valvular heart disease (in combination with pericarditis, cardiomyopathy and congestive heart failure) (Borger, Hooning et al. 2007). In contrast, an analysis of the SEER-Medicare study with 9.5 years of follow-up found a non-significant (p=0.93) left-sided excess of valvular heart disease (Patt, Goodwin et al. 2005). This chapter provides further evidence that it may well be a radiation effect yet more studies are needed to fully characterise the risk.

The radiation-induced risk of IHD and myocardial infarction (MI) has been investigated by a number of authors. The incidence ratios, left-sided versus right-sided, ranged from 1.03 to 1.35 for IHD (Patt, Goodwin et al. 2005, Borger, Hooning et al. 2007, Doyle, Neugut et al. 2007, McGale, Darby et al. 2011), and ranged from 0.74 to 7.92 for MI (Rutqvist, Liedberg et al. 1998, Vallis, Pintilie et al. 2002, Harris, Correa et al. 2006, Doyle, Neugut et al. 2007, Hooning, Botma et al. 2007, Jagsi, Griffith et al. 2007, Paszat, Vallis et al. 2007, McGale, Darby et al. 2011). Variations in the estimates of IHD and MI risk from the published studies could be attributed to differences in average follow-up time, treatment period, study size, and distribution of tumour and patient characteristics. Therefore, the results for IHD in the worldwide collaboration in this thesis were very consistent (taking into account variations in study populations) with the published results. The wide range of estimates for MI makes it difficult to make a concluding statement regarding the consistency with published studies. However, the MI estimates found in this chapter was consistent with the estimate for IHD and the larger published studies.

As this chapter was based on a collaboration of registries worldwide, natural variation existed in the distribution of patient characteristics, and treatment exposure across the registries. The univariable analysis controlled for these variations through stratification. However, a second analysis was performed in order to average the rate ratios estimated from a multivariable model of all categories of the explanatory variables (age, calendar year and country of treatment, and years since treatment), weighted by the corresponding person-years. This method was most

useful when investigating the variation in radiation-related risk by patient characteristics, but it was also applied to the overall estimates (Figure 5-3). The incidence ratios calculated by multivariable regression were lower than the estimates from the corresponding univariable model for all cardiac endpoints, except AMI and aortic valvular disease. The majority of women (60%) included in this study were aged 60 years or older. This was largely due to the fact that SEER-Medicare accounts for 62% of the study population, which only records follow-up information on women aged 65 years and older. As demonstrated in both this study, and the study of cardiac mortality, older women were at a lower proportional risk than younger women. Thus, the risk in older women would have had a greater influence on the cardiac incidence ratios in the multivariable analysis, resulting in lower left-sided excesses.

The risk of incident heart disease was investigated using two approaches: a first event only analysis and an analysis of any cardiac event. All results were similar when the analysis took account of all diagnoses of heart disease, rather than only the first event. For ease of discussion, only the results corresponding to the mutually exclusive analysis of first event after breast cancer will be discussed. It is important to note that the comparison of left-sided versus right-sided breast cancer patients was likely to underestimate the extent of the cardiac risk of both fatal and non-fatal events, because the laterality comparison is a comparison of 'higher versus lower dose received by the heart. However, the risk compared to no dose, i.e. a comparison of radiotherapy versus not, was not possible in observational cohorts due to selection biases previously discussed (Chapter 3).

5.4.2 Risk of incident heart disease by treatment period and age of diagnosis

It is believed that modern radiotherapy has reduced the radiation-related heart disease risk, as no study yet has demonstrated an elevated risk in women treated after 1990. For instance, Doyle and colleagues stated that there was no laterality difference in the risk of MI in women treated after 1992 (Doyle, Neugut et al. 2007). The findings of this COBS study provided

evidence to the contrary. For women diagnosed during 2000 to 2007, the incidence ratio, left-sided versus right-sided, was 1.10 (95% CI 1.06-1.16). This was greater than the estimate for women diagnosed during the 1990s, potentially suggesting that the proportional excess may be increasing again for women treated in more recent calendar years. It was not possible to know whether this suggestion is true until extended follow-up is collected. This highlights the need for continued follow-up for late cardiac events, particularly among women treated for breast cancer more recently.

No study, as yet, has demonstrated such a clear progressive decrease with increasing age at cancer diagnosis in the proportional risk of cardiac incidence in breast cancer patients treated with radiotherapy. Women treated for breast cancer before age 50 were at a 14% (95% CI 5%-23%) left-sided excess compared to right-sided events of all heart disease combined. This decrease in proportional risk with age at radiation was present in IHD, cardiomyopathy and heart failure, pericarditis and valvular heart disease. A laterality comparison has been used to investigate the association with age at cancer diagnosis in a number of studies with varying results. No strong association with age was found in three studies (Patt, Goodwin et al. 2005, McGale, Darby et al. 2011, Darby, Ewertz et al. 2013). A study of 834 women from the University of Michigan found that the occurrence of a first event of MI was positively associated with age ($p=0.0004$), where age was treated as continuous (Jagsi, Griffith et al. 2007). Two other studies also found that the MI risk was higher in older women, where age 60 years was used as the cut-off (Doyle, Neugut et al. 2007, Paszat, Vallis et al. 2007). For a direct comparison to the work by Paszat and colleagues, the incidence ratios, left-sided versus right-sided, were calculated using a univariable model for the first event of acute MI. The incidence ratios were found to be 1.20 (95% CI 1.03-1.40), 1.05 (95% CI 0.94-1.17), 1.11 (95% CI 1.03-1.21) and 1.11 (95% CI 1.02-1.20) for ages <50, 50-59, 60-69 and 70-79, respectively. Thus, the three published studies with a significant association of MI risk with age demonstrated an opposite

trend to that shown in this COBS study. This may be due to the substantial differences between the study populations of this study and those in the published literature. One potential explanation may be due to the large proportion of elderly women in this cohort. It has been shown that, particularly in older women, radiotherapy was less likely to be administered to a patient with a pre-existing cardiac condition, or a previous cardiac event (Doyle, Neugut et al. 2007). Therefore, the selection of patients to radiotherapy may have varied substantially between this COBS study and the work by Paszat and colleagues, causing the inconsistent results. In addition, awareness of the cardiotoxicity of radiotherapy has resulted in changes to clinical practice, and in more recent years some policies have been adjusted to reduce the risk of radiation-related heart disease. For example, as of 2003 the policy in Denmark is to only use internal mammary chain radiation on right-sided breast cancer patients (McGale, Darby et al. 2011). However, this level of treatment detail was not available and so without this information the cause of the different findings could not be fully dissected.

5.4.3 Risk of incident heart disease in relation to chemotherapy

It is believed that the cardiotoxic risks associated with chemotherapy and radiotherapy are additive due to the distinct mechanisms of cardiac damage from the two treatments (Shapiro and Recht 2001, Bovelli, Plataniotis et al. 2010, Cutter, Taylor et al. 2010). There is evidence that chemotherapy (namely anthracyclines and taxanes) is cardiotoxic, even in the absence of radiotherapy (Yeh and Bickford 2009). Meta-analyses of all available randomised trials of chemotherapy in early breast cancer have been completed by the Early Breast Cancer Collaborative Group (Early Breast Cancer Trialists' Collaborative Group 2005). The meta-analysis of polychemotherapy versus not found a rate ratio of 1.21 (95% CI 0.93-1.59) for all heart disease, and 1.78 (95% CI 1.00-3.17) for all heart disease when only anthracycline-based regimens were considered. This clearly showed the cardiotoxic effects of anthracycline-based chemotherapy regimens. However, there has been little evidence, particularly in observational

data, to demonstrate this additive effect. The potential interaction between chemotherapy and radiotherapy may vary on the chemotherapy agent administered as they use different mechanisms. In the early calendar periods, the main chemotherapy regime used was Cyclophosphamide Methotrexate Fluorouracil (CMF), but from the 1990s onwards anthracycline-based regimens were introduced. A comprehensive history of the use of chemotherapy drugs has been reviewed elsewhere (Verrill 2009). However, as the COBS cohort does not hold detailed information on the type chemotherapy received, the possible variation in interaction based on chemotherapy regimen could not be analysed.

Four papers investigated the association between chemotherapy and radiotherapy in terms of the risk of heart disease incidence in breast cancer patients, and none of the studies found a significant association the two treatments (Doyle, Neugut et al. 2007, Jagsi, Griffith et al. 2007, McGale, Darby et al. 2011, Darby, Ewertz et al. 2013). However, this COBS study of nearly 700,000 women treated for breast cancer over a 50 year period found a significant interaction between radiotherapy and chemotherapy for IHD and cardiomyopathy / congestive heart failure. The left-sided excess of IHD events was highest in women who received chemotherapy and radiotherapy. Women who only received chemotherapy had the greatest left-sided excess of cardiomyopathy and congestive heart failure events. The finding of an association for IHD events was expected, as radiation is most strongly associated with ischaemic heart disease (Cutter, Taylor et al. 2010). The finding for cardiomyopathy was likely a fluke result, as event though it has been shown that chemotherapy was most strongly associated with cardiomyopathy, there should be no difference by laterality for the effect of chemotherapy.

5.4.4 Comparison of cardiac incidence risk to cardiac mortality risk

The overall conclusions drawn from the analyses of cardiac mortality and cardiac incidence in COBS were similar, and the key points will now be discussed. The initial difference between the two chapters was that not all registries contributed non-fatal data, and so the

number of patients in Chapter 4 was approximately double that here. The mortality ratio, left-sided versus right-sided, was 1.07 (95% CI 1.04-1.10) and the incidence ratio was 1.08 (95% CI 1.06-1.10) for all heart disease among irradiated women. In both studies, the proportional risk increased (non-significantly in a multivariable model) with increasing time from cancer diagnosis, and continued into the third decade since treatment. This might suggest that this trend was confounded by calendar year of diagnosis, as to be expected as more recent years have limited follow-up. There was a significant left-sided excess in the first five years following diagnosis for incidence, which was also shown in the most recent published study (Darby, Ewertz et al. 2013), suggesting that radiation-related heart disease is not only a late effect. The proportional increase was highest for younger women. A potential chemotherapy interaction was found in both studies, which was mainly present in younger women in terms of mortality. This interaction was shown for all heart disease combined in the mortality study, and for ischaemic heart disease events in the incidence study.

Three published studies also included an analysis of radiation-related mortality as a comparison to their analyses of incidence (Harris, Correa et al. 2006, Borger, Hooning et al. 2007, McGale, Darby et al. 2011). In all three studies, there was no significant excess in mortality, but a significant left-sided excess was present in the analyses of incident events. This difference was likely due to statistical power.

5.4.5 Incident heart disease risk in SEER-Medicare

As mentioned earlier, 62% of the study population is data from the SEER-Medicare dataset. Medicare is a health insurance program for individuals aged 65 and older in the USA. The Medicare claims were linked to individuals recorded with cancer in SEER, and provide information on the medical treatment received which was covered by Medicare health services. Three studies have previously investigated the risk of cardiac incidence using a comparison of left-sided versus right-sided breast cancer patients recorded in the SEER-Medicare database (Patt,

Goodwin et al. 2005, Doyle, Neugut et al. 2007, Pinder, Duan et al. 2007). None of the three studies found a significant excess of cardiac events among left-sided breast cancer patients. However, the average follow-up was less than 10 years for these studies.

5.4.6 Strengths of study

The main strength of this study was the size of the population, with 670,850 patients contributing a total of 6,386,597 person-years and 88,960 events. The collaboration has allowed direct comparison of the radiation-related heart disease risk among women in eight countries, from 14 registries. This is the first collaboration of population-based cohorts of this scale for the study of cardiac incidence in breast cancer patients. This allowed investigation of the variation in risk by important patient characteristics thought to be associated with radiation-related incident heart disease risk.

5.4.7 Limitations of study

As with the cardiac mortality study, the main limitation of this cardiac incidence study is the lack of detailed treatment information for individual women. This prevents investigation of dose-response relationships. However, when investigating risk on this scale it would be very challenging to collect individual treatment information. The cohort was designed to collect basic information on a large scale with the intention of understanding the 'big picture'.

The other potential limitation of this study is that not all registries supplied information on non-fatal events. This meant that the range of calendar periods and ages of diagnosis supplied to the incidence study was smaller than the mortality study, and the number of events that could be analysed was limited.

5.4.8 Conclusion

A significant excess of incident heart disease events, in left-sided versus right-sided breast cancer patients, was demonstrated in this large-scale population-based cohort of breast cancer survivors treated with radiotherapy. The proportional risk appeared within the first few years, and continued for at least three decades, with a significant left-sided excess still present in women treated recently, i.e. from 2000 onwards. A possible interaction between chemotherapy and radiotherapy was found, particularly in ischaemic heart disease. This study highlights the importance of large-scale data, which provide enough events to analyse subgroups of clinically relevant categories. Also, as breast cancer survival increases continued follow-up is still very important as it should provide more evidence on the lifelong hazards associated with radiotherapy for breast cancer. The growing collection of published studies of radiation-related heart disease with extended follow-up in the literature provides an evidence-base to support monitoring cancer survivors for heart disease for decades after treatment.

CHAPTER 6:
LUNG CANCER RISK FOLLOW BREAST CANCER RADIOTHERAPY

6.1 Introduction

Meta-analyses conducted by the Early Breast Cancer Collaborative Group have shown that lung cancer is the most commonly diagnosed second cancer among women treated with radiotherapy for breast cancer. Among 42,000 women from 78 randomised trials, 156 women died from lung cancer (Early Breast Cancer Trialists' Collaborative Group 2005). This translated to 48.6 events attributable to radiotherapy. As such, investigation of radiation-related lung disease in a large population-based cohort is important, as a greater number of events will allow investigation of the variation in risk by patient and treatment characteristics.

As explained in Chapter 3, selection effects prevent a comparison of irradiated and unirradiated women from producing reliable results in observational data. Previous chapters have studied the risk of radiation-related heart disease using a laterality comparison, which is the most common side-effect associated with radiotherapy accounting for 30% of the total non-breast-cancer deaths in randomised meta-analyses (Early Breast Cancer Trialists' Collaborative Group 2005). Similarly, the lungs are a paired organ, and their positioning means that the lung on the same side as the breast receiving radiation will be subjected to a higher radiation dose than the opposite lung. Thus, a comparison of ipsilateral versus contralateral lung cancer is equivalent to a comparison of higher versus lower radiation dose. This should allow analyses comparable to those presented on radiation-related heart disease.

Information gathered on the risk of radiation-related lung cancer could help to improve the long-term survivorship of breast cancer patients. Both breast cancer and lung cancer are commonly diagnosed in the general population, meaning that proportional increases in the risk of radiation-related lung cancer could have a large absolute effect. With the increasing survival of breast cancer patients (1-year survival is currently at ~95% in developed countries (95.8% in the UK, (Cancer Research UK 2014)), the focus is shifting towards the reduction of late adverse effects, in which lung cancer features prominently.

6.2 Aim

This study aimed to characterise the long-term risk of microscopically confirmed lung cancer in terms of both fatal and non-fatal events in a population-based cohort of breast cancer survivors who were recorded to have received radiotherapy.

6.3 Results

The lungs are a common site of breast cancer metastases; therefore care must be taken when studying this endpoint. To reduce the possibility of misclassification of metastases, only lung cancer cases which were microscopically confirmed were considered in this analysis. The study protocol sent to the contributing registries requested as a desirable variable the "basis of diagnosis of any subsequent invasive cancer". Using this information, a cancer was classified as microscopically confirmed if it was recorded as: cytology; histology of metastases; histology of primary tumour. It was not classified as microscopically confirmed if it was recorded as: death certificate only; clinical; clinical investigation; specific tumour markers; unknown. Out of a possible 7,133 lung cancer events, only 1,309 deaths and 3,457 events were suitable for analysis. Despite this, this study is still the largest population-based study of radiation-related lung cancer among breast cancer patients. A flowchart detailing the selection of lung cancer events is shown in Figure 6-1.

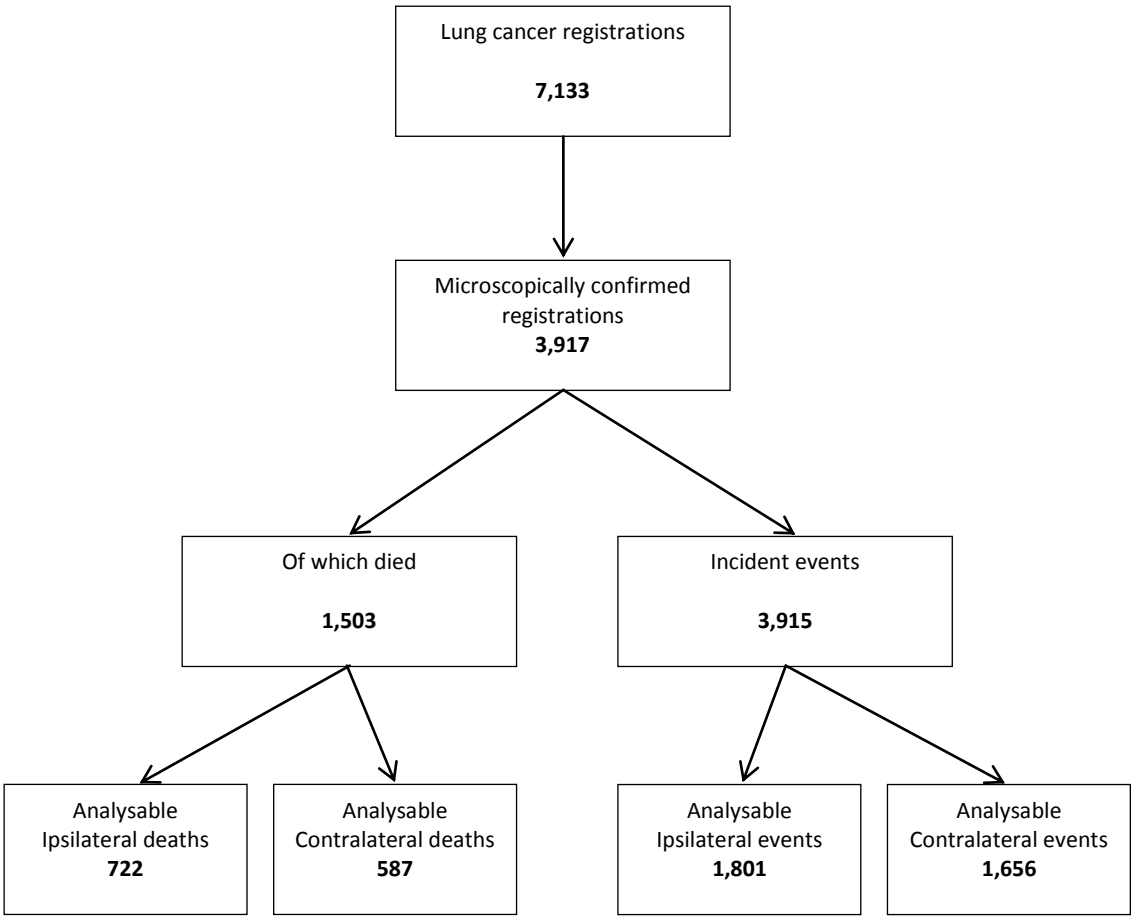


Figure 6-1: Flowchart of selection of microscopically confirmed lung cancers.

6.3.1 Characteristics of the study population

A total of 1,608,812 women diagnosed with breast cancer in 18 countries were included in this study (Table 6-1). Fifty percent were recorded as having received radiotherapy. 3,457 of the women were known to have experienced microscopically confirmed lung cancer, of which 1,309 died.

	Number of women	Percent irradiated	Lung cancer Events	Deaths
Calendar year of diagnosis				
1935-79	167,147	49	286	75
1980-89	279,245	42	659	319
1990-99	504,823	50	971	435
2000+	657,597	55	1,541	480
Age at diagnosis				
<50	439,294	53	609	205
50 – 59	431,457	54	920	323
60 – 69	420,494	51	1,145	466
70 – 79	317,563	41	783	315
Country				
Australia	46,993	58	175	96
Austria	6,011	59	11	3
Brazil	507	66	1	0
Canada	50,634	59	414	239
Denmark	57,663	49	391	162
Estonia	11,043	45	28	0
France	6,017	74	12	5
Germany	236,846	57	653	113
Iceland	960	96	6	2
Ireland	13,594	45	35	14
Israel	4,827	31	21	1
Italy	39,188	52	35	8
Japan	1,333	56	11	8
Slovakia	28,139	65	68	13
Slovenia	8,863	42	34	10
Switzerland	802	79	1	1
UK	343,984	54	373	228
USA	751,408	45	1,188	386
Total	**1,608,812**	**50**	**3,457**	**1,309**

Table 6-1: Patient characteristics of lung cancer study.

6.3.2 Mortality from lung cancer

A univariable analysis found a significant 43% ipsilateral excess among irradiated women, compared to a non-significant 6% ipsilateral excess in unirradiated women (Figure 6-2). These estimates were heterogeneous (2p=0.008) providing a strong argument for a radiation-related difference.

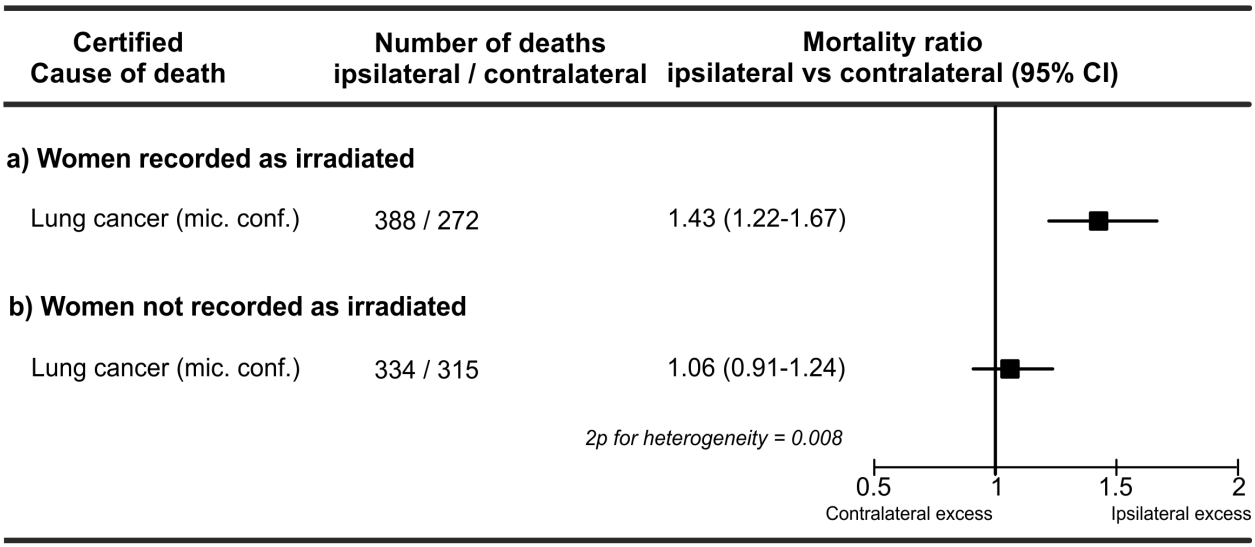


Figure 6-2: Microscopically confirmed lung cancer mortality ratio, ipsilateral versus contralateral, subdivided by radiotherapy status calculated using a univariable model.

In order to remove dependence on a baseline, a multivariable model including time since diagnosis, age, calendar year, and country of diagnosis was used. The estimates provided from this model were adjusted using a person-years weighted average across all of the levels of age, country, calendar year and time since diagnosis. As shown in Figure 6-3, among women who were recorded as having received radiotherapy, the lung cancer mortality ratio for ipsilateral versus contralateral lung cancer was 1.65 (95% CI 1.30-2.21). For unirradiated women, there was no significant ipsilateral excess in lung cancer deaths (1.26 95% CI 0.96-1.65).

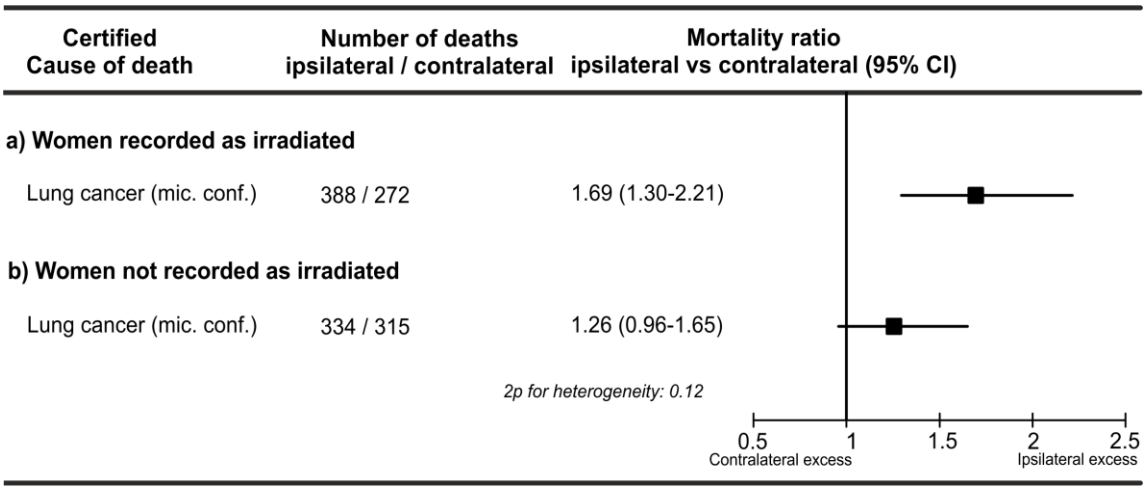


Figure 6-3: Microscopically confirmed lung cancer mortality ratios, ipsilateral versus contralateral, subdivided by radiotherapy status and calculated using a multivariable model and additional person-years weighting.

Using univariable models with a baseline group of 0-4 years since diagnosis, <40 years old, diagnosed during 1953 to 1969 in the UK (Figure 6-4), significant heterogeneity was found by country (2p=0.02), and a significant linear trend was found by years since diagnosis, age (2p=0.09) and calendar year of diagnosis (2p=0.003).

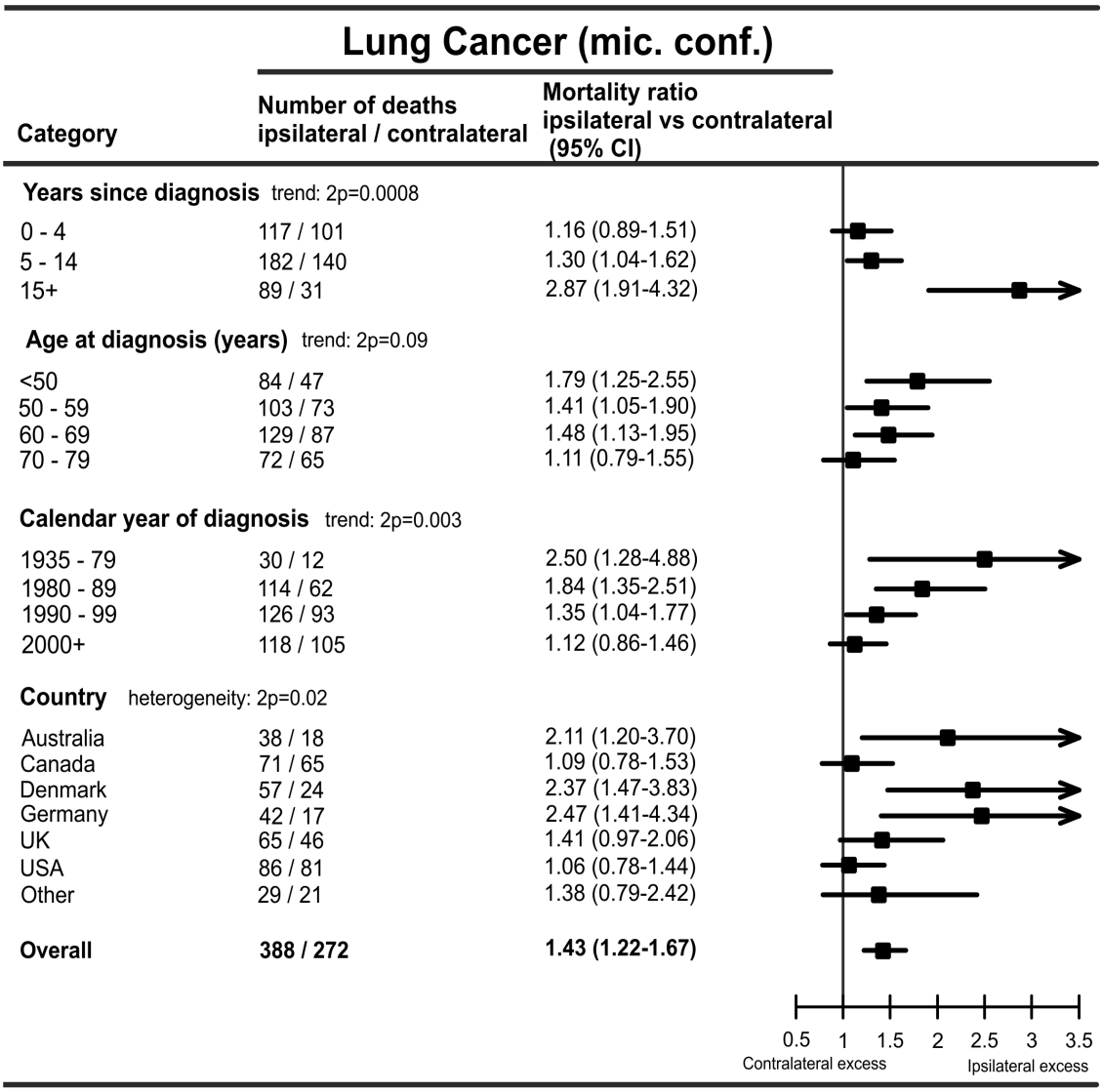


Figure 6-4: Microscopically confirmed lung cancer mortality ratio, ipsilateral versus contralateral, in irradiated women estimated using univariable model subdivided by years since diagnosis, age, calendar year and country of treatment.

This analysis was repeated using a multivariable model and additional person-years weighting (Figure 6-5). The proportional increase in the mortality ratio, ipsilateral versus contralateral, was greatest at 15+ years after irradiation (2.75 95% CI 1.74-4.35) (Figure 6-5). This trend of mortality ratios across time since diagnosis reached statistical significance (2p=0.05). No significant trend was found by age at diagnosis (2p=0.51) or calendar year of diagnosis (2p=0.58). However, the mortality ratios by calendar period of diagnosis were suggestive of a decreasing trend. Australia, Denmark and Germany all had a significant ipsilateral lung cancer excess, yet the heterogeneity across the countries did not reach statistical significant (2p=0.31).

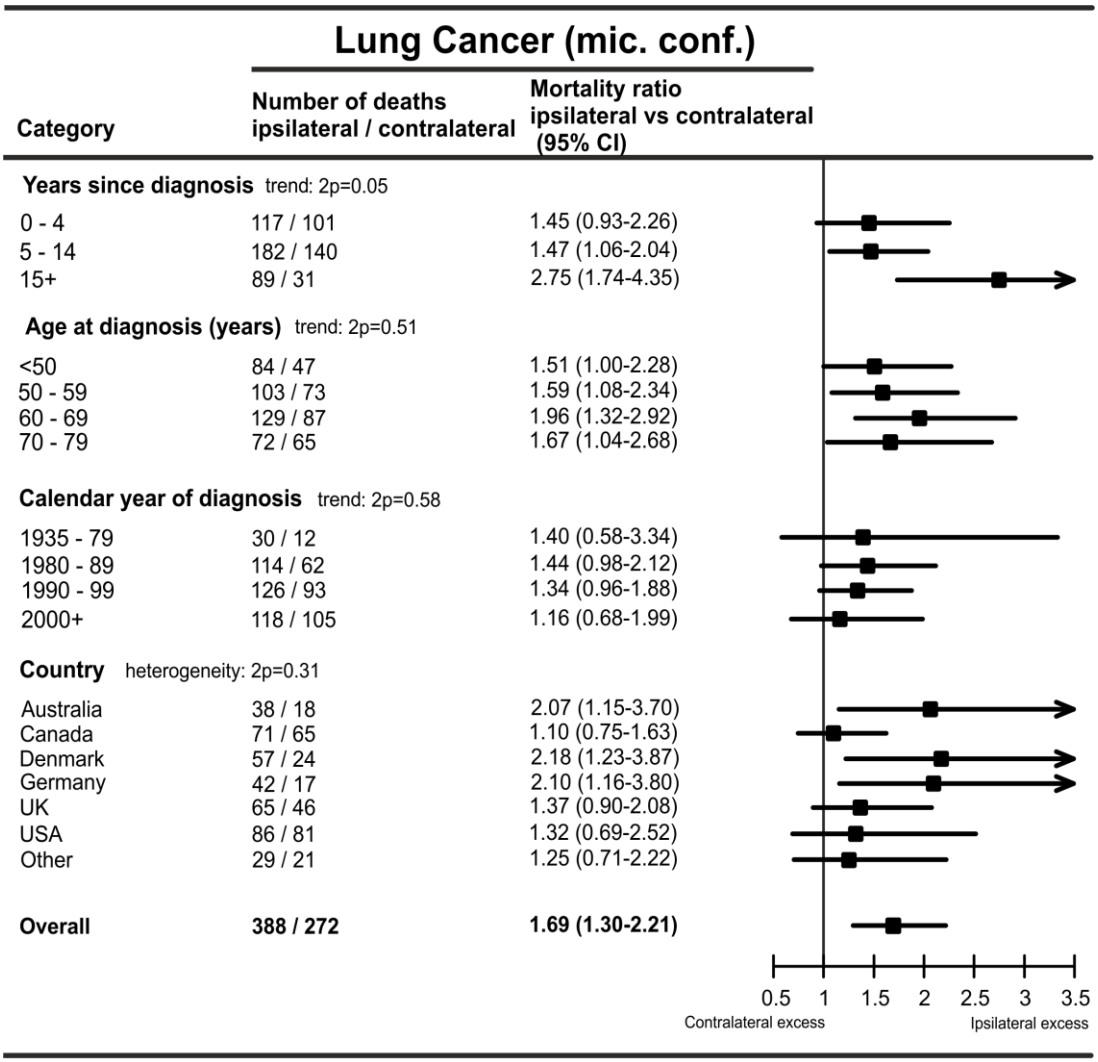


Figure 6-5: Microscopically confirmed lung cancer mortality ratio, ipsilateral versus contralateral, in irradiated women subdivided by years since diagnosis, age, calendar year and country of treatment calculated using a multivariable model and additional person-years weighting.

The lack of significant linear trend by age and calendar year of diagnosis in Figure 6-5 was surprising, and it was hypothesised that the highly significant increasing trend by years since diagnosis in Figure 6-4 might have cancelled out the other trends in the person-years weighted average. To investigate this, the multivariable analysis was repeated, but without including years since diagnosis, see Figure 6-6. The decreasing linear trend by calendar year of diagnosis was significant (2p=0.04). However, there was no significant trend by age at diagnosis, and no significant heterogeneity by country of diagnosis.

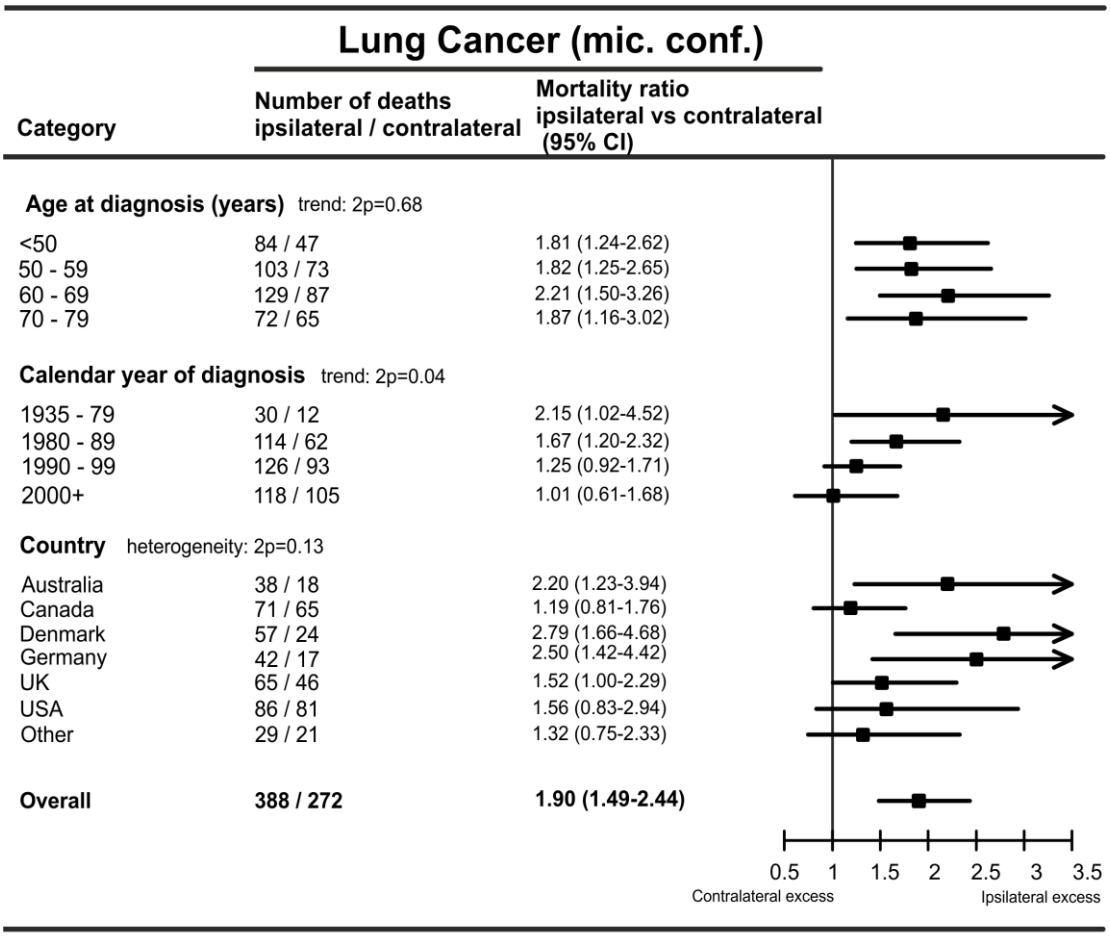


Figure 6-6: Microscopically confirmed lung cancer mortality ratio, ipsilateral versus contralateral, in irradiated women subdivided by age, calendar year and country of treatment calculated using a multivariable model and additional person-years weighting.

In order to directly compare the estimates for calendar period, Figure 6-7 shows the mortality ratios, ipsilateral versus contralateral, subdivided by calendar year of diagnosis, calculated using three models: univariable model; multivariable model with calendar year, age, country and time since diagnosis; multivariable model with calendar year, age and country of diagnosis. This clearly shows that the significant decreasing trend found using a univariable model is cancelled out by inclusion of years since diagnosis in the multivariable model.

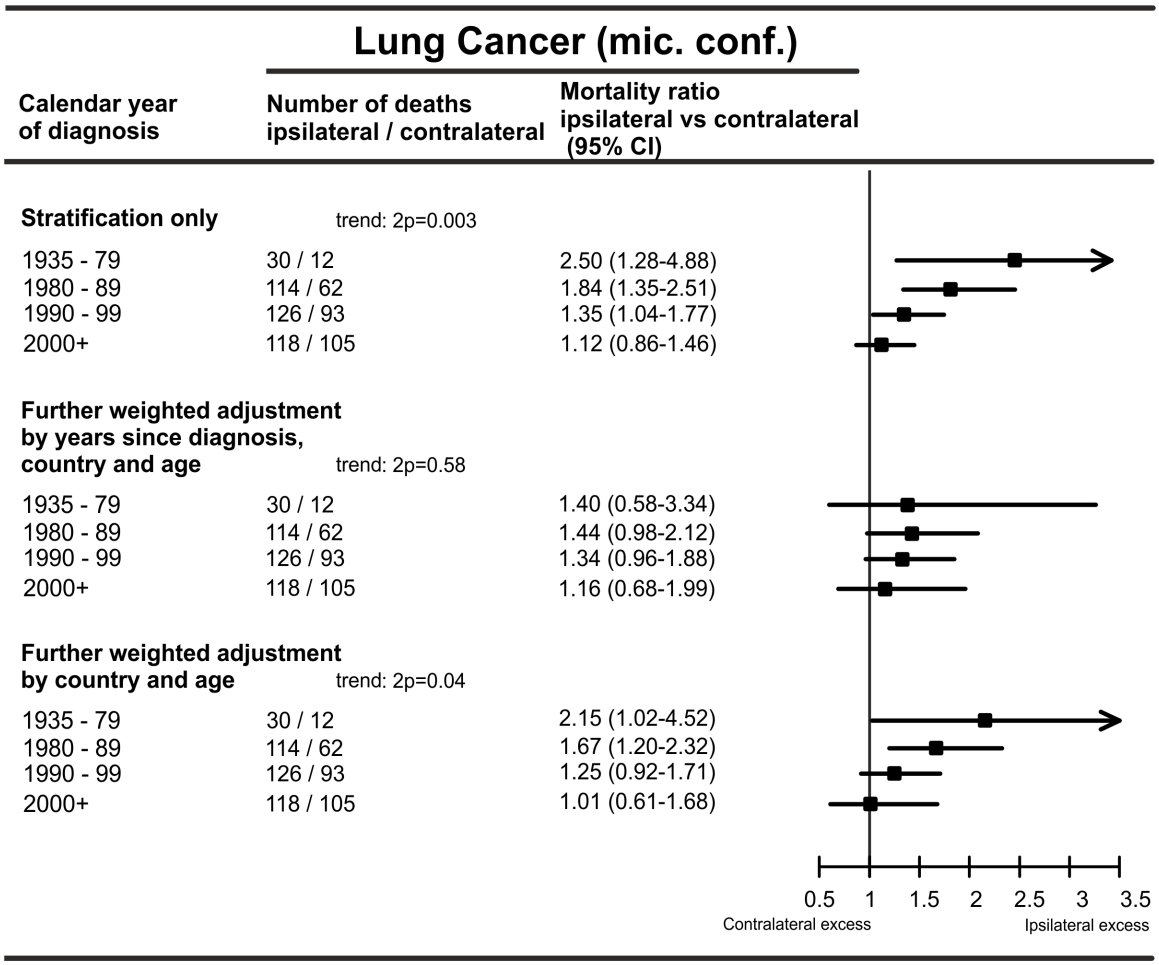


Figure 6-7: Microscopically confirmed lung cancer mortality ratio, ipsilateral versus contralateral, in irradiated women subdivided by calendar year of diagnosis calculated using three methods: a univariable model; a multivariable model with calendar year, age, country and time since diagnosis; and a multivariable model with calendar year, age and country of diagnosis.

6.3.3 Cumulative mortality of lung cancer

The cumulative mortality risk was calculated for microscopically confirmed lung cancer for an absolute measure (Figure 6-8). The reference population used was the most recent values available at analysis (2010) for the 15 westernmost countries of the European Union. This reference population represented the irradiated women diagnosed with subsequent contralateral lung cancer. It is important to note that these reference rates were for all certified lung cancer deaths, and not only microscopically confirmed cases. Therefore the cumulative mortality of this reference population may be an overestimation, but the relative values are accurate. The relative risk ratios for each age group were applied to the cumulative mortality of the reference

population. In order to account for the variation with time since diagnosis, the relative ratios used were age- and follow-up period specific. For women diagnosed with breast cancer aged 45, 55 and 65 and treated with radiotherapy, the cumulative mortality by age 80 of ipsilateral lung cancer did not exceed 4%. The specific estimates that produced the cumulative mortality graphs are shown in Appendix F. The absolute difference between ipsilateral and contralateral lung cancer in cumulative mortality by age 80 was greatest for women irradiated for breast cancer at age 55, with an absolute difference of 2%. The absolute difference was 1.63% and 1.41% by age 80 for women irradiated at age 45 and 65, respectively. For women irradiated for breast cancer age 45 years, the cumulative mortality increased gradually until age 80. In contrast, among women irradiated for breast cancer age 65, the cumulative mortality of ipsilateral lung cancer sharply increased for ten years, and then began to level off aged 75 years.

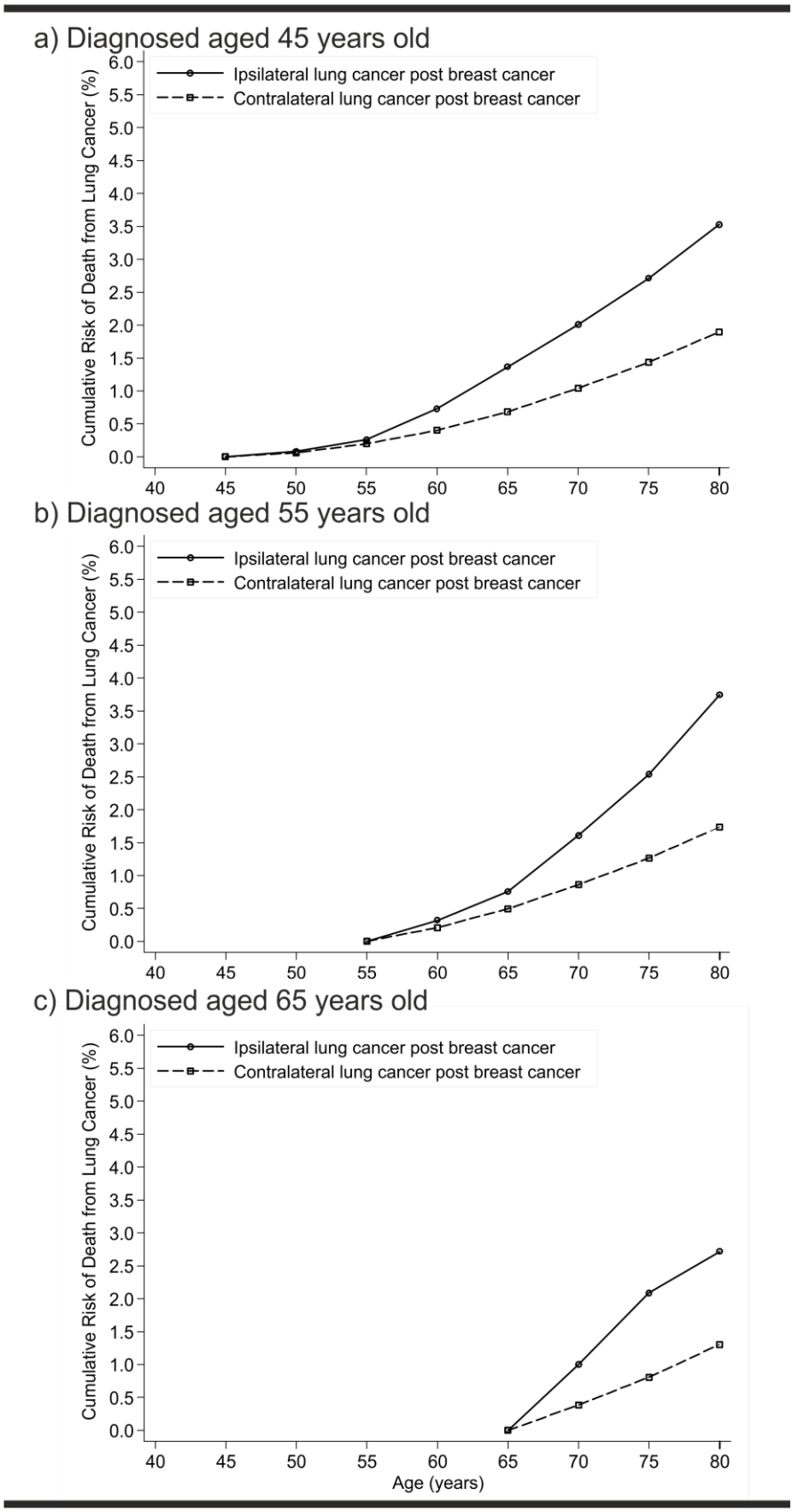


Figure 6-8: Cumulative mortality risk (%) of microscopically confirmed lung cancer in irradiated women subdivided by age at cancer diagnosis.

6.3.4 Variation in lung cancer mortality by treatment and tumour characteristics

Among women recorded to have received radiotherapy, the lung cancer mortality ratio, ipsilateral versus contralateral, was 2.33 (95% CI 1.40-3.89) for women who also received chemotherapy, and 1.44 (95% CI 1.16-1.79) for women who did not receive chemotherapy (Table 6-2). This difference was borderline significant (2p=0.08). The lung cancer mortality ratio was also greater among right-sided breast cancer patients (1.72 95% CI 1.36-2.16) than among left-sided breast cancer patients (1.21 95% CI 0.98-1.50). This difference was significant (2p=0.03). No heterogeneity existed between known categories of hormonal therapy, stage of breast cancer, surgery type or race in irradiated women.

		Deaths		Lung cancer mortality ratio (95% CI)	Heterogeneity test *	
		Ipsilateral	Contralateral		χ^2	p-value
Chemo-therapy received	Yes	49	21	2.33 (1.40-3.89)	3.03	0.08
	No	200	139	1.44 (1.16-1.79)		
	Unknown	9	9	1.00 (0.40-2.52)		
	Not recorded †	130	103	1.26 (0.97-1.63)		
Hormonal therapy received	Yes	100	75	1.33 (0.99-1.80)	1.48	0.22
	No	147	86	1.71 (1.31-2.23)		
	Unknown	9	7	1.29 (0.48-3.45)		
	Not recorded	132	104	1.27 (0.98-1.64)		
Stage of breast cancer	DCIS ‡	10	13	0.77 (0.34-1.75)	3.34	0.19
	Localised	162	122	1.33 (1.05-1.68)		
	Regional	95	57	1.67 (1.20-2.31)		
	Metastatic	2	0	-		
	Unknown	66	43	1.53 (1.05-2.25)		
	Not recorded	52	36	1.44 (0.94-2.21)		
Surgery	BCS §	155	126	1.23 (0.97-1.56)	1.18	0.27
	Mastectomy	62	39	1.59 (1.07-2.37)		
	None	2	4	0.50 (0.09-2.73)		
	Unknown	158	96	1.65 (1.28-2.12)		
	Not recorded	11	7	1.57 (0.61-4.05)		
Race	Asian / Pacific	2	2	1.00 (0.14-7.10)	2.89	0.41
	Black	6	2	3.00 (0.61-14.86)		
	White	164	121	1.36 (1.07-1.71)		
	Other	5	1	5.00 (0.58-42.80)		
	Unknown	37	24	1.54 (0.92-2.58)		
	Not recorded	174	122	1.43 (1.13-1.80)		
Laterality	Left-sided	189	156	1.21 (0.98-1.50)	4.77	0.03
	Right-sided	199	116	1.72 (1.36-2.16)		

* Between known categories
† Data not provided by registry, including the period before common use of therapy
‡ Ductal carcinoma in situ
§ Breast conserving surgery

Table 6-2: Microscopically confirmed lung cancer mortality ratio, ipsilateral versus contralateral, in irradiated women subdivided by chemotherapy and hormonal therapy receipt, stage of breast cancer, surgery type, race and laterality of breast cancer.

6.3.5 Incidence of lung cancer

Using a univariable model, the incidence ratio, ipsilateral versus contralateral, was 1.15 (95% CI 1.05-1.26) and 1.02 (95% CI 0.93-1.13) for irradiated and unirradiated women, respectively (Figure 6-9). These estimates were borderline heterogeneous (2p=0.08).

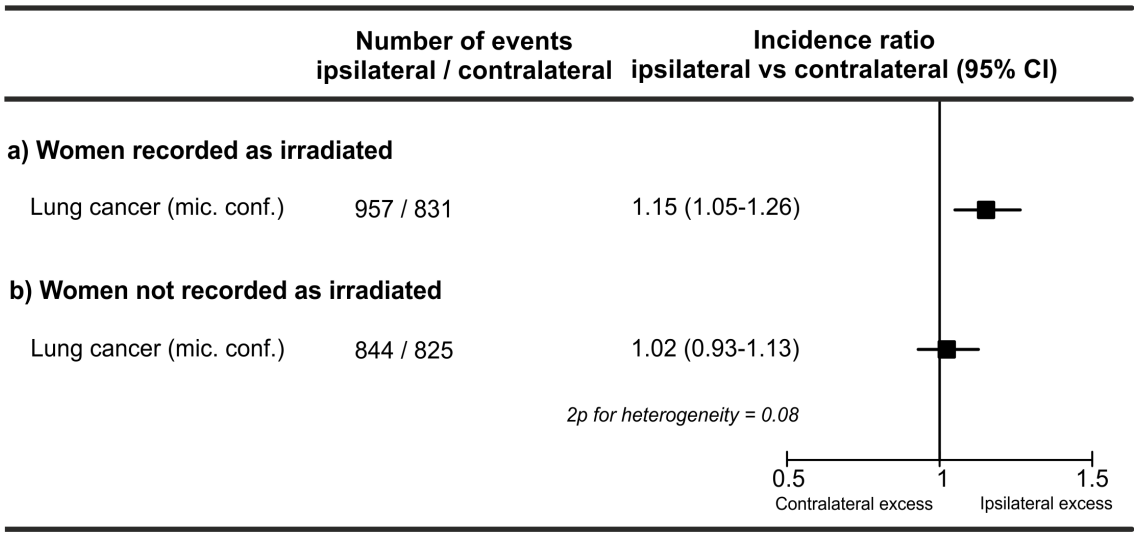


Figure 6-9: Microscopically confirmed lung cancer incidence ratio, ipsilateral versus contralateral, subdivided by radiotherapy status and calculated using a univariable model.

After an additional person-years weighted average (based on a multivariable model) was applied, the incidence ratio was 1.16 (95% CI 1.01-1.34) and 1.03 (95% CI 0.89-1.20) for irradiated and unirradiated women, respectively (Figure 6-10). These two incidence ratios were not heterogeneous (2p=0.25).

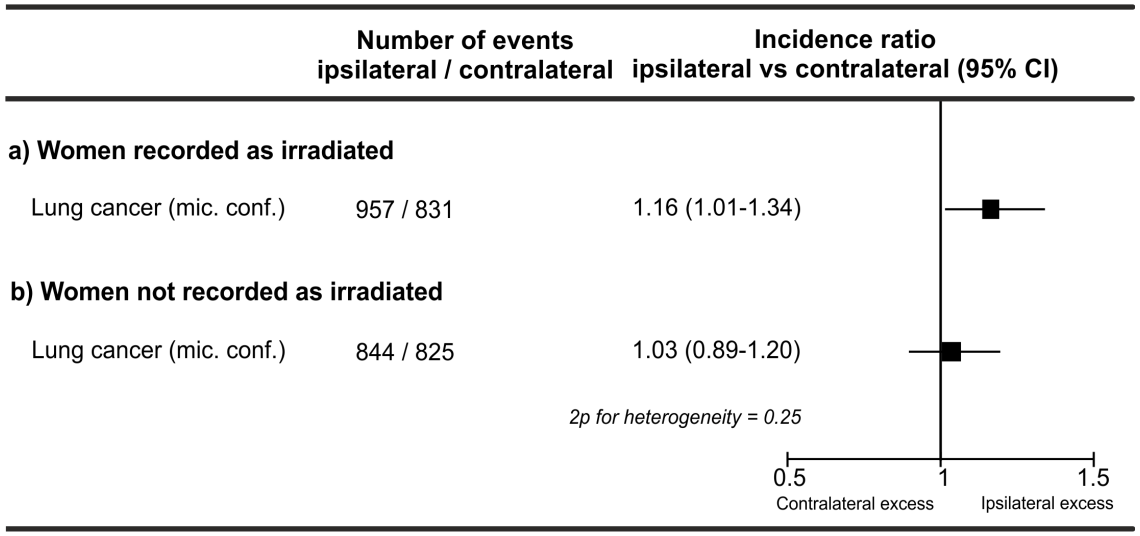


Figure 6-10: Microscopically confirmed lung cancer incidence ratios, ipsilateral versus contralateral, subdivided by radiotherapy status and calculated using a multivariable model and additional person-years weighting.

Among those women recorded to have received radiotherapy, a 2-fold significant excess was seen at 15+ years after diagnosis. Using a univariable model (Figure 6-11), the increasing trend with years since diagnosis was highly significant (2p=0.04). There was also a highly significant decreasing trend with age at diagnosis. The proportional increase was greatest for women diagnosed before age 50, with an incidence ratio, ipsilateral versus contralateral, of 1.34 (95% CI 1.08-1.65). However, there was no significant linear trend (2p=0.08) with calendar year of diagnosis, and no significant heterogeneity (2p=0.37) between countries of diagnosis.

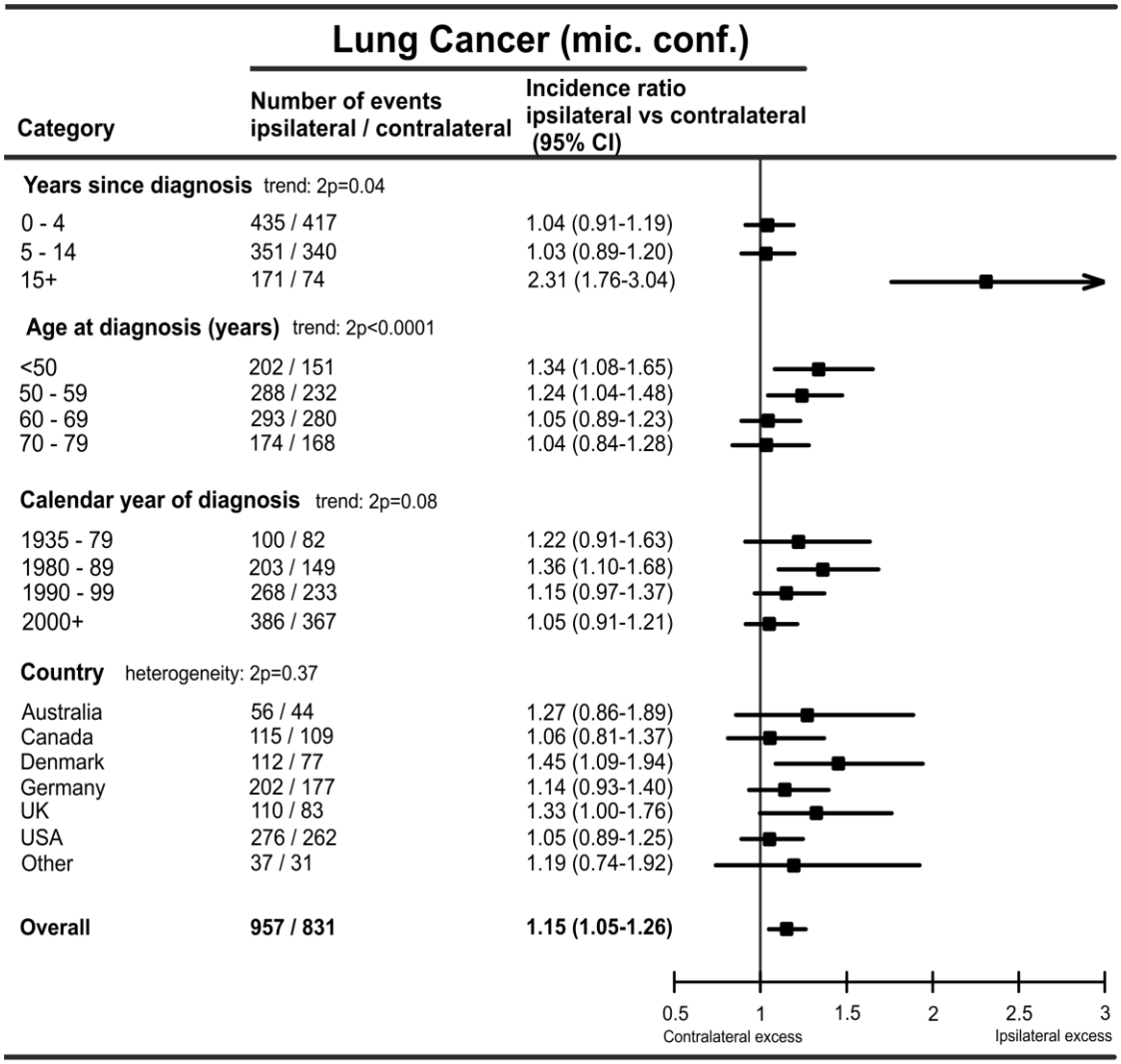


Figure 6-11: Microscopically confirmed lung cancer incidence ratio, ipsilateral versus contralateral, in irradiated women estimated using a univariable model subdivided by years since diagnosis, age, calendar year and country of treatment.

The increasing linear trend with years since diagnosis was still present during analyses using a multivariable model (Figure 6-12). At 15+ years since diagnosis the incidence ratio, ipsilateral versus contralateral, was 2.46 (95% CI 1.82-3.34). No significant linear trend was found by age or calendar year of diagnosis, and no significant heterogeneity was found by country of diagnosis.

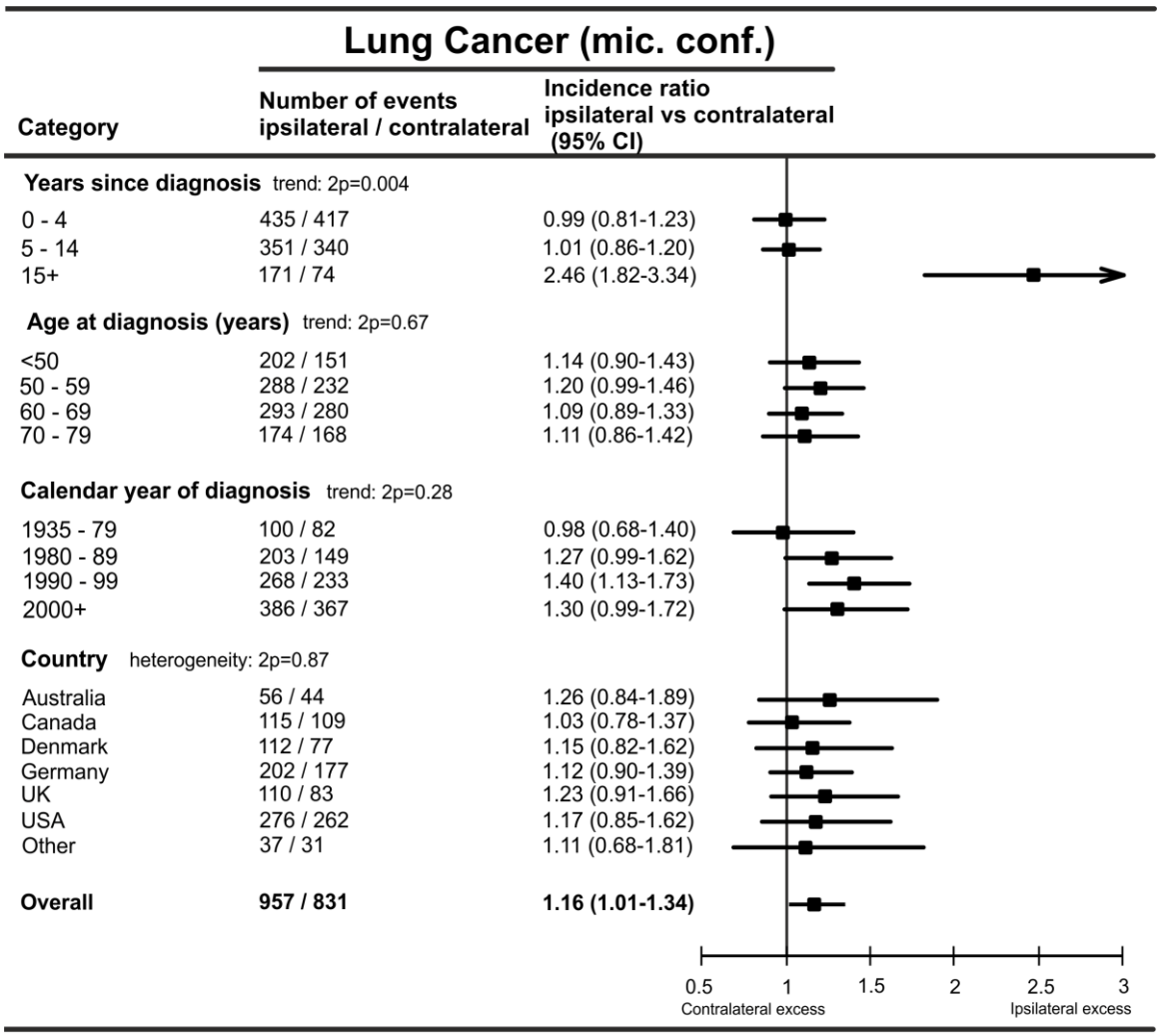


Figure 6-12: Microscopically confirmed lung cancer incidence ratio, ipsilateral versus contralateral, in irradiated women subdivided by years since diagnosis, age, calendar year and country of treatment calculated using a multivariable model and additional person-years weighting.

6.3.6 Variation in lung cancer incidence by treatment and tumour characteristics

Among women recorded to have received radiotherapy, the lung cancer incidence ratio, ipsilateral versus contralateral, was 1.60 (95% CI 0.52-4.89), 2.55 (95% CI 1.27-5.11) and 1.06 (95% CI 0.92-1.21) for Asian/Pacific Islanders, black and white women, respectively. These incidence ratios were heterogeneous (2p=0.03), and despite a low number of events, black women had the highest ipsilateral excess. There was a significant difference between the incidence ratios, ipsilateral versus contralateral, for left-sided breast cancer patients and right-sided breast cancer patients (2p<0.0001). No significant heterogeneity existed between known categories of chemotherapy, hormonal therapy, stage of breast cancer or surgery type in irradiated women.

		Events		Lung cancer incidence ratio	Heterogeneity test *	
		Ipsilateral	Contralateral	(95% CI)	χ^2	p-value
Chemo-therapy received	Yes	124	91	1.36 (1.04-1.79)	0.82	0.36
	No	425	359	1.18 (1.03-1.36)		
	Unknown	16	19	0.84 (0.43-1.64)		
	Not recorded†	392	362	1.08 (0.94-1.25)		
Hormonal therapy received	Yes	196	166	1.18 (0.96-1.45)	0.07	0.79
	No	342	300	1.14 (0.98-1.33)		
	Unknown	15	19	0.79 (0.40-1.55)		
	Not recorded	404	346	1.17 (1.011-1.35)		
Stage of breast cancer	DCIS ‡	33	39	0.85 (0.53-1.35)	1.90	0.39
	Localised	404	341	1.18 (1.03-1.37)		
	Regional	229	204	1.12 (0.93-1.36)		
	Metastatic	4	0	-		
	Unknown	162	134	1.21 (0.96-1.52)		
	Not recorded	117	105	1.11 (0.86-1.45)		
Surgery	Unknown	391	347	1.13 (0.98-1.30)	0.70	0.40
	BCS §	136	106	1.13 (0.98-1.31)		
	Mastectomy	10	11	0.91 (0.39-2.14)		
	None	401	354	1.13 (0.98-1.31)		
	Not recorded	19	13	1.46 (0.72-2.96)		
Race	Asian / Pacific	8	5	1.60 (0.52-4.89)	8.75	0.03
	Black	28	11	2.55 (1.27-5.11)		
	White	421	398	1.06 (0.92-1.21)		
	Other	8	3	2.67 (0.71-10.05)		
	Unknown	61	47	1.30 (0.89-1.90)		
	Not recorded	431	367	1.17 (1.02-1.35)		
Laterality	Left-sided	428	484	0.88 (0.78-1.01)	32.33	<0.0001
	Right-sided	529	347	1.52 (1.33-1.75)		

* Between known categories
† Data not provided by registry, including the period before common use of therapy
‡ Ductal carcinoma in situ
§ Breast conserving surgery

Table 6-3: Microscopically confirmed lung cancer incidence ratio, ipsilateral versus contralateral, in irradiated women subdivided by chemotherapy and hormonal therapy receipt, stage of breast cancer, surgery type, race and laterality of breast cancer.

6.4 Discussion

6.4.1 Lung doses from radiotherapy regimens

Women receive substantial doses to the ipsilateral lung during radiation for breast cancer. A number of studies have estimated the mean dose received by the lung during radiation treatment using a variety of populations (Neugut, Lee et al. 1993, Inskip, Stovall et al. 1994, Prochazka, Hall et al. 2005). The mean dose to the ipsilateral lung was in the range of 13 - 24Gy, compared to a range of 0.4-8.6Gy for the contralateral lung. This study of the COBS cohort covered a wide range of calendar periods, which made it more difficult to estimate the treatment techniques that were used and subsequent lung doses received, as average mean lung dose received by women treated with breast cancer in a given decade depends on the prescribed target dose, the targets irradiated and the techniques used.

Current average mean lung doses are around 7-18Gy for the ipsilateral, and 0.1-3Gy for the contralateral lung (Jagsi, Moran et al. 2010, Schubert, Gondi et al. 2011). Therefore, modern treatment techniques have reduced the incidental radiation exposure that the lungs receive. Despite this, the present study found no reduction in the proportional risk in the more recent calendar periods of diagnosis, for both mortality and incidence. This could suggest that radiation exposure is equally as harmful to the lungs at low doses. It is also possible that follow-up of patients diagnosed more recently has not yet been long enough to detect a trend.

6.4.2 Overall Findings

This study has shown that in women diagnosed with breast cancer in 18 countries during 1935-2008, mortality from subsequent microscopically confirmed lung cancer was significantly increased among irradiated women with ipsilateral tumours compared to women with contralateral tumours, and a significant difference between the rate ratios (ipsilateral versus contralateral) in irradiated and unirradiated women was found ($2p=0.008$) suggesting a

radiation-related effect. In considering incidence, among women recorded to have received radiotherapy, a significant excess was found, but no significant difference (2p=0.08) was present between the incidence ratios for irradiated and unirradiated women, which was unexpected. However, for unirradiated women the ratio was very close to 1 (1.02 95% CI 0.93-1.13).

A number of studies have investigated the risk of radiation-related lung cancer in observational data using a comparison of women treated to those not treated. As discussed in Chapter 3, the conclusions derived from a treatment comparison using observational data are not reliable. There are a variety of factors that influence the selection of a patient to treatment, for example: comorbidities, age, race and geographical location. Therefore, a treatment comparison in observational data is a comparison of the women selected to treatment rather than the treatment effect. As the lungs are a paired organ positioned behind the breasts, a comparison of ipsilateral versus contralateral lung cancer is equivalent to a comparison of higher versus lower radiation dose. These results are reliable and have been shown to be in agreement with randomised evidence, thus only studies to use this comparison will be discussed here.

6.4.3 Mortality from radiation-related lung cancer

The present study found a significant 65% excess of ipsilateral microscopically confirmed lung cancer deaths, compared to contralateral deaths using a univariable model. This means that women diagnosed with breast cancer and treated with radiotherapy are 65% more likely to be die from ipsilateral compared to contralateral lung cancer. A radiation-related effect was suggested by analyses using a univariable model, with 2p of difference between the rate ratios subdivided by radiotherapy status of 0.0008. This was in agreement with randomised evidence (Early Breast Cancer Trialists' Collaborative Group 2005) which found a rate ratio of fatal lung cancer events, irradiated versus unirradiated women, of 1.78 (SE: 0.22, 2p=0.0004). However, when additional person-years weighting was applied, the difference between the irradiated and unirradiated estimates was no longer heterogeneous (2p: 0.12). This may be explained by the wider

confidence intervals found by the multivariable model (1.69 95% CI 1.30-2.21 for RT+ women and 1.26 95% CI 0.96-1.65 for RT- women). Univariable analyses of time since diagnosis, age, calendar year and country of diagnosis found significant heterogeneity across the levels of these four factors. Thus, a person-years weighted average of these four factors would introduce more variation resulting in wider confidence intervals.

Only two studies have focused on the risk of lung cancer mortality associated with radiotherapy for breast cancer using observational data using a comparison of ipsilateral and contralateral lung cancer (Darby, McGale et al. 2005, Henson, McGale et al. 2013). The most recent study was an updated version of the paper published in 2005, and used a more recent version of the public-use SEER registry data. Both papers used a comparison of ipsilateral versus contralateral microscopically confirmed lung tumours among breast cancer patients. The diagnosis period was 1973-2001 (Darby, McGale et al. 2005) and then an update up to 2008 (Henson, McGale et al. 2013). No excess was found in unirradiated women, but a significant mortality excess among ipsilateral tumours was found in women recorded to have received radiotherapy. The lung cancer mortality ratio, ipsilateral versus contralateral, was 1.41 (95% CI 1.19-1.70) and 1.30 (95% CI 1.16-1.45) for the two studies, respectively. This was in agreement with the overall estimate of lung cancer mortality in this population, which was to be expected as SEER contributed information to the present study.

6.4.4 Incidence of radiation-related lung cancer

Unexpectedly, this study found no significant difference between the estimates in irradiated and unirradiated women in the incidence, ipsilateral versus contralateral, of lung cancer. The overall lung cancer incidence ratio, ipsilateral versus contralateral, in irradiated women was 1.15 (95% CI 1.05-1.26) using a univariable model, and 1.16 (95% CI 1.01-1.34) using a multivariable model. This means that there was a significant excess among ipsilateral lung cancer events as compared to contralateral lung cancer in irradiated women, which was

expected. The meta-analysis of randomised controlled trials of early breast cancer found a significant incidence of lung cancer events in the irradiated group (2p=0.0007) with a rate ratio of 1.61 (SE: 0.18) (Early Breast Cancer Trialists' Collaborative Group 2005). Therefore, the incidence rate found in COBS suggested a lower risk, but was consistent with randomised evidence. However, a heterogeneity test between the incidence ratio for irradiated and unirradiated women found no significant difference, which was not expected, but reassuringly the rate ratio in unirradiated women was very close to 1.

Again, the ipsilateral excess among irradiated women, and lack thereof among unirradiated women, was in agreement with the literature and findings from the mortality analysis presented in the first half of this chapter. However, it was expected that a significant difference would exist between the incidence ratios of the irradiated and unirradiated group, particularly as this was the case in the mortality analyses presented. The risks for radiation-related lung cancer have been shown to vary by certain factors. Variations in the distribution of these factors among the women who contributed to the mortality compared to the incidence analyses may explain the unexpected result. For example, a greater proportion of women had known chemotherapy status in the mortality analysis than those who contributed to the incidence analysis (62% vs 56%). It has been shown that the concurrent use of several chemotherapeutic agents with radiotherapy has increased the risk of radiation-related lung injury (Merril 2014), which was also suggested in the mortality analyses presented in Table 6-2. Thus, the women with unknown chemotherapy status in the mortality analysis may actually have received chemotherapy, but the women in the incidence analysis may not have received chemotherapy, contributing to the difference in the overall findings.

It was not possible to distinguish between radiation-related lung cancers or otherwise or to control for patient characteristics and genetics that may have predisposed women to lung cancer but that were not recorded in the COBS cohort. This may be a partial explanation, as some

of the incidence of lung cancer among this COBS population may have been due to other causes than radiotherapy. For instance, the mean time of lung cancer incidence was shorter than the mean time to lung cancer death, with 6.5 and 8.1 years respectively. Section 6.4.5 discusses the latency period shown to exist in radiation-related lung cancer, which was usually of at least a decade. Therefore, the shorter mean time to lung cancer incidence may suggest that a proportion of the incident lung cancer cases may be due to non-radiation-related causes. Consider the time period 15+ years. The incidence ratio (using the univariable model) for women recorded to have received radiotherapy was 2.31 (95% CI 1.76-3.04, see Figure 6-11) and for women not recorded to have received radiotherapy was 1.18 (95% CI 0.90-1.56), where 2p for difference was 0.0008. Therefore, suggesting a radiation-related effect in the second decade since treatment and this was in agreement with the literature on the latency period of radiation-related lung cancer. When all time periods were considered together the radiation-related effect was not suggested, but this may be due to the fact that the large proportion (48%) of events occurred in the first five years, and so the smaller incidence ratio found in the earlier time periods would have the greatest influence on the overall estimate.

Three papers investigated the incidence of lung cancer using a comparison of ipsilateral and contralateral lung tumours (Neugut, Lee et al. 1993, Prochazka, Granath et al. 2002, Prochazka, Hall et al. 2005). Prochazka published two studies using the Swedish Cancer Registry data. The most recent study took a case-only approach, in which every woman contributed a pair of lungs, allowing for a comparison of concordant versus discordant lung cancer. An overall excess of concordant lung cancer was found, with an estimate of 2.04 (95% CI 1.24-3.36). This was substantially higher than the result of the present study. The earlier Prochazka paper, with an average follow-up of 12.2 years did not find an overall ipsilateral excess. However, the incidence ratio reached statistical significance in the second decade of follow-up (2.0, 95% CI 1.3-3.0). In addition, the authors investigated the effect of both smoking and

radiotherapy on lung cancer risk in women with previous breast cancer (Prochazka, Granath et al. 2002) using a comparison to the population. It was found that the birth cohorts with a higher smoking prevalence also had a higher risk of lung cancer. An ipsilateral lung cancer excess was found 10+ years after diagnosis, but explicit analyses were not performed on the interaction between smoking and radiotherapy status. Analyses of women diagnosed during 1973-86 in the SEER data (Neugut, Lee et al. 1993) found a non-significant excess of ipsilateral events, which became borderline significant after ten years. Variations in the incidence ratios observed between the studies presumably reflect differences between the populations, in terms of patient and treatment characteristics. The distribution of patients across the era of diagnosis and age range, the treatment dose and technique, and the length of follow-up could all influence the magnitude of the radiation-related lung cancer risk.

As mentioned in Chapter 1, a study using the SEER cancer registry data found an increased risk of lung cancer among ER negative patients (Schonfeld, Curtis et al. 2012). This was considered to be a hypothesis generating result. In this COBS study, no difference was found in the risk of lung cancer among ipsilateral and contralateral tumour patients, regardless of radiotherapy status (data not shown). Nalbantov and colleagues also found that cardiac comorbidity increased the risk of radiation-related lung cancer (Nalbantov, Kietselaer et al. 2013). This was not confirmed by the present study, which found no significant heterogeneity in the lung cancer risk by prior heart disease (data not shown).

6.4.5 Latency period of radiation-related lung cancer

An increasing trend was apparent with continued follow-up in the present study. The trend was highly significant for both events (2p=0.04) and deaths (2p=0.0008) in the univariable model, and was confirmed in the multivariable model among the lung cancer events (2p=0.004), but not deaths (2p=0.30). The greatest proportional risk was evident in the second decade since treatment, with an almost tripling of risk for both mortality and incidence of lung cancer. This

was in agreement with other studies, which found lung cancer to have a long latency, with much less hazard during the first decade (Neugut, Lee et al. 1993, Inskip, Stovall et al. 1994, Travis 1995, Prochazka, Granath et al. 2002, Darby, McGale et al. 2005, Prochazka, Hall et al. 2005, Brown, Chen et al. 2007, Henson, McGale et al. 2013).

6.4.6 Treatment effects other than radiotherapy and effect of laterality on lung cancer risk

Chemotherapy receipt was not recorded for all women included in this study, but the ipsilateral proportional excess was greater in women who received both chemotherapy and radiotherapy than in patients who only received radiotherapy. This difference was borderline significant for the mortality analysis (2p=0.08). One study with only 5.2 years of follow-up found no combined effect of radiotherapy and chemotherapy in women treated during 1970-81 (Lavey, Eby et al. 1990). A retrospective review of women enrolled on five randomised trials who all received chemotherapy also found low rates of radiotherapy associated lung complications (Woodward, Strom et al. 2003). Polychemotherapy has been shown to increase the risk of lung cancer events, both fatal and non-fatal, in meta-analysis of 144,939 women and 4,675 deaths in 194 randomised trials (Early Breast Cancer Trialists' Collaborative Group 2005). The rate ratio, polychemotherapy versus not, was 1.35 (95% CI 0.73-2.49) for fatal lung cancer events and 1.26 (95% CI 0.82-1.95) for lung cancer incidence. This analysis was based on 30 lung cancer deaths and 57 lung cancer events in women treated with polychemotherapy, and so the statistical power of the analysis was limited by these low numbers. This suggests that there was the potential for an interaction, but it will need to be replicated elsewhere before any conclusions are drawn.

Other studies have found that the radiation-related lung cancer risks are higher after mastectomy than after breast conserving surgery (Obedian, Fischer et al. 2000, Kaufman, Jacobson et al. 2008). This was also shown in the context of a randomised trial (Deutsch, Land et al. 2003). It has been suggested that this may be a reflection on the differing volumes of normal

tissue that remain in the treatment fields after the two types of surgery (Travis, Ng et al. 2012). Patients who undergo a mastectomy often have more advanced disease, and if they are selected to receive radiotherapy are more likely to receive irradiation to nodal areas, thus adding to the total lung-dose volume. The present study did not find any significant differences in the risks of ipsilateral lung cancer among irradiated patients, for either mortality or incidence. There was a greater excess of ipsilateral lung cancer deaths after mastectomy than breast conserving surgery, but this difference in mortality ratios was not statistically significant.

This study suggested that the ipsilateral excess was greater among irradiated women with right-sided breast cancer than among irradiated women with left-sided breast cancer. This may be due to the fact that there is a higher volume exposed to radiation in the right lung, as the left lung is shielded by the heart. It is also interesting to note that the majority of lung cancers are found in the airways and not in the peripheral lung, particularly among cases attributed to smoking. Most treatment regimens however, deliver low doses to the airways, with the highest dose delivered to the anterior of the lung, and the bottom portion. This is further evidence that the cases investigated in this chapter could be related to radiotherapy, particularly among right-sided breast cancer patients, and further research is needed on this interaction. Also, an ipsilateral excess was also found among right-sided breast cancer patients (data not shown). This may indicate the presence of misclassification by laterality. In general, a number of cancers are found in the middle of the lung, and are therefore difficult to classify as left-sided or right-sided.

6.4.7 Strengths of study

The main strengths of this study are the size of the population-based cohort, and its extended follow-up. It is the largest cohort available to investigate the risk of radiation-related lung disease. The cohort size and person-years of follow-up allow investigation over a wide range of ages, follow-up and calendar periods.

Within the literature, there has yet to be many studies to investigate the mortality risk of radiation-related lung cancer, and the majority of studies published have focused on incidence. This is likely due to the low numbers of events, and even lower numbers of deaths, which the COBS study overcame.

The selection effects, and the other biases inherent in observational data, have been minimised through the comparison of ipsilateral and contralateral lung cancer. Breast cancer laterality had little influence on treatment selection, allowing an independent comparison of more or less lung cancer dose.

6.4.8 Limitations of study

As with the other studies presented in this thesis, one potential limitation of this study is the lack of individual treatment information, such as radiotherapy dose, beam type, fractionation schedule. The aim of the COBS collaboration was to collect a small number of data items on a large number of individuals. The treatment information was thus limited to a record of "Yes / No / Unknown" for radiotherapy, chemotherapy and hormonal therapy. This lack of treatment information prevents any detailed analyses on the effect of radiotherapy, or the dose-response relationship.

A second potential limitation of this study was the lack of smoking information. Due to the nature of the laterality comparison, smoking is not likely to be a confounder, but it is a known risk factor for lung cancer which could not be studied. A number of population-based studies have assessed the relative role of both radiotherapy and smoking in the risk of lung cancer after breast cancer treatment (Neugut, Murray et al. 1994, Obedian, Fischer et al. 2000, Ford, Sigurdson et al. 2003, Kaufman, Jacobson et al. 2008), and found a significant interaction between the two. A multiplicative effect was found between smoking and radiotherapy, resulting in a rate ratio (smoking + radiotherapy versus neither) of

9.0 (95% CI 5.08-15.95) (Ford, Sigurdson et al. 2003), 37.6 (95% CI 10.2-139.0) (Kaufman, Jacobson et al. 2008) and 32.7 (95% CI 6.9-154) (Neugut, Murray et al. 1994). Smoking independently increased the lung cancer risk, with persistent smoking associated with the greatest risk, but radiotherapy was not independently associated with lung cancer risk in these populations.

6.4.9 Conclusion

The present study, together with the available literature, may indicate that the carcinogenic radiotherapy effects were limited, but not isolated, to the ipsilateral lung. The radiation-related risk appeared to be mainly present in the second decade following treatment. Thus, long-term monitoring of patients is still of great importance, particularly of those treated in more recent decades.

CHAPTER 7:
CARDIAC MORTALITY RISK AMONG 5-YEAR SURVIVORS OF CANCER DIAGNOSED IN TEENAGERS AND YOUNG ADULTS

7.1 Introduction

Survivors of cancer diagnosed in teenagers or young adults aged 15-39 are internationally acknowledged as an understudied population(Adolescent and Young Adult Oncology Progress Review Group 2006). The majority of published survivorship research has focused on survivors of either specific cancers of mature adulthood, or childhood cancer, with individuals diagnosed with TYA cancers falling into a gap in medical practice and research (Pollock and Birch 2008, Stock, La et al. 2008, Desandes, Lacour et al. 2013). Findings from studies of adult and childhood populations should not be extrapolated to populations of individuals diagnosed with teenage and young adult cancers as they are distinct in terms of tumour distribution, hormonal factors (for example puberty, pregnancy), socio-economic and lifestyle factors (for example mobile population, early career), reluctance or readiness to engage with clinicians and tumour biology (Scottish Intercollegiate Guidelines Network , Skinner, Wallace et al. , Landier, Bhatia et al. 2004, Fernandez and Barr 2006, Bleyer, Barr et al. 2008, National Cancer Research Institute 2008, Croucher, Whelan et al. 2009, Tonorezos and Oeffinger 2011, Coccia, Altman et al. 2012).

Heart disease has been found to be the leading cause of non-neoplastic death among a number of populations of cancer survivors: childhood cancer (Moller, Garwicz et al. 2001, MacArthur, Spinelli et al. 2007, Armstrong, Liu et al. 2009, Mulrooney, Yeazel et al. 2009, Reulen, Winter et al. 2010), Hodgkin lymphoma (Ng, Bernardo et al. 2002, Aleman, van den Belt-Dusebout et al. 2003, Swerdlow, Higgins et al. 2007), and breast cancer. Particularly among individuals diagnosed at a young age (namely childhood cancer survivors) this excess of heart disease is substantially higher as compared to the general population or a control population. Chapters 4 and 5 investigated the heart disease mortality and incidence risk among a large observational cohort of breast cancer survivors. Those chapters demonstrated that the risk of radiation-related heart disease, with respect to both fatal and non-fatal events, was greater among patients who received radiation to the left-sided breast, thereby receiving a greater radiation dose to the heart,

compared to right-sided breast cancer patients. Importantly, this risk was proportionally greater in younger women, and extended into the third decade since treatment. This has previously been demonstrated in meta-analyses of randomised controlled trials (Early Breast Cancer Trialists' Collaborative Group 2005, Early Breast Cancer Trialists' Collaborative Group 2014). Chemotherapy has also been shown to increase the risk of heart disease among breast cancer patients (Early Breast Cancer Trialists' Collaborative Group 2005).

As yet, the risk of heart disease mortality has not been investigated comprehensively within the teenage and young adult cancer population. Only two studies have analysed cause-specific mortality among individuals diagnosed with cancer in the age range of 15-39 (Prasad, Signorello et al. 2012, Kero, Jarvela et al. 2014), but modest cohort sizes (n=9,245 and n=16,769) left a number of questions unanswered, particularly regarding the specific mortality risk from heart disease (as opposed to all cardiovascular diseases combined) and how this risk varies, especially by specific cancer types. Thus, there is clearly a great need for accurate estimates of cardiac risk among TYA cancers, particularly in the long-term. In addition, coronary heart disease is the leading cause of death in the UK; therefore any additional heart disease risk associated with cancer and its treatment could result in a large public health impact. This is particularly relevant among individuals diagnosed with cancer at this young age as they have potentially many decades to live in which they could develop late effects.

7.2 Aim

The objective of this large-scale population-based study was to investigate the long-term risk of heart disease mortality within the population of 5-year survivors of cancer diagnosed in individuals aged 15-39. This cohort is the largest yet in this age range, with over 230,000 5-year survivors and 3 million person-years of follow-up which extended to at least 25 years from cancer diagnosis for 28% of the cohort. This has over 9 times more cancer survivors than the two published studies combined to investigate cause-specific mortality (Prasad, Signorello et al. 2012,

Kero, Jarvela et al. 2014). This chapter aimed to provide a comprehensive overview of cardiac mortality risk for the entire spectrum of first primary tumours diagnosed amongst teenagers and young adults.

7.3 Results

7.3.1 Characteristics of the study population

This cohort consisted of 233,081 5-year survivors of cancer diagnosed aged 15-39, contributing a total of 3,325,102 person-years with an average follow-up of 14.3 years from 5-year survival (19.3 years post cancer diagnosis). By the end of February 2014, 36,868 (16%) of the cohort had died, including 2,327 (6%) where the cause of death was heart disease. The cardiac subtypes were: 1,812 (78%) ischaemic heart disease, 243 (10%) cardiomyopathy and congestive heart failure, 114 (5%) valvular heart disease, 40 (2%) rheumatic valvular heart disease, 24 (1%) arrhythmias, 18 (1%) pericardial heart disease and 76 (3%) deaths due to other cardiac causes. Hodgkin lymphoma survivors experienced the greatest number of cardiac deaths, with 469 out of 2,327 deaths. The majority of the cohort consisted of individuals diagnosed at older ages; with 6% diagnosed with cancer aged 15-19, compared to 40% aged 35-39. Refer to Table 7-1 for a detailed description of the cohort.

	5-year survivors	Total Deaths	Cardiac Deaths	Cardiac deaths over total (%)
Total	**233,081**	**36,868**	**2,327**	**(6.3)**
Gender				
Male	90,970	13,504	1,460	(10.8)
Female	142,111	23,364	867	(3.7)
Age at Cancer Diagnosis				
15-19	13,046	1,453	99	(6.8)
20-24	23,100	2,523	168	(6.7)
25-29	40,347	4,984	328	(6.6)
30-34	63,460	9,843	565	(5.7)
35-39	93,128	18,065	1,167	(6.5)
Calendar Year of Cancer Diagnosis				
1970-79	28,737	10,471	1,082	(10.3)
1980-89	58,756	13,443	852	(6.3)
1990-99	77,642	9,407	327	(3.5)
2000+	67,946	3,547	66	(1.9)
Years since Cancer Diagnosis				
5-9	43,617	15,074	296	(2.0)
10-14	50,433	6,936	332	(4.8)
15-19	41,197	4,650	391	(8.4)
20-24	33,058	3,795	433	(11.4)
25-29	28,017	3,064	393	(12.8)
30+	36,759	3,349	482	(14.4)
First Primary Cancer				
Breast	35,689	10,489	212	(2.0)
NMSC	27,372	1,816	256	(14.1)
Testicular	24,537	2,024	275	(13.6)
Cervix	22,669	2,628	155	(5.9)
Melanoma	22,102	2,298	61	(2.7)
Hodgkin	16,703	3,058	469	(15.3)
CNS tumour	16,609	3,913	140	(3.6)
Other	11,373	2,019	149	(7.4)
NHL	9,811	1,777	130	(7.3)
Thyroid	7,686	408	38	(9.3)
Other GU	7,248	1,234	151	(12.2)
GI	7,057	1,392	74	(5.3)
Ovary	6,383	744	23	(3.1)
STS	5,639	798	49	(6.1)
Leukaemia	4,942	948	37	(3.9)
Head & Neck	3,875	680	53	(7.8)
Bone Tumour	2,210	361	19	(5.3)
Lung	1,176	281	36	(12.8)
Attained Age (Years)				
20-39	31,487	7,433	157	(2.1)
40-49	83,015	15,398	641	(4.2)
50-59	68,369	8,248	769	(9.3)
60+	50,210	5,789	760	(13.1)

Table 7-1: Patient characteristics of the TYACSS.

7.3.2 Mortality risk of all heart disease combined

7.3.2.1 All First Primary Cancers

The SMR (standardised mortality ratio) for all types of heart disease combined was 1.29 (95% confidence interval 1.24, 1.34) and the AER (absolute excess rate) per 10,000 person-years was 1.57 (95% CI 1.29 - 1.85). Deaths from heart disease accounted for 2% of all excess deaths from any cause, and the proportion due to heart disease increased slightly with attained age, contributing 1% among ages 20-39 compared to 3% at age 60+ (Table 7-4).

A highly significant decreasing trend (2p<0.0001) with age at cancer diagnosis was shown for both SMRs and AERs (Table 7-3). The SMR was greatest for individuals diagnosed with cancer aged 15-19 (4.39 95% CI 3.6 - 5.3), and subsequently decreased to 1.10 (1.0, 1.2) aged 35-39. The AERs declined with age, ranging from AER=3.75 (95% CI 2.8 - 4.7) to AER=0.86 (95% CI 0.3 - 1.4) following diagnosis at ages 15 to 19 and ages 35 to 39, respectively, 2p<0.0001.

The SMRs were homogenous across decade of cancer diagnosis, 2p=0.39, with cancer survivors at 1.3-fold increased cardiac mortality compared to the general population (Table 7-3). However, there was evidence of a decline in AERs across the decade of diagnosis (2p<0.0001). Appendix Table G-3 demonstrated an increase in AERs with attained age (2p<0.0001). The AER among those aged 60+ was 8-fold that among those aged 20 to 39. There was a decreasing trend with attained age for the SMRs (2p<0.0001, Table 7-3).

The highest estimate of cardiac mortality, in terms of both SMRs and AERs, was observed after Hodgkin lymphoma (SMR: 3.88 95% CI 3.5 - 4.3), AER: 13.2 (95% CI 11.6 - 14.8)). The first primary cancer groups with a significantly raised SMR for cardiac mortality were: leukaemia (1.91 95% CI 1.4 - 2.6), lung cancer (1.89 95% CI 1.4 - 2.6), non-Hodgkin lymphoma (1.72 95% CI 1.5 - 2.0), CNS tumours (1.46 95% CI 1.2 - 1.7), genitourinary cancers (1.41 95% CI 1.2 - 1.7), cervical cancer (1.30 95% CI 1.1 - 1.5) and breast cancer (1.24 95% CI 1.1 - 1.4). Heterogeneity existed across the cancer types for both SMRs and AERs

(2p<0.0001). Therefore, the cancers with at least 100 cardiac deaths and a significantly elevated SMR were investigated separately. See

Table 7-2 below for a summary of the main findings for all cancers combined, and the specific cancer groups using both the SMR, AER and adjusted results. See Appendix Tables G-2, G-3, G-4 and G-5 for multivariable estimates of the SMRs and AERs. These adjusted estimates were calculated to check that the SMR and AER estimates were robust. See Chapter 2 Section 2.3.2 for an explanation of this methodology.

	All Cancers Combined	Breast	Cervical	HL	CNS	NHL	Other GU
Multiplicative results (SMRs)	**1.29 (1.24-1.34)**	1.24 [1.1,1.4]	1.30 [1.1,1.5]	3.88 [3.5,4.3]	1.46 [1.2,1.7]	1.72 [1.5,2.0]	1.41 [1.2,1.7]
Gender	Females at greater risk compared to general population	N/A	N/A				
Age at cancer diagnosis	Decreasing trend (2p<0.0001) 15-19 year olds at 4-fold the general population		No trend	15-19 year olds at 11-fold the general population	No trend	No trend after adjustment (2p=0.18)	No trend after adjustment (2p=0.28)
Decade of cancer diagnosis	Survivors at 1.3-fold risk of population	Survivors at 1.2-fold risk of population		Survivors at 4-fold risk of population	Survivors at 1.5-fold risk of population	Survivors at 1.7-fold risk of population	Increasing trend (2p=0.0004), with SMR=5 during 2000+
Attained age	Decreasing trend (2p<0.0001) with SMR=2.6 among age 20-39	No trend after adjustment, older ages at 0.4-fold the 20-39 year olds	Borderline decreasing trend after adjustment (2p=0.05)	No trend after adjustment (2p=0.23)	No trend after adjustment (2p=0.36)	No trend after adjustment (2p=0.17)	
Cancer	Heterogeneity (2p<0.0001). HL SMR=3.9 & all other FPTs SMR<2	N/A	N/A	N/A	N/A	N/A	N/A
Absolute results (AERs)	**1.57 (1.29-1.85)**	0.95 [0.3,1.6]	0.97 [0.3,1.6]	13.2 [11.6,14.8]	2.05 [1.0,3.1]	4.23 [2.5,6.0]	3.72 [1.7,5.8]
Gender	Males higher AER with 2 extra deaths per 10,000 pyrs	N/A	N/A		Homogeneity	Homogeneity	Females higher AER with 7 extra deaths per 10,000 pyrs
Age at cancer diagnosis	Decreasing trend (2p<0.0001), with 3.8 extra deaths per 10,000 pyrs among 15-19 year olds	After adjustment significant decreasing trend (2p=0.04)	No trend between estimates for 30-34 and 30-39 year olds after adjustment	Increasing trend (2p=0.006), AER=20 per 10,000 pyrs among 35-39 year olds	No trend	No trend	No trend
Decade of cancer diagnosis	Decreasing trend (2p<0.0001) with AER=2.8 in 1970s and AER 0.4 in 2000+ per 10,000 person-years		Borderline decreasing trend (2p=0.05)		No trend	No trend after adjustment (2p=0.27)	No trend
Attained age	After adjustment for other factors, AERs among individuals age 60+ are 8-fold the AER of 20-39 years (trend 2p<0.0001)	No trend across AERs (2p=0.92)	No trend across AERs (2p=0.24)	Increasing trend across AERs (2p<0.0001) with AER=54 at age 60+	No trend	No trend after adjustment (2p=0.06)	No trend
Cancer	Heterogeneity (2p<0.0001). HL AER = 13, Lung AER = 9, all other AER < 5 per 10,000	N/A	N/A	N/A	N/A	N/A	N/A
Cumulative risk of all heart disease combined by age 70	**Obs: 2.6%** **Exp: 3.0%**	Obs: 1.4% Exp: 1.8%	Obs: 2.0% Exp: 1.7%	Obs: 8.5% Exp: 3.7%	Obs: 2.6% Exp: 3.2%	Obs: 4.2% Exp: 3.8%	Obs: 5.5% Exp: 3.9%
Cardiac proportion of total excess deaths							
Overall	**2%**	0.5%	2%	14%	1%	4%	6%
After age 60	**3%**	2%	4%	27%	6%	13%	11%

Table 7-2: Summary of key findings for all heart disease combined, based on Tables 7-3, 7-5, 7-6, 7-7, and Appendix Tables.

A blank cell indicates that the key message is the same as for all cancers combined.

		All heart disease		
		O	SMR (95% CI)	AER per 10,000 (95% CI)
Total		**2,327**	**1.29 (1.24-1.34)**	**1.57 (1.29-1.85)**
Gender				
	Male	1,460	1.24 [1.2,1.3]	2.18 [1.6,2.8]
	Female	867	1.38 [1.3,1.5]	1.18 [0.9,1.5]
	2p for heterogeneity		*0.02*	*0.002*
Age at cancer diagnosis				
	15-19	99	4.39 [3.6,5.3]	3.75 [2.8,4.7]
	20-24	168	2.38 [2.1,2.8]	2.73 [2.0,3.4]
	25-29	328	1.67 [1.5,1.9]	2.18 [1.6,2.8]
	30-34	565	1.24 [1.1,1.3]	1.21 [0.7,1.7]
	35-39	1,167	1.10 [1.0,1.2]	0.86 [0.3,1.4]
	2p for trend		*<0.0001*	*<0.0001*
Calendar year of cancer diagnosis				
	1970-79	1,082	1.25 [1.2,1.3]	2.82 [2.0,3.7]
	1980-89	852	1.34 [1.3,1.4]	1.81 [1.3,2.3]
	1990-99	327	1.29 [1.2,1.4]	0.75 [0.4,1.1]
	2000+	66	1.27 [1.0,1.6]	0.38 [-0.06,0.8]
	2p for trend		*0.39*	*<0.0001*
Years since cancer diagnosis				
	5-9	296	1.36 [1.2,1.5]	0.72 [0.4,1.0]
	10-14	332	1.07 [1.0,1.2]	0.28 [-0.2,0.7]
	15-19	391	1.07 [1.0,1.2]	0.43 [-0.2,1.1]
	20-24	433	1.10 [1.0,1.2]	0.99 [-0.02,2.0]
	25-29	393	1.08 [1.0,1.2]	1.15 [-0.4,2.7]
	30+	482	1.17 [1.1,1.3]	3.70 [1.4,6.0]
	2p for trend		*0.30*	*0.30*
Attained Age (years)				
	20-39	157	2.64 [2.3,3.1]	1.24 [0.9,1.6]
	40-49	641	1.54 [1.4,1.7]	1.60 [1.2,2.0]
	50-59	769	1.22 [1.1,1.3]	1.70 [1.0,2.4]
	60+	760	1.09 [1.0,1.2]	1.91 [0.3,3.5]
	2p for trend		*<0.0001*	*0.09*

First Primary Cancer					
Breast	212	1.24	[1.1,1.4]	0.95	[0.3,1.6]
NMSC	256	0.82	[0.7,0.9]	-1.45	[-2.2,-0.7]
Testicular	275	0.98	[0.9,1.1]	-0.12	[-1.0,0.8]
Cervix	155	1.30	[1.1,1.5]	0.97	[0.3,1.6]
Melanoma	61	0.51	[0.4,0.7]	-2.05	[-2.6,-1.5]
Hodgkin	469	3.88	[3.5,4.3]	13.2	[11.6,14.8]
CNS tumour	140	1.46	[1.2,1.7]	2.05	[1.0,3.1]
Other	149	1.25	[1.1,1.5]	1.44	[0.3,2.6]
NHL	130	1.72	[1.5,2.0]	4.23	[2.5,6.0]
Thyroid	38	0.95	[0.7,1.3]	-0.18	[-1.3,0.9]
Other GU	151	1.41	[1.2,1.7]	3.72	[1.7,5.8]
GI	74	0.90	[0.7,1.1]	-0.86	[-2.6,0.8]
Ovary	23	0.87	[0.6,1.3]	-0.39	[-1.4,0.6]
STS	49	1.25	[0.9,1.6]	1.22	[-0.5,3.0]
Leukaemia	37	1.91	[1.4,2.6]	3.05	[1.0,5.1]
Head & Neck	53	1.20	[0.9,1.6]	1.59	[-1.0,4.1]
Bone Tumour	19	1.44	[0.9,2.3]	1.75	[-0.8,4.3]
Lung	36	1.89	[1.4,2.6]	9.26	[2.8,15.7]
2p for heterogeneity			*<0.0001*		*<0.0001*

Table 7-3: SMR and AERs subdivided by gender, age at cancer diagnosis, calendar year of cancer diagnosis, years since cancer diagnosis, attained age and first primary cancer for all heart disease combined.

7.3.2.2 Hodgkin lymphoma Survivors

Survivors of Hodgkin lymphoma experienced 14% of all excess deaths due to cardiac causes and the proportion increased substantially with attained age reaching 27% among survivors aged 60+ (see Table 7-4).

	AER (% of all cause) by Attained Age				Total AER (%)
	20-39	**40-49**	**50-59**	**60+**	
			All Cancers Combined [% of cardiac]		
IHD	0.79 [63.7]	1.06 [66.7]	1.13 [66.5]	0.97 [51.1]	1.00 (63.7)
Valvular HD	0.06 [4.8]	0.12 [7.5]	0.37 [21.8]	0.50 [26.3]	0.21 (13.4)
Cardiomyopathy / CHF	0.30 [24.2]	0.25 [15.7]	0.05 [2.9]	-0.004 [-0.2]	0.19 (12.1)
Other HD	0.09 [7.3]	0.16 [10.1]	0.15 [8.8]	0.45 [23.7]	0.17 (10.8)
Cardiac	1.24 (1.4)	1.6 (1.8)	1.7 (2.9)	1.9 (3.2)	1.57 (2.0)
All cause	**86.1**	**91.2**	**59.1**	**59.1**	**79.0**
			Breast Cancer		
Cardiac	1.17 (0.3)	0.72 (0.3)	0.72 (0.5)	2.15 (2.5)	0.95 (0.5)
All cause	**365.1**	**262.2**	**131**	**85.4**	**208.3**
			Cervical Cancer		
Cardiac	0.42 (1.0)	0.69 (1.8)	0.94 (2.7)	2.86 (4.1)	0.97 (2.3)
All cause	**40.4**	**38.9**	**34.9**	**70**	**41.6**
			Hodgkin lymphoma		
Cardiac	3.94 (5.1)	12.3 (16.1)	25.5 (21.0)	54.4 (27.1)	13.2 (14.5)
All cause	**77.7**	**76.5**	**121.3**	**200.8**	**91.1**
			CNS Tumours		
Cardiac	1.58 (0.8)	1.09 (0.7)	3.93 (4.0)	4.84 (5.7)	2.05 (1.3)
All cause	**187.2**	**167.1**	**98.6**	**85.1**	**155.4**
			Non-Hodgkin lymphoma		
Cardiac	1.75 (2.2)	4.51 (3.5)	3.89 (3.7)	13.8 (12.7)	4.23 (3.9)
All cause	**79.5**	**129.1**	**105.3**	**108.3**	**107.7**
			Other GU		
Cardiac	6.66 (13.0)	3.85 (5.1)	0.79 (1.8)	6.53 (10.7)	3.72 (6.2)
All cause	**51.3**	**74.8**	**42.9**	**61.3**	**60.1**

Table 7-4: Proportion of total AER of cardiac deaths, subdivided by attained age and main cancer groups for all heart disease combined.

The cumulative mortality was also greatest for individuals diagnosed with Hodgkin lymphoma at a younger age; by age 55, the cumulative mortality was 6.8% for individuals

diagnosed at 15-19 years compared to 1.9% for 35-39 years (log-rank 2p < 0.0001). The corresponding range expected was 0.7% to 0.9% (Figure 7-1). For all other cancers there was no difference in the cumulative mortality by age at cancer diagnosis with 2p>0.15 (Appendix Figure G-1).

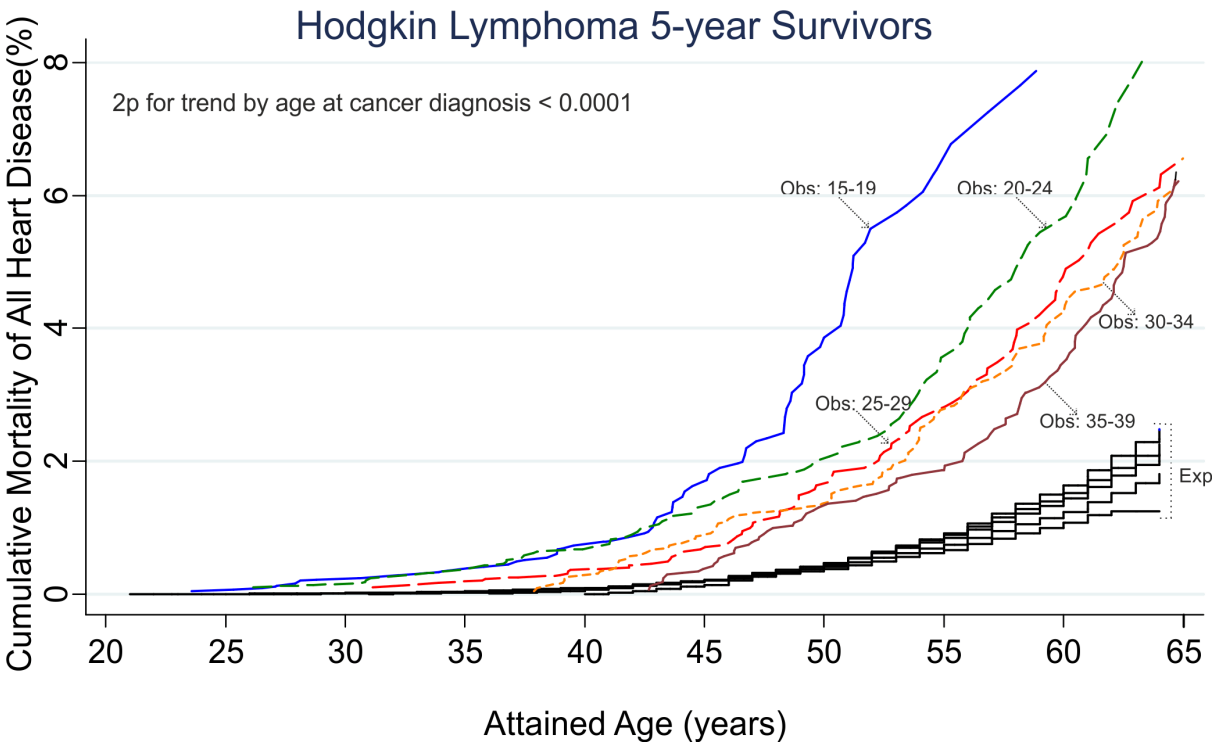


Figure 7-1: Cumulative mortality by attained age of all heart disease combined for Hodgkin lymphoma 5-year survivors, subdivided by age at cancer diagnosis and observed versus expected deaths.

Individuals diagnosed with Hodgkin lymphoma at a young age were at considerable risk, with an SMR of 10.7 (95% CI 8.3 - 13.7) for those diagnosed aged 15-19. Table 7-5 demonstrated an increasing trend in the AERs with attained age (2p<0.0001), and the AER per 10,000 person-years at ages 60+ was 54.4 (95% CI 39.8 - 69.0). However, no trend across attained age was found for SMRs (2p=0.23, Appendix Table G-5).

7.3.2.3 Non-Hodgkin lymphoma Survivors

Table 7-4 demonstrated that among survivors of non-Hodgkin lymphoma, 4% of the total excess deaths were due to heart disease. The proportion of excess deaths due to heart disease increased strongly with attained age, reaching 13% among those aged at least 60.

Among individuals diagnosed with non-Hodgkin lymphoma, survivors were at a 1.7-fold risk of cardiac mortality compared to the general population, which was homogeneous across treatment decade (Table 7-5). After adjustment, no trend was present across the SMRs by age at cancer diagnosis or attained age (Appendix Table G-5). There was also no trend present across AERs after adjustment for all factors.

	Hodgkin lymphoma		Non-Hodgkin lymphoma	
	SMR (95% CI)	**AER per 10,000 (95% CI)**	**SMR (95% CI)**	**AER per 10,000 (95% CI)**
Total	3.88 [3.5,4.3]	13.2 [11.6,14.8]	1.72 [1.5,2.0]	4.23 [2.5,6.0]
Gender				
Male	3.48 [3.1,3.9]	16.8 [14.3,19.2]	1.53 [1.3,1.9]	4.25 [1.8,6.7]
Female	5.91 [4.9,7.1]	8.59 [6.7,10.4]	2.76 [2.0,3.9]	4.21 [2.0,6.5]
2p for het	*<0.0001*	*<0.0001*	0.006	0.98
Age at cancer diagnosis				
15-19	10.7 [8.3,13.7]	11.8 [8.5,15.0]	1.81 [0.6,5.6]	0.97 [-1.5,3.4]
20-24	5.66 [4.6,7.0]	10.4 [7.8,13.1]	2.52 [1.3,4.8]	3.21 [-0.3,6.7]
25-29	3.78 [3.1,4.6]	11.4 [8.4,14.5]	2.24 [1.4,3.5]	4.51 [0.9,8.1]
30-34	3.28 [2.7,4.0]	15.4 [11.2,19.6]	2.17 [1.6,3.0]	7.01 [3.0,11.0]
35-39	2.80 [2.3,3.4]	20.3 [14.6,26.1]	1.36 [1.0,1.8]	3.54 [0.07,7.0]
2p for trend	*<0.0001*	*0.006*	*0.03*	*0.09*
Calendar year of cancer diagnosis				
1970-79	4.35 [3.9,4.9]	27.5 [23.3,31.7]	1.69 [1.3,2.2]	8.40 [2.9,13.9]
1980-89	3.16 [2.7,3.8]	8.99 [6.7,11.3]	1.53 [1.1,2.1]	3.35 [0.4,6.3]
1990-99	3.59 [2.7,4.7]	5.27 [3.2,7.3]	2.28 [1.6,3.3]	4.03 [1.5,6.6]
2000+	5.00 [2.8,8.8]	4.56 [1.3,7.8]	1.33 [0.5,3.5]	0.58 [-1.7,2.9]
2p for trend	*0.08*	*<0.0001*	*0.54*	*0.02*
Years since cancer diagnosis				
5-9	4.51 [3.5,5.8]	5.84 [3.9,7.8]	2.15 [1.4,3.2]	2.84 [0.7,5.0]
10-14	2.29 [1.7,3.1]	3.99 [1.9,6.1]	1.27 [0.8,2.0]	1.24 [-1.4,3.8]
15-19	2.57 [2.0,3.3]	7.99 [4.8,11.2]	1.35 [0.9,2.0]	2.56 [-1.6,6.7]
20-24	3.45 [2.8,4.2]	19.4 [13.8,24.9]	1.43 [1.0,2.2]	4.82 [-1.7,11.4]
25-29	3.37 [2.7,4.2]	27.4 [19.2,35.6]	1.08 [0.7,1.8]	1.32 [-7.7,10.3]
30+	4.28 [3.6,5.1]	54.1 [41.6,66.6]	1.91 [1.3,2.8]	21.2 [4.5,38.0]
2p for trend	*0.04*	*<0.0001*	*0.72*	*0.24*
Attained Age (years)				
20-39	6.14 [4.7,8.0]	3.94 [2.7,5.2]	3.10 [1.7,5.8]	1.75 [0.1,3.3]
40-49	4.33 [3.7,5.1]	12.3 [9.7,14.9]	2.17 [1.6,2.9]	4.51 [2.1,6.9]
50-59	3.55 [3.0,4.2]	25.5 [19.9,31.0]	1.38 [1.0,1.9]	3.89 [-0.6,8.4]
60-79	3.29 [2.7,4.0]	54.4 [39.8,69.0]	1.55 [1.1,2.1]	13.8 [1.3,26.3]
2p for trend	*0.0002*	*<0.0001*	*0.03*	*0.02*

Table 7-5: SMR and AERs subdivided by gender, age at cancer diagnosis, calendar year of cancer diagnosis, years since cancer diagnosis and attained age for all heart disease combined for survivors of Hodgkin lymphoma and Non-Hodgkin lymphoma.

7.3.2.4 Breast Cancer Survivors

Results were similar to the findings of all cancers combined (refer to Table 7-2), except that no trend was present by attained age. Survivors of breast cancer were at a 1.24-fold increased risk of cardiac mortality compared to the general population (Table 7-6). The decreasing trend with age at cancer diagnosis shown for all cancers confirmed in the multivariable model for breast cancer survivors (Appendix Table G-5).

7.3.2.5 Cervical Cancer and Central Nervous System Survivors

There was no significant variation across the SMRs or AERs for either age at cancer diagnosis, calendar year of cancer diagnosis or attained age. See Table 7-6 and Table 7-7 for SMR and AER estimates.

	Breast cancer		Cervical Cancer	
	SMR (95% CI)	AER per 10,000 (95% CI)	SMR (95% CI)	AER per 10,000 (95% CI)
Total	1.24 [1.1,1.4]	0.95 [0.3,1.6]	1.30 [1.1,1.5]	0.97 [0.3,1.6]
Gender				
Male	--	--	--	--
Female	1.24 [1.1,1.4]	0.95 [0.3,1.6]	1.30 [1.1,1.5]	0.97 [0.3,1.6]
2p for het	--	--	--	--
Age at cancer diagnosis				
15-19	28.7 [4.0,203.8]	14.8 [-15.2,44.7]	-	-
20-24	4.09 [1.0,16.3]	2.75 [-2.3,7.8]	-	-
25-29	2.15 [1.2,3.9]	1.72 [-0.2,3.6]	0.90 [0.5,1.6]	-0.15 [-1.0,0.7]
30-34	1.42 [1.1,1.9]	1.08 [-0.02,2.2]	1.51 [1.2,2.0]	1.37 [0.3,2.4]
35-39	1.15 [1.0,1.3]	0.74 [-0.1,1.6]	1.30 [1.1,1.6]	1.45 [0.1,2.8]
2p for trend	*0.004*	*0.09*	*0.69*	*0.04*
Calendar year of cancer diagnosis				
1970-79	1.09 [0.9,1.3]	0.77 [-1.2,2.7]	1.30 [1.0,1.6]	1.97 [0.0,3.9]
1980-89	1.65 [1.3,2.0]	2.35 [1.1,3.6]	1.35 [1.1,1.7]	1.02 [0.04,2.0]
1990-99	1.06 [0.7,1.6]	0.10 [-0.6,0.8]	1.23 [0.8,2.0]	0.32 [-0.5,1.1]
2000+	0.78 [0.3,2.1]	-0.21 [-0.9,0.5]	1.00 [0.2,4.0]	-0.003 [-1.0,1.0]
2p for trend	*0.64*	*0.005*	*0.85*	*0.05*
Years since cancer diagnosis				
5-9	1.19 [0.8,1.8]	0.25 [-0.4,0.9]	1.73 [1.1,2.7]	0.74 [-0.05,1.5]
10-14	0.88 [0.6,1.3]	-0.28 [-1.1,0.6]	0.83 [0.5,1.4]	-0.33 [-1.2,0.5]
15-19	1.19 [0.9,1.6]	0.79 [-0.8,2.4]	1.20 [0.8,1.7]	0.63 [-0.8,2.1]
20-24	1.03 [0.7,1.4]	0.22 [-2.3,2.7]	1.10 [0.8,1.6]	0.55 [-1.5,2.7]
25-29	1.13 [0.8,1.5]	1.53 [-2.7,5.8]	1.19 [0.8,1.7]	1.64 [-1.9,5.2]
30+	1.16 [0.9,1.5]	3.34 [-3.2,9.9]	1.06 [0.8,1.5]	0.82 [-4.5,6.1]
2p for trend	*0.70*	*0.50*	*0.48*	*0.97*
Attained Age (years)				
20-39	3.67 [1.6,8.2]	1.17 [-0.1,2.5]	1.99 [0.8,4.8]	0.42 [-0.3,1.1]
40-49	1.51 [1.1,2.0]	0.72 [0.10,1.3]	1.51 [1.1,2.1]	0.69 [-0.009,1.4]
50-59	1.18 [0.9,1.5]	0.72 [-0.5,1.9]	1.25 [0.9,1.6]	0.94 [-0.4,2.2]
60-79	1.14 [0.9,1.4]	2.15 [-1.2,5.5]	1.23 [1.0,1.6]	2.86 [-0.8,6.5]
2p for trend	*0.04*	*0.92*	*0.25*	*0.24*

Table 7-6: SMR and AERs subdivided by gender, age at cancer diagnosis, calendar year of cancer diagnosis, years since cancer diagnosis and attained age for all heart disease combined for survivors of breast and cervical cancer.

7.3.2.6 Other Genitourinary Cancers Survivors

Other genitourinary cancers consisted of 23.9% kidney tumours, 37.7% bladder tumours, 38.0% other GU tract tumours and 0.4% Wilms tumour. Of interest among survivors of other genitourinary cancers was that both the SMRs and AERs were significantly higher among females

than among males. Females experienced 7 extra deaths per 10,000 person-years compared to the general population (see Table 7-7).

	CNS Tumours				Other GU			
	SMR (95% CI)		AER per 10,000 (95% CI)		SMR (95% CI)		AER per 10,000 (95% CI)	
Total	1.46	[1.2,1.7]	2.05	[1.0,3.1]	1.41	[1.2,1.7]	3.72	[1.7,5.8]
Gender								
Male	1.31	[1.1,1.6]	2.16	[0.3,4.0]	1.08	[0.9,1.3]	1.05	[-2.0,4.1]
Female	1.89	[1.4,2.5]	1.96	[0.8,3.1]	2.58	[2.0,3.3]	6.68	[3.9,9.4]
2p for het		0.04		0.86		*<0.0001*		0.007
Age at cancer diagnosis								
15-19	2.78	[1.4,5.6]	1.72	[-0.1,3.6]	8.88	[2.9,27.5]	13.2	[-3.6,30.1]
20-24	1.80	[1.0,3.3]	1.46	[-0.5,3.4]	2.32	[1.0,5.6]	3.90	[-2.1,9.9]
25-29	1.89	[1.3,2.8]	2.67	[0.4,4.9]	1.58	[0.9,2.8]	2.79	[-1.5,7.1]
30-34	1.11	[0.8,1.6]	0.53	[-1.5,2.6]	1.47	[1.1,2.0]	3.60	[-0.03,7.2]
35-39	1.42	[1.1,1.8]	3.43	[0.7,6.2]	1.31	[1.1,1.6]	3.70	[0.5,6.9]
2p for trend		*0.07*		*0.60*		*0.03*		*0.46*
Calendar year of cancer diagnosis								
1970-79	1.26	[1.0,1.7]	2.44	[-0.9,5.7]	1.14	[0.9,1.4]	2.28	[-2.1,6.7]
1980-89	1.52	[1.2,2.0]	2.44	[0.6,4.3]	1.56	[1.2,2.0]	4.52	[1.2,7.8]
1990-99	1.72	[1.2,2.5]	1.73	[0.2,3.2]	1.83	[1.2,2.9]	3.02	[0.02,6.0]
2000+	1.81	[0.8,4.0]	1.09	[-0.9,3.0]	5.08	[2.6,9.8]	7.90	[1.5,14.3]
2p for trend		*0.15*		*0.33*		*0.0004*		*0.29*
Years since cancer diagnosis								
5-9	1.39	[0.9,2.2]	0.72	[-0.4,1.9]	2.73	[1.9,3.9]	5.74	[2.5,8.9]
10-14	1.65	[1.2,2.4]	2.20	[0.2,4.2]	1.25	[0.8,1.9]	1.51	[-1.7,4.8]
15-19	1.02	[0.7,1.6]	0.11	[-2.3,2.5]	1.05	[0.7,1.6]	0.50	[-3.8,4.8]
20-24	1.14	[0.8,1.7]	1.19	[-2.7,5.0]	0.89	[0.6,1.4]	-1.58	[-7.3,4.1]
25-29	1.29	[0.9,1.9]	3.63	[-2.8,10.1]	1.16	[0.8,1.7]	3.35	[-6.2,12.9]
30+	1.23	[0.8,1.9]	4.15	[-5.3,13.6]	1.11	[0.8,1.6]	3.46	[-8.9,15.8]
2p for trend		*0.44*		*0.42*		*0.005*		*0.07*
Attained Age (years)								
20-39	3.26	[2.0,5.2]	1.58	[0.5,2.7]	7.49	[4.3,13.2]	6.66	[2.3,11.0]
40-49	1.35	[1.0,1.9]	1.09	[-0.3,2.5]	1.93	[1.4,2.6]	3.85	[1.3,6.3]
50-59	1.47	[1.1,1.9]	3.93	[0.6,7.3]	1.07	[0.8,1.5]	0.79	[-2.7,4.3]
60-79	1.23	[0.9,1.7]	4.84	[-3.5,13.2]	1.25	[1.0,1.6]	6.53	[-1.8,14.9]
2p for trend		*0.04*		*0.35*		*0.0002*		*0.17*

Table 7-7: SMR and AERs subdivided by gender, age at cancer diagnosis, calendar year of cancer diagnosis, years since cancer diagnosis and attained age for all heart disease combined for survivors of CNS tumours and other GU cancers.

7.3.3 Mortality Risk of Ischaemic Heart Disease

Ischaemic heart disease was the largest cause of cardiac death, accounting for 78% of all deaths from heart disease. The SMR was 1.23 (95% CI 1.17 - 1.28) and the AER per 10,000 person-years was 1.00 (95% CI 0.75 - 1.26, see Table 7-8). Within each age group considered in Table 7-4, ischaemic heart disease deaths accounted for at least 51% of the total excess cardiac deaths.

Subdivision into ischaemic and non-ischaemic heart disease indicated that the cumulative mortality risk from ischaemic heart disease in cancer survivors was appreciably greater than from other heart disease (Figure 7-2). The solid line represents the observed number of deaths in the cohort of TYA cancer survivors, the dotted line is the 95% confidence interval around this estimate, and the dashed line is the expected cumulative mortality calculated from a matched general population. At age 70, the cumulative mortality from IHD was 6.4%, compared to 2.4% for non-IHD.

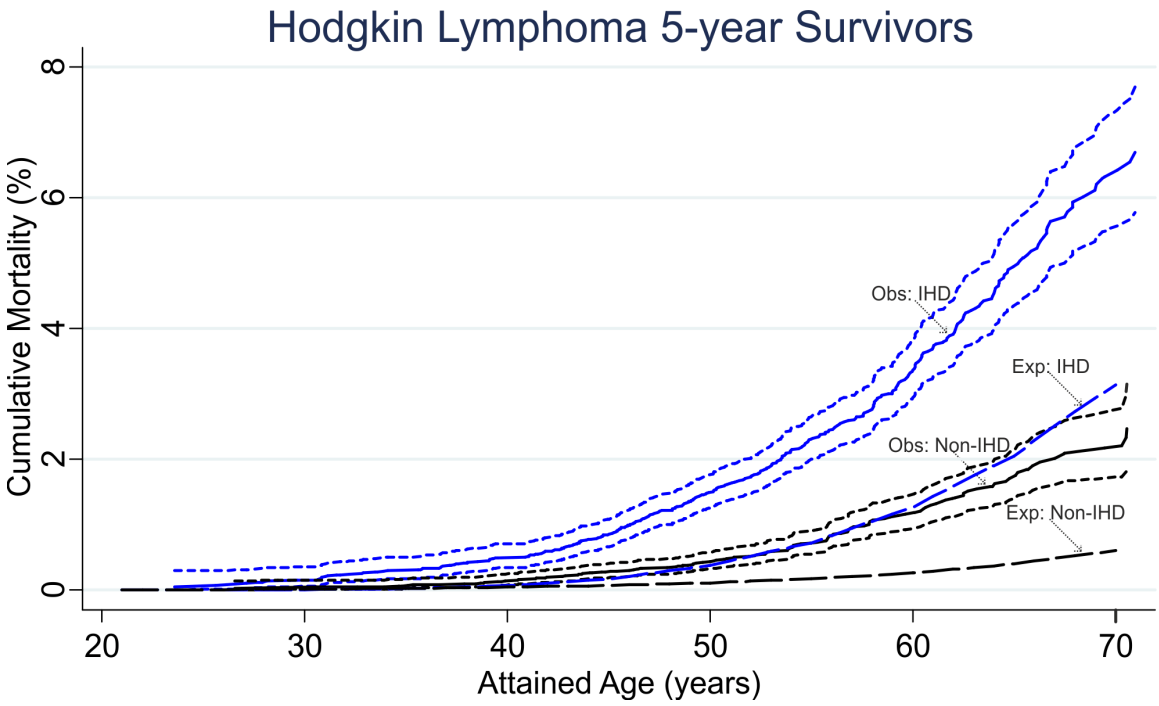


Figure 7-2: Cumulative mortality (with 95% confidence intervals) by attained age of IHD and non-IHD deaths among Hodgkin lymphoma 5-year survivors, subdivided by age at cancer diagnosis and observed versus expected deaths.

Heterogeneity existed across the cancer groups for both SMRs and AERs of ischaemic heart disease mortality (Table 7-8). Significantly raised SMRs were found for survivors of breast, cervical, other GU and lung cancers, Hodgkin and non-Hodgkin lymphoma, CNS tumours and leukaemia. Compared to the general population, survivors of Hodgkin lymphoma had 9 extra deaths per 10,000 person-years. The AER of IHD among lung cancer survivors was also relatively high, with 7 extra deaths per 10,000 person-years.

	Ischaemic heart disease		
	O	**SMR (95% CI)**	**AER per 10,000 (95% CI)**
Total	1,812	1.23 (1.17-1.28)	1.00 (0.75-1.26)
Gender			
Male	1,199	1.19 [1.1,1.3]	1.47 [1.0,2.0]
Female	613	1.30 [1.2,1.4]	0.70 [0.5,0.9]
2p for heterogeneity		*0.08*	*0.007*
Age at cancer diagnosis			
15-19	55	3.49 [2.7,4.5]	1.92 [1.2,2.6]
20-24	121	2.25 [1.9,2.7]	1.88 [1.3,2.5]
25-29	243	1.55 [1.4,1.8]	1.42 [0.9,1.9]
30-34	430	1.15 [1.0,1.3]	0.63 [0.2,1.1]
35-39	963	1.10 [1.0,1.2]	0.67 [0.2,1.2]
2p for trend		*<0.0001*	*<0.0001*
Calendar year of cancer diagnosis			
1970-79	853	1.17 [1.1,1.3]	1.61 [0.9,2.4]
1980-89	675	1.30 [1.2,1.4]	1.30 [0.9,1.7]
1990-99	242	1.25 [1.1,1.4]	0.49 [0.2,0.8]
2000+	42	1.16 [0.9,1.6]	0.16 [-0.2,0.5]
2p for trend		*0.23*	*<0.0001*
Years since cancer diagnosis			
5-9	219	1.29 [1.1,1.5]	0.46 [0.2,0.7]
10-14	257	1.02 [0.9,1.2]	0.07 [-0.3,0.5]
15-19	317	1.04 [0.9,1.2]	0.22 [-0.4,0.8]
20-24	359	1.09 [1.0,1.2]	0.75 [-0.2,1.7]
25-29	304	1.00 [0.9,1.1]	0.02 [-1.3,1.4]
30+	356	1.06 [1.0,1.2]	1.16 [-0.8,3.2]
2p for trend		*0.12*	*0.83*
Attained Age (years)			
20-39	100	2.61 [2.1,3.2]	0.79 [0.5,1.0]
40-49	485	1.44 [1.3,1.6]	1.06 [0.8,1.4]
50-59	622	1.17 [1.1,1.3]	1.13 [0.5,1.7]
60+	605	1.06 [1.0,1.1]	0.97 [-0.5,2.4]
2p for trend		*<0.0001*	*0.18*

First Primary Cancer					
Breast	158	1.22	[1.0,1.4]	0.66	[0.10,1.2]
NMSC	218	0.83	[0.7,0.9]	-1.14	[-1.9,-0.4]
Testicular	225	0.95	[0.8,1.1]	-0.34	[-1.2,0.5]
Cervix	125	1.40	[1.2,1.7]	0.97	[0.4,1.6]
Melanoma	43	0.45	[0.3,0.6]	-1.84	[-2.3,-1.4]
Hodgkin	348	3.48	[3.1,3.9]	9.39	[8.0,10.8]
CNS tumour	110	1.41	[1.2,1.7]	1.48	[0.5,2.4]
Other	124	1.26	[1.1,1.5]	1.24	[0.2,2.3]
NHL	94	1.49	[1.2,1.8]	2.41	[0.9,3.9]
Thyroid	24	0.76	[0.5,1.1]	-0.70	[-1.6,0.2]
Other GU	123	1.36	[1.1,1.6]	2.75	[0.9,4.6]
GI	59	0.85	[0.7,1.1]	-1.04	[-2.6,0.5]
Ovary	15	0.76	[0.5,1.3]	-0.53	[-1.4,0.3]
STS	32	0.99	[0.7,1.4]	-0.03	[-1.4,1.4]
Leukaemia	25	1.61	[1.1,2.4]	1.64	[-0.06,3.3]
Head & Neck	46	1.23	[0.9,1.6]	1.55	[-0.8,3.9]
Bone Tumour	14	1.29	[0.8,2.2]	0.96	[-1.3,3.2]
Lung	29	1.77	[1.2,2.6]	6.90	[1.1,12.7]
2p for heterogeneity			*<0.0001*		*<0.0001*

Table 7-8: SMR and AERs subdivided by gender, age at cancer diagnosis, calendar year of cancer diagnosis, years since cancer diagnosis, attained age and first primary tumour for ischaemic heart disease.

7.3.4 Mortality Risk of Valvular Heart Disease, Cardiomyopathy and Congestive Heart Failure

Mortality from valvular heart disease and cardiomyopathy/CHF was increased compared to the general population, with SMRs taking values of 2.53 (95% CI 2.08 - 3.03) and 1.35 (95% CI 1.18 - 1.53), respectively (see Table 7-9). Hodgkin lymphoma survivors had the greatest valvular heart disease SMR (15.2 95% CI 11.2 - 20.7)), which was almost four times greater than the SMR for all heart disease combined. However, this only corresponded to an AER per 10,000 person-years of 1.42 (95% CI 0.9 - 1.9), likely due to the low number of valvular heart disease deaths.

As shown in Table 7-4, the proportion of cardiac deaths due to cardiomyopathy and CHF decreased from 26% at among those aged 20-39 to 9% among those aged 60+. In contrast, the

proportion of cardiac deaths due to valvular heart disease increased with attained age, from 6% to 20% in those aged 20-39 to those aged 60+.

	Valvular Heart Disease			Cardiomyopathy / CHF		
	O	SMR (95% CI)	AER per 10,000 (95% CI)	O	SMR (95% CI)	AER per 10,000 (95% CI)
Total	**114**	**2.53 (2.08-3.03)**	**0.21 (0.14-0.27)**	**243**	**1.35 (1.18-1.53)**	**0.19 (0.10-0.28)**
Gender						
Male	53	2.32 [1.8,3.0]	0.23 [0.1,0.3]	132	1.29 [1.1,1.5]	0.23 [0.06,0.4]
Female	61	2.74 [2.1,3.5]	0.19 [0.1,0.3]	111	1.42 [1.2,1.7]	0.16 [0.06,0.3]
2p for heterogeneity		*0.37*	*0.57*		*0.48*	*0.51*
Age at cancer diagnosis						
15-19	11	17.6 [9.7,31.7]	0.51 [0.2,0.8]	16	3.77 [2.3,6.2]	0.58 [0.2,1.0]
20-24	16	9.25 [5.7,15.1]	0.40 [0.2,0.6]	21	2.05 [1.3,3.1]	0.30 [0.05,0.6]
25-29	21	4.54 [3.0,7.0]	0.27 [0.1,0.4]	37	1.59 [1.2,2.2]	0.23 [0.03,0.4]
30-34	22	1.99 [1.3,3.0]	0.12 [0.02,0.2]	66	1.41 [1.1,1.8]	0.21 [0.04,0.4]
35-39	44	1.62 [1.2,2.2]	0.13 [0.03,0.2]	103	1.07 [0.9,1.3]	0.06 [-0.1,0.2]
2p for trend		*<0.0001*	*0.0005*		*<0.0001*	*0.005*
Calendar year of cancer diagnosis						
1970-79	60	2.72 [2.1,3.5]	0.50 [0.3,0.7]	85	1.21 [1.0,1.5]	0.19 [-0.04,0.4]
1980-89	39	2.54 [1.9,3.5]	0.20 [0.09,0.3]	86	1.33 [1.1,1.6]	0.17 [0.02,0.3]
1990-99	13	2.06 [1.2,3.6]	0.07 [-0.004,0.1]	55	1.55 [1.2,2.0]	0.20 [0.05,0.3]
2000+	2	1.38 [0.3,5.5]	0.02 [-0.06,0.09]	17	1.78 [1.1,2.9]	0.21 [-0.02,0.4]
2p for trend		*0.22*	*<0.0001*		*0.07*	*0.86*
Years since cancer diagnosis						
5-9	9	1.92 [1.0,3.7]	0.04 [-0.01,0.09]	50	1.70 [1.3,2.2]	0.19 [0.06,0.3]
10-14	9	1.49 [0.8,2.9]	0.04 [-0.04,0.1]	43	1.22 [0.9,1.6]	0.10 [-0.06,0.3]
15-19	15	2.07 [1.2,3.4]	0.13 [0.003,0.3]	43	1.18 [0.9,1.6]	0.11 [-0.1,0.3]
20-24	13	1.51 [0.9,2.6]	0.11 [-0.07,0.3]	33	0.91 [0.6,1.3]	-0.08 [-0.4,0.2]
25-29	28	2.96 [2.0,4.3]	0.74 [0.3,1.2]	38	1.19 [0.9,1.6]	0.25 [-0.2,0.7]
30+	40	2.68 [2.0,3.7]	1.36 [0.7,2.0]	36	0.97 [0.7,1.3]	-0.05 [-0.7,0.6]
2p for trend		*0.05*	*<0.0001*		*0.02*	*0.23*
Attained Age (years)						
20-39	7	3.69 [1.8,7.7]	0.06 [-0.001,0.1]	37	2.78 [2.0,3.8]	0.30 [0.1,0.5]
40-49	25	3.14 [2.1,4.6]	0.12 [0.05,0.2]	85	1.71 [1.4,2.1]	0.25 [0.1,0.4]
50-59	43	3.32 [2.5,4.5]	0.37 [0.2,0.5]	62	1.07 [0.8,1.4]	0.05 [-0.1,0.2]
60+	39	1.75 [1.3,2.4]	0.50 [0.1,0.9]	59	1.00 [0.8,1.3]	-0.004 [-0.5,0.4]
2p for trend		*0.006*	*0.0001*		*<0.0001*	*0.04*

Table cont. on next page

First Primary Tumour								
Breast	9	1.50	[0.8,2.9]	0.07	[-0.07,0.2]	21	1.04	[0.7,1.6]	0.02	[-0.2,0.2]
NMSC	4	0.54	[0.2,1.4]	-0.08	[-0.2,0.01]	19	0.68	[0.4,1.1]	-0.22	[-0.4,-0.01]
Testicular	13	2.39	[1.4,4.1]	0.21	[0.01,0.4]	27	1.05	[0.7,1.5]	0.03	[-0.2,0.3]
Cervix	8	1.93	[1.0,3.9]	0.10	[-0.05,0.3]	11	0.74	[0.4,1.3]	-0.10	[-0.3,0.1]
Melanoma	3	0.94	[0.3,2.9]	-0.01	[-0.1,0.1]	9	0.69	[0.4,1.3]	-0.14	[-0.3,0.1]
Hodgkin	40	15.2	[11.2,20.7]	1.42	[0.9,1.9]	42	3.42	[2.5,4.6]	1.13	[0.6,1.6]
CNS tumour	6	2.65	[1.2,5.9]	0.17	[-0.05,0.4]	15	1.49	[0.9,2.5]	0.23	[-0.1,0.6]
NHL	4	1.39	[0.5,3.7]	0.06	[-0.1,0.2]	14	1.21	[0.7,2.0]	0.12	[-0.2,0.5]
Thyroid	4	2.43	[0.9,6.5]	0.18	[-0.1,0.5]	22	3.02	[2.0,4.6]	1.14	[0.4,1.9]
Other GU	4	3.53	[1.3,9.4]	0.26	[-0.1,0.6]	5	1.11	[0.5,2.7]	0.05	[-0.4,0.4]
GI	7	2.85	[1.4,6.0]	0.39	[-0.05,0.8]	11	1.20	[0.7,2.2]	0.16	[-0.4,0.7]
Ovary	3	1.55	[0.5,4.8]	0.11	[-0.2,0.4]	9	1.24	[0.6,2.4]	0.18	[-0.4,0.8]
STS	2	2.12	[0.5,8.5]	0.12	[-0.2,0.4]	6	1.81	[0.8,4.0]	0.30	[-0.2,0.8]
Other	2	2.13	[0.5,8.5]	0.13	[-0.2,0.5]	14	3.45	[2.0,5.8]	1.26	[0.3,2.2]
Leukaemia	1	2.22	[0.3,15.8]	0.10	[-0.2,0.4]	8	3.48	[1.7,7.0]	0.99	[0.03,1.9]
Head & Neck	1	1.03	[0.1,7.3]	0.01	[-0.3,0.4]	4	1.04	[0.4,2.8]	0.03	[-0.7,0.7]
Bone Cancer	1	3.33	[0.5,23.7]	0.21	[-0.4,0.8]	2	1.42	[0.4,5.7]	0.18	[-0.7,1.0]
Lung	2	4.90	[1.2,19.6]	0.87	[-0.6,2.4]	4	2.67	[1.0,7.1]	1.37	[-0.8,3.5]
2p for heterogeneity			*<0.0001*		*<0.0001*			*<0.0001*		*<0.0001*

Table 7-9: SMR and AERs subdivided by gender, age at cancer diagnosis, calendar year of cancer diagnosis, years since cancer diagnosis, attained age and first primary tumour for valvular heart disease and cardiomyopathy / congestive heart failure .

7.3.5 Ischaemic Heart Disease Mortality Risk in Context with Systolic Blood Pressure

Figure 7-3 presents the cumulative mortality of ischaemic heart disease among survivors of Hodgkin lymphoma, as compared to the general population. Age-specific hazard ratios from the Prospective Studies collaboration (Lewington, Clarke et al. 2002) were applied to estimate the cumulative mortality risk for assumed healthy individuals with an increased systolic blood pressure. At age 65, the cumulative mortality from ischaemic heart disease for Hodgkin lymphoma survivors was 5.0%. Among the general population, the cumulative mortality by age 65 was 2.0%. An increased systolic blood pressure of 20mmHg and 40mmHg above usual blood pressure levels (hazard ratios calculated from re-measurements of systolic blood pressure) resulted in a cumulative mortality by age 65 of 3.9 % and 7.4 %, respectively.

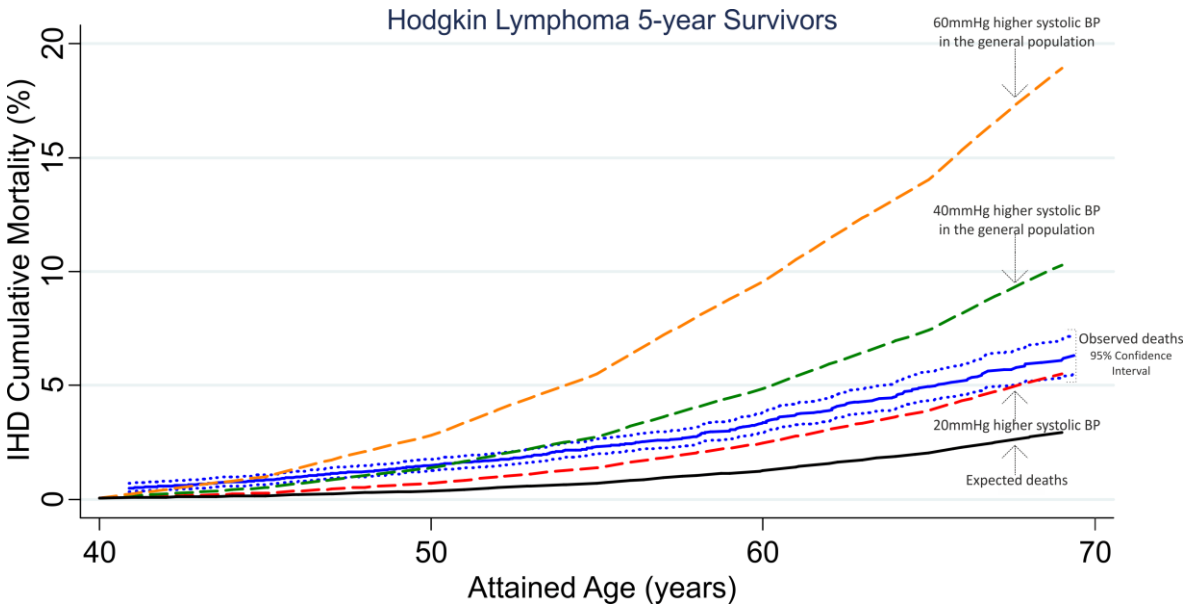


Figure 7-3: Ischaemic heart disease cumulative mortality (%) among Hodgkin lymphoma survivors compared to the general population with a raised systolic blood pressure (estimates obtained from Prospective Studies Collaboration).

7.4 Discussion

7.4.1 Overall findings

This largest ever study of over 230,000 survivors of cancer diagnosed in teenage and young adulthood revealed that there was a small 1.3-fold excess risk of mortality from heart disease compared to the general population, which varied little with decade of treatment. This suggests that improvements in cancer treatments have not reduced cardiotoxicity. No study, as yet, has investigated cardiac mortality risk among survivors of TYA cancers on such a large scale. The slight increase in mortality risk among all cancers combined can be reassuring for clinicians and patients. However, there are still high risk groups that need to be considered carefully, namely survivors of Hodgkin and non-Hodgkin lymphoma survivors were at a highly increased cardiac risk. This was expected as treatment for Hodgkin lymphoma involves thoracic radiotherapy and chemotherapy, both of which are known to be cardiotoxic (Floyd, Nguyen et al. 2005, Cutter, Taylor et al. 2010, Monsuez, Charniot et al. 2010).

The excess risk of cardiac death was greatest among survivors of Hodgkin lymphoma. Among survivors of Hodgkin and non-Hodgkin lymphoma, heart disease accounted for 14% and 4% of the total excess deaths, respectively. The proportion of excess deaths due to heart disease was 6 times greater among ages 60+ compared to ages 20-39 for survivors of both cancers. This suggests an extended period of risk, and Hodgkin and non-Hodgkin lymphoma survivors should be followed-up carefully for cardiac risk factors and symptoms. This also has important public health implications as these high-risk cancer survivors may need treatment for management of heart disease over an extended period.

7.4.2 Variation in Cardiac Mortality Risk by Type of Heart Disease

The excess mortality of heart disease deaths was largely due to ischaemic heart disease, accounting for 64% of the total excess cardiac deaths. However, the proportion of excess valvular heart disease and cardiomyopathy / CHF deaths varied with follow-up. Valvular heart disease accounted for a greater proportion of excess cardiac deaths with increasing attained age, reaching 26% of all excess cardiac deaths at ages 60+. This may be a radiation-related effect, as radiation-related valvular heart disease has been shown to have a long latency period compared to other heart diseases (Cutter, Taylor et al. 2010), with one study of Hodgkin lymphoma survivors finding a median interval of 22 years between treatment and symptomatic heart disease (Hull, Morris et al. 2003). In comparison, at ages 20-39, 24% of the excess cardiac deaths were due to cardiomyopathy and congestive heart failure. Anthracyclines have been shown to be cardiotoxic, with a recent meta-analysis of randomised controlled trials finding that anthracyclines were associated with a 5-fold significant risk of congestive heart failure compared to non-anthracycline regimens (Smith, Cornelius et al. 2010). Anthracyclines were developed in the 1960s, and trialled for different cancer types during the 1970s and 1980s. In this TYACSS cohort, the individuals who were treated in more recent decades had the greatest proportion of

excess deaths due to cardiomyopathy and congestive heart failure, which was consistent with the relatively recent introduction of anthracyclines.

7.4.3 Cardiac Mortality Risk in Context

Results from the Prospective Studies Collaboration (Lewington, Clarke et al. 2002) were used to compare the cumulative mortality of Hodgkin lymphoma survivors (the subgroup of individuals at greatest cardiac mortality risk in the TYACSS) to the cumulative mortality of the general population with an increase of both 20mmHg and 40mmHg systolic blood pressures (SBP) applied. The Prospective Studies Collaboration holds information from 61 prospective observational studies, mainly from North America and Western Europe. These studies contained baseline measurements of blood pressure from individuals without previous disease between the ages of 40 and 89 years, assumed to be representative of the general population. This was done as it is important to present findings in an accessible manner for use by clinicians, for example by comparing to traditional cardiac risk factors. According to the NICE hypertension guidelines (National Institute for Health and Clinical Excellence 2011), this TYACSS study suggested than even a person with a healthy initial blood pressure (for example ideal SBP: 90 – 120mmHg) and a subsequent increase of either 20 or 40mmHg could be classified as Stage 1 hypertension, and considered for antihypertensive drugs. High cholesterol and high systolic blood pressure can be treated with medication (statins and antihypertensive drugs) if modifications of diet and lifestyle were not successful. Within the general population, antihypertensive drugs are widely used, as confirmed by the NICE guidelines: “the clinical management of hypertension is one of the most common interventions in primary care, accounting for approximately £1 billion in drug costs alone in 2006”. This provides evidence that survivors of Hodgkin lymphoma should be monitored very closely for heart disease, as their cumulative mortality of ischaemic heart disease was higher than individuals in the general population who would likely be diagnosed with Stage 1 hypertension.

A study by the Childhood Cancer Survivor Study sought to evaluate the contribution of modifiable cardiovascular risk factors in addition to the treatment related cardiac damage (Armstrong, Oeffinger et al. 2013). The authors concluded that "it is imperative that childhood cancer survivors exposed to chest-directed RT or anthracycline chemotherapy have regular blood pressure monitoring and appropriate management as a high-risk group" (Armstrong, Oeffinger et al. 2013). Among survivors of TYA cancer, this type of study should be replicated to evaluate whether intervention for cardiac management can be justified after cancer treatment. Currently it is only apparent that a history of cancer should be considered as a risk factor during routine monitoring for heart disease symptoms and risk profiling.

7.4.4 Risk of heart disease in Comparison to Childhood Cancer Survivors

This study suggests that survivors of TYA cancers were at a lower risk of cardiac mortality than childhood cancer survivors. In the British Childhood Cancer Survivor Study, an SMR of 3.5 (95% 2.9-3.2) corresponding to 2 excess deaths per 10,000 person-years was found (Reulen, Winter et al. 2010). Among survivors recorded in the Childhood Cancer Survivor Study in the USA, the overall cardiac risk was much greater, with a 7-fold raised risk compared to the general population (Armstrong, Liu et al. 2009). However, shorter follow-up was available in the TYACSS cohort compared to the cohorts of childhood cancer survivors. Studies combining all cancer survivors diagnosed before age 40 could be considered for a direct comparison.

7.4.5 Strengths of study

This is the largest study yet to investigate cardiac mortality risk among survivors of cancer diagnosed in teenagers and young adults with a total of 3,325,102 person-years. The follow-up of 5-year survivors extended to 38 years, with a mean period of 14.3 years. 16% of the population were followed for at least 25 years, 44% for between 10 and 25 years and 10% were followed for a maximum of 10 years. Thus, it has the highest number of 5-year survivors and person years of

follow-up of any study of cardiac mortality in TYA cancer survivors worldwide, with the follow-up exceeding two decades for a large portion of the cohort.

7.4.6 Limitations of study

A main potential limitation is the lack of detailed information on exposure from the main adjuvant treatment modalities: radiotherapy and chemotherapy. Receipt of the main treatments was recorded in the cohort from 1993 onwards, but among individuals treated after 1993 in England, 48% were missing radiotherapy information and 45% were missing chemotherapy. It is likely that a majority of the excess cardiac deaths would be due to the adjuvant treatments received by the patient. Ideally, individual treatment regimens would be available for each survivor to enable examination of the dose-response relationship to cardiac mortality risk.

Limitations present in the cause of death recording mean that the estimates of excess risk presented in this study may be an under-ascertainment of the mortality burden from heart disease. Inaccuracies in death certification can be caused from inaccuracies in or failure to record relevant information, or from mistakes in formulation of the cause of death (Devis and Rooney 1999). Some diseases are more frequently selected as the underlying cause of death whenever they appear on the death certificate, for instance cancer will tend to be assumed to be the underlying cause. Yet, even with this conservative estimate, there is substantial mortality risk from heart disease among survivors of TYA cancer.

7.4.7 Conclusion

In conclusion, for most survivors of cancer diagnosed in teenagers and young adults individuals were found to only be at a slightly raised risk of heart disease, which is reassuring for both clinicians and patients. This is not to say that there was no risk of heart disease mortality, and worryingly there was no reduction in excess cardiac mortality in more recent decades of diagnosis. The heart should continue to be considered an organ at risk during treatment of

cancer, but during long-term monitoring particular attention should be placed on survivors at the greatest risk, namely Hodgkin and non-Hodgkin lymphoma, and particularly those diagnosed with cancer as teenagers.

CHAPTER 8:
GENERAL DISCUSSION AND CONCLUSIONS

This thesis has characterised the risk of radiation-related heart disease and lung cancer in a large collaborative cohort of breast cancer survivors, and in the understudied cancer survivor population of teenagers and adults aged 15-39 has characterised the risk of heart disease as compared to the matched general population. No study as yet has presented a description of burden of the heart disease mortality among survivors of teenage and young adult cancer on a big data scale, and this thesis investigated the cardiac risk using a cohort with the highest number of individuals and person years of follow-up of any investigation of TYA cancer survivors worldwide.

As discussed in Chapter 3, observational cohort studies have been increasingly used by researchers. Observational data provides a valuable source of information which tends to be representative of treatment routinely received by patients. As a wealth of information is now routinely collected by cancer registries or national bodies, observational data can be an extensive resource, which, when analysed carefully, can provide valuable evidence for cancer outcomes research. The purpose of such observational analyses is usually to identify associations and characterise factors that influence any treatment associations, which can then be more fully investigated within nested case-control studies.

The late adverse effects of the radiation protocols used today are unknown; however results from past regimens and knowledge of current treatment regimens can provide evidence of future potential risks. Investigation of late effects provides evidence both for the development of radiotherapy techniques used in current practise and the continued monitoring and follow-up of cancer survivors. Awareness and understanding of late effects can help to improve care and quality of life for cancer survivors, as symptoms can be managed and hopefully controlled. This thesis provides evidence to support the continued follow-up for cancer patients, potentially into the second or third decade after diagnosis.

At the beginning of this thesis three aims were set out. These aims will now each be addressed in turn.

8.1 Methodology-based discussion of the potential pitfalls of observational data that need to be considered carefully during analysis

Observational cohorts have a wealth of data which can provide very valuable information for the current literature base. However, determining treatment-outcome associations in observational data is challenging as selection biases may incorrectly indicate that links exist which are in fact due to confounding rather than causal mechanisms. The problem of selection bias was previously demonstrated in a study of SEER-Medicare using patients diagnosed with prostate and colon cancer (Giordano, Kuo et al. 2008). Despite this publication, the systematic review presented in Chapter 3 demonstrated that the issues discussed by Giordano and colleagues may not have been fully absorbed by researchers and are thus still very relevant. The majority (85%) of eligible articles analysed radiation-related outcomes after breast cancer in the SEER or SEER-Medicare using a comparison of irradiated versus unirradiated women. Therefore, the systematic review confirmed that a clear description of the problem should be very important for clinicians and epidemiologists.

The availability of the EBCTCG meta-analyses provided an opportunity to directly compare the results from observational and randomised data. Analyses presented in Chapter 3 of the SEER data produced highly dubious results, which were in stark contrast to the randomised evidence. The association between radiotherapy and the outcome of interest varied dependent on the type of surgery received. One particular analysis of the outcome accidents and violence demonstrated the spurious results very clearly. The mortality ratios suggested that among women who received breast conserving surgery, radiotherapy reduced their risk of death from accidents or violence, yet no association was present for post-mastectomy radiotherapy. It was known from randomised evidence that this is not true and rather it is a reflection of the type of

women selected to receive radiotherapy. Women who do not receive radiotherapy after breast conserving surgery are unusual, and may have had particularly poor health or have been too frail to cope with radiation which may be a reflection on their lifestyle or socio-economic status.

In general, it was thought that stratification by all known patient and tumour characteristics, for example tumour grade, nodal involvement or age, should mostly remove the effect of selection and other biases. Chapter 3 demonstrated that this was not the case, and the inclusion of tumour size, grade, surgery type, number of involved nodes, axillary clearance, clinical nodal status (from 2004 onwards), ER status and disease stage in the stratification made no substantial difference to the spurious results produced by the mortality ratios comparing irradiated and unirradiated women. Thus, there must be many more biases inherent in observational data which cannot be controlled for. An alternative method was presented which used the fact that the breasts are a paired organ. This method is only useful for some outcomes. Analyses using this laterality comparison produced results consistent with the randomised trials evidence. This provided the reasoning for the use of the laterality comparison in the following three chapters, and also reinforced the decision to not include treatment information in the stratification of the COBS analyses.

As awareness of the heart and lungs as organs-at-risk increases, the laterality approach may become less suitable. As an example, when heart disease is the outcome of interest, the laterality comparison relies on the fact that the dose received by the heart is higher during treatment for left-sided than for right-sided breast cancer, producing a comparison of higher dose versus lower dose. However, in recent years measures have been introduced to limit the radiation dose received by the heart during left-sided breast cancer radiotherapy. For example, cardiac shielding is used during tangential breast radiotherapy, which has been shown to reduce the mean heart dose in left-sided breast cancer patients to 0.8Gy (Bartlett, Yarnold et al. 2013). However, this benefit of low cardiac dose was offset by a reduced coverage of the target tissue.

Therefore, it is important that treatment techniques are monitored to ensure that the dose difference does exist before using the laterality comparison by collected information, where possible, on the radiotherapy technique used. It is also important to check that the proportion of women receiving radiotherapy in the cohort does not vary by laterality. Further work is needed to develop alternative methods to reduce the effect of selection biases if and when the difference in cardiac dose between left-sided and right-sided breast cancer is negligible.

8.2 The radiation-related risks of heart disease and lung cancer in survivors of breast cancer

Chapters 4, 5 and 6 characterised the long-term risk of radiation-related heart disease and lung cancer among breast cancer patients using the largest observational cohort available. The clear benefits of radiotherapy in terms of reduction in breast cancer mortality and recurrence have been shown to be offset by increases in mortality from other causes (Early Breast Cancer Trialists' Collaborative Group 2005). Individual patient data meta-analyses of randomised trials have demonstrated that heart disease and lung cancer are the largest causes of mortality before recurrence, from causes other than breast cancer. Until now, little was known on the factors, other than radiation dose, which influenced the extent of these radiation-related risks. Findings from this analysis of the collaborative cohort of cancer registries have provided evidence on these other factors. Both mortality and incidence analyses were presented, which strengthened the findings as inclusion of non-fatal event allows the investigation of potentially less serious diagnoses that may not have resulted in death.

COBS - the Collaborative Groups on Observational Studies of Breast Cancer - collated individual patient data on over 2 million women diagnosed with breast cancer worldwide. This has provided the statistical power to demonstrate clear progressive trends in factors that have previously not been shown. Radiotherapy is a key component of adjuvant treatment for breast cancer, with 95.4% and 77.6% of women with strong indications recorded to have been irradiated

after breast conserving surgery and mastectomy, respectively, in the USA (Jagsi, Abrahamse et al. 2010). As a result, efforts to reduce the late adverse effects of radiotherapy could improve the survivorship of a large proportion of women previously diagnosed with breast cancer. In addition, as breast cancer is one of the most common cancers diagnosed among women in the developed world, the results presented in this thesis could have a large public health impact due to the size of the population at risk.

The first two chapters to present findings from the COBS study investigated the risk of radiation-related mortality and incidence from heart disease using a comparison of left-sided and right-sided breast cancer patients. A significant left-sided excess was present for both mortality and incidence among women recorded to have received radiotherapy, with rate ratios of 1.07 (95% CI 1.04-1.14) and 1.08 (95% CI 1.06-1.10), respectively. There was a significant difference between the rate ratios, left- versus right-sided breast cancer of irradiated and unirradiated women (2p=0.003 for mortality and 2p=0.0002 for incidence), suggesting that it was a radiation-related effect. The left-sided mortality excess was present for ischaemic and non-ischaemic heart disease, in particular non-rheumatic valvular heart disease. Within the incidence analysis, finer subgroups of clinically relevant cardiac diagnoses were analysed. A significant left-sided excess of ischaemic heart disease, valvular disease and pericarditis was found. Investigation of this increased incidence of pericarditis found a highly significant increasing trend with time since diagnosis, with the greatest proportional increase (of 15%) in left-sided compared to right-sided breast cancer patients at 25+ years since diagnosis. The first event of each particular cardiac diagnosis (irrespective of previous cardiac diagnoses but subsequent to breast cancer diagnosis) was considered, and found that the left-sided excess of acute pericarditis became highly elevated. This could suggest that women often experience acute pericarditis after a previous cardiac event.

Interestingly, among younger women there was significant variation across a number of patient and treatment factors, for example time since cancer diagnosis. However, there was no variation across these factors among older women (ages 60+). Among women diagnosed with cancer aged less than 60, the mortality ratios significantly increased with time since diagnosis into the second decade, and there was little evidence that the risk was lower in more recent years when newer treatments were likely employed. In addition, the proportional risk was substantially higher in women who received chemotherapy as well as radiotherapy. This coupled with the decreasing proportional trend with increasing age suggested that efforts to minimise cardiac irradiation should be focused on younger women, for example through the use of alternative treatment protocols. This age trend was confirmed in the analysis of cardiac incidence.

The combination of chapters 4 and 5 allowed a number of conclusions to be drawn. Radiation-related cardiac risk is not a short-term problem as it has been shown to continue into the third decade following breast cancer treatment. It also does not appear to be limited to treatment techniques of the 'old era', as the incidence ratio was still significantly elevated in the most recent calendar period. This significant excess of cardiac incident events among women diagnosed after 2000 was particularly interesting. The risk does not seem to be limited to a few countries, as no heterogeneity was found across countries or regions during the mortality or incidence analysis (once an extreme outlier, Spain, had been removed). There was also a suggestion that an interaction exists between radiotherapy and chemotherapy. When both fatal and non-fatal events were considered together, there was a significant interaction between radiotherapy and chemotherapy for cardiomyopathy / congestive heart failure and ischaemic heart disease separately. Therefore, to conclude, breast cancer radiotherapy can cause appreciable increases in heart disease in younger women with left-sided cancer, especially if chemotherapy was also given. Measures to reduce the risk, such as breathing adapted radiotherapy or the use of less cardiotoxic chemotherapies may be appropriate for some women.

It is important to note that the comparison of left-sided versus right-sided breast cancer patients is likely to underestimate the extent of the cardiac risk of both fatal and non-fatal events, because the laterality comparison is a comparison of 'higher versus lower' dose as opposed to a comparison of 'dose versus no dose'. This also applies to the comparison of ipsilateral versus contralateral lung cancer.

The COBS cohort was then analysed with the aim of characterising the radiation-related risk of lung cancer – the most commonly diagnosed neoplasm other than the breast cancer itself. Chapter 6 confirmed previously published work using the largest cohort to date, and found that radiotherapy increased the risk of lung cancer, particularly in the lung ipsilateral to the breast being irradiated. The rate ratios of microscopically confirmed lung cancer among irradiated women were 1.43 (95% CI 1.22-1.67) and 1.15 (95% CI 1.05-1.26) for mortality and incidence, respectively, indicating a highly significant excess of lung cancer in the ipsilateral lung as compared to the contralateral lung. For both mortality and incidence, a highly significant increasing trend with years since diagnosis was present, which was confirmed by the multivariable model to suggest that the trend was true and not due to confounding. At 15+ years after diagnosis, breast cancer survivors were at a 2.3-fold excess of lung cancer events in the ipsilateral lung as compared to the contralateral. There was a suggestion that the mortality and incidence risk was reducing with recent decades, but an ipsilateral excess was still present in the most recent calendar period of breast cancer diagnosis. As breast cancer survival is increasing, there are an increasing number of people living for decades after their diagnosis that may be at risk of late effects. Thus, an increased awareness of treatment-related lung cancer is required, which should help physicians to try to reduce those risks by using radiotherapy techniques that spare normal tissue as much as possible, and also monitor any symptoms into the long-term.

The clinical implications of the findings from the COBS study are in terms of evidence for clinical guidelines. Firstly, the findings presented in this thesis are strong evidence for continued

follow-up of breast cancer survivors. They provide an evidence-base to support monitoring cancer survivors for decades after treatment, with particular emphasis on heart disease. Secondly, understanding late effects can influence treatment guidelines, for example through the recommendation of treatment protocols which are known to minimise incidence radiation of organs that have been shown to be radiosensitive, i.e. the heart and lungs. These measures would be particularly relevant for subgroups of patients shown to be at particularly high risk in this thesis, for example those diagnosed with cancer at a young age.

The objective of the COBS collaboration was to collate a large amount of basic information. The next step would be to update this cohort, ideally expanding the scope of the study to include information on traditional cardiovascular risk factors (for example smoking, BMI, family history), as well as more detailed treatment information. Practically, this would be very difficult, as cancer registries don't routinely collect this high level of detail. It could be achieved through the use of a prospective study, but the financial and time burden can become limiting. However, the increasing availability of nationwide standardised data, for example the Hospital Episode Statistics and Clinical Practice Research Datalink in the UK suggest that, through the linkage of datasets, this may be possible in the future. The data sources listed above currently hold some, but not all, of the information mentioned on traditional risk factors and treatment. This would allow direct investigation of the interaction between all of the various factors which have been shown individually to increase the risk of both heart disease and lung cancer.

The proportional measures presented throughout this thesis permitted investigation of the strength of the association between radiotherapy and the outcome of interest. The additional use of absolute measures then puts this risk into a public health perspective. It is important to remember that over the past decade, there have been steep drops in the rate of heart disease death in the population. For example, in the UK, the 10-year change in mortality rate of coronary heart disease among females was -51% (Nichols, Townsend et al. 2014). This is

in contrast to lung cancer, in which there is an increase in the mortality rate among females, largely due to the epidemic of smoking among women. The World Health Organisation estimated than it 2006, the prevalence of female smoking was approximately 17% in the Americas, and 22% in Europe (World Health Organization 2010). It has also been estimated that in the year 2010, 70% of lung cancer deaths among women were attributed to smoking (Peto, Lopez et al. 2010). Smoking has been shown to be strongly associated with both lung cancer mortality and heart disease mortality. The relative risk associated with smoking (current- versus never-smoker) was 21.4 (95% CI 19.7-23.2) for lung cancer and 4.47 (95% CI 4.19-4.77) in a prospective study in the UK of one million women (Pirie, Peto et al. 2013). Therefore, this all suggests that both types of side effects presented in the thesis (lung cancer and heart disease) may be as important as each other, especially for smokers.

8.3 The long-term risk of heart disease for the entire spectrum of cancers diagnosed in teenagers and young adults aged 15-39

The first chapter clearly established that survivors of cancers diagnosed in teenagers and young adults aged 15-39 are a highly understudied population. Thus far, only two studies have published analyses of cause-specific mortality (with a focus on cardiovascular disease) within the entire spectrum of teenage and young adult (TYA) cancer survivors. Chapter 7 presented the long-term risk of heart disease mortality using the largest ever cohort of TYA cancer survivors. The Teenage and Young Adult Cancer Survivor Study presented is over 9 times larger than the two relevant published studies combined (Prasad, Signorello et al. 2012, Kero, Jarvela et al. 2014). Analyses demonstrated that TYA 5-year cancer survivors in England and Wales have a slightly raised cardiac mortality risk compared to the matched general population, but that the risk was greatest among survivors of Hodgkin lymphoma. This was expected as treatment for Hodgkin lymphoma involves thoracic radiotherapy and certain chemotherapy agents, both of which are known to be cardiotoxic (Floyd, Nguyen et al. 2005, Cutter, Taylor et al. 2010, Monsuez, Charniot

et al. 2010). This increase was still present after an attained age of 60, which has substantial public health implications as cancer survivors may need treatment for management of heart disease over an extended time period. Age at exposure was found to be critical when determining risk. This is important risk stratification evidence relevant to the clinical follow-up of such survivors. Breast cancer survivors, in the TYA age range, were also at a significantly raised mortality risk as compared to the general population. Consideration of Chapters 5 and 6 indicate that this raised risk would likely be partially due to radiotherapy. Most of the excess deaths among all cancer survivors were due to ischaemic heart disease although mortality from valvular heart disease, cardiomyopathy and congestive heart failure were also in excess. This was in agreement with the results presented in Chapter 5 which demonstrated a significant excess among irradiated left-sided breast cancer patients as compared to right-sided for ischaemic heart disease and valvular disease. Further research, for example case-control studies, are needed to define the dose-response relationships for specific cardiac diagnoses and structures (i.e. valves) and to provide further insight on the findings presented in this thesis with respect to the raised risk of valvular heart disease.

Evidence was provided that survivors of Hodgkin lymphoma should be monitored very closely for heart disease as TYA cancer survivors are at as great a risk of ischaemic heart disease as persons with an increase in blood pressure. Among TYA cancer survivors their cumulative mortality of ischaemic heart disease is higher than individuals from the general population who would likely be diagnosed with stage 1 hypertension and prescribed antihypertensive drugs. Thus, one advantage of Chapter 7 was the ability to put the risk among cancer survivors into context. This was done by using the Prospective Studies Collaboration (Lewington, Clarke et al. 2002), which presented hazard ratios of 'lower than usual' systolic blood pressure. These hazard ratios were inverted and applied to the cumulative mortality risk of ischaemic heart disease among the general population. This allowed comparison of the cumulative mortality of Hodgkin

lymphoma 5-year survivors, who were the group at the greatest risk of cardiac mortality, to the cumulative mortality of the general population with an increase of both 20mmHg and 40 mmHg systolic blood pressures. As an example, take an individual in the general population with a systolic blood pressure in the ideal range: 90 – 120mmHg. An increase by 20mmHg would give this individual a systolic blood pressure in the range of 110-140mmHg, and equivalently an increase by 40mmHg would put them in the range of 130-150mmHg. According to the NICE guidelines of hypertension (National Institute for Health and Clinical Excellence 2011), the recommendation is to offer antihypertensive drugs to: individuals of any age with stage 1 hypertension (defined as a clinic blood pressure of at least 140/90mmHg) who have other risk factors; individuals of any age with stage 2 hypertension (defined as a clinic blood pressure of at least 160/100mmHg); or individuals younger than 40 with stage 1 hypertension. Thus, this suggests than even a person with a healthy initial blood pressure and a subsequent increase of either 20 or 40mmHg could be classified as Stage 1 hypertension, and considered for antihypertensive drugs. Among survivors of TYA cancer, further research is needed to evaluate whether intervention can be justified. It is apparent that a history of cancer should be considered as an important risk factor during routine monitoring for heart disease symptoms and risk profiling. However, this thesis provides an argument for continued follow-up of TYA cancer survivors at the greatest risk – Hodgkin lymphoma survivors – which would include the consideration of traditional measures to reduce cardiovascular risk, i.e. antihypertensive medication. Continued follow-up would also allow physicians to monitor and help minimise traditional modifiable risk factors, for example obesity and smoking. Even just considering the findings of the cancer survivors in isolation, the extended period of raised risk suggests that continued monitoring of cancer survivors is vital.

As the teenage and young adult cancer population has been greatly understudied thus far this thesis provided a vital overview of the risk of heart disease in a large number of TYA cancer

survivors. The next step to further understanding of the survivorship of the TYA cancer population would be to collect detailed treatment information for the TYA cancer survivors. The significant heterogeneity across cancer types was likely due to the differences in treatment received for each specific cancer type, and the variation across centres in the use of adult or paediatric treatment protocols. Yet, the influence of varying treatment protocols cannot be characterised without individual patient treatment information. Understanding the treatment associations could further the implications of this research, as national cancer treatment guidelines could be adjusted to minimise the long-term adverse health risks in TYA cancer survivors. The findings presented provide evidence for future TYA-cancer specific follow-up guidelines; particularly as published clinical guidelines on the long term follow-up of childhood cancer survivors do not provide recommendations past puberty.

Summary

This thesis demonstrated that adjuvant radiotherapy for breast cancer significantly increased the risk of heart disease among women with left-sided breast cancer and ipsilateral lung cancer in the largest observational cohort worldwide. It was shown that younger women were at the highest risk of heart disease, and a progressive monotonic proportional decrease with increasing age at diagnosis was found which has not been shown before. The excess of heart disease did not seem to be reduced in recent decades, with a significant risk of incident cardiac events in women diagnosed after 2000. A possible interaction between radiotherapy and chemotherapy was suggested, which warrants further careful investigation particularly in the observational setting as it is representative of general practise. It was also demonstrated that selection effects and other biases can still be very problematic during analyses of observational data, and a systematic review highlighted the lack of consideration for these selection effects in the published literature. However, careful consideration of the limitations of observational data can result in meaningful and clinically useful results, for example through the use of the laterality comparison employed throughout the analyses presented. In addition, this thesis presented an overview of the risk of heart disease mortality among the internationally acknowledged understudied population of individuals diagnosed with cancer as teenagers and young adults aged 15-39 years. Overall, the 5-year survivors were at a significantly raised cardiac mortality risk compared to the matched general population, and survivors of Hodgkin lymphoma were at the greatest risk. It is hoped that the findings presented here will influence clinical guidelines, particularly guidelines on surveillance following completion of therapy and late effects. This thesis provides evidence to advocate the continued follow-up for cancer patients, potentially into the second or third decade after diagnosis, as the cancer survivors were found to be at a substantially increased risk for many decades following treatment. During this suggested long-term monitoring particular attention

should be placed on survivors at the greatest risk, namely Hodgkin and non-Hodgkin Lymphoma, and particularly those diagnosed with cancer as teenagers.

REFERENCES

National Cancer Institute DCCPS Surveillance Research Program Cancer Statistics Branch (released January 2011). Surveillance, Epidemiology and End Results (SEER) Program (www.seer.cancer.gov Research Data (1973-2008)).

Aben, K. K., C. van Gaal, N. A. van Gils, W. T. van der Graaf and G. A. Zielhuis (2012). "Cancer in adolescents and young adults (15–29 years): A population-based study in the Netherlands 1989–2009." Acta Oncol **51**(7): 922-933.

Adams, M. J., P. H. Hardenbergh, L. S. Constine and S. E. Lipshultz (2003). "Radiation-associated cardiovascular disease." Crit Rev Oncol Hematol **45**(1): 55-75.

Adolescent and Young Adult Oncology Progress Review Group (2006). Closing the gap: Research and care imperatives for adolescents and young adults with cancer.

Aleman, B. M., A. W. van den Belt-Dusebout, W. J. Klokman, M. B. Van't Veer, H. Bartelink and F. E. van Leeuwen (2003). "Long-term cause-specific mortality of patients treated for Hodgkin's disease." J Clin Oncol **21**(18): 3431-3439.

American Cancer Society (2011). Global Cancer Facts & Figures 2nd Edition. Atlanta.

Armstrong, G. T., Q. Liu, Y. Yasui, J. P. Neglia, W. Leisenring, L. L. Robison and A. C. Mertens (2009). "Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study." J Clin Oncol **27**(14): 2328-2338.

Armstrong, G. T., K. C. Oeffinger, Y. Chen, T. Kawashima, Y. Yasui, W. Leisenring, M. Stovall, E. J. Chow, C. A. Sklar, D. A. Mulrooney, A. C. Mertens, W. Border, J.-B. Durand, L. L. Robison and L. R. Meacham (2013). "Modifiable risk factors and major cardiac events among adult survivors of childhood cancer." J Clin Oncol.

Azizova, T. V., C. R. Muirhead, M. B. Druzhinina, E. S. Grigoryeva, E. V. Vlasenko, M. V. Sumina, J. A. O'Hagan, W. Zhang, R. G. E. Haylock and N. Hunter (2010). "Cardiovascular diseases in the cohort of workers first employed at Mayak PA in 1948–1958." Radiat Res **174**(2): 155-168.

Baade, P. D., J. A. Royle, D. J. Joske and L. Fritschi (2011). "Non-cancer mortality among people diagnosed with lymphohaematopoietic neoplasm in Australia." Cancer Causes Control **22**(5): 715-723.

Barr, R. D., E. J. Holowaty and J. M. Birch (2006). "Classification schemes for tumours diagnosed in adolescents and young adults." Cancer **106**(7): 1425-1430.

Bartlett, F. R., J. R. Yarnold, E. M. Donovan, P. M. Evans, I. Locke and A. M. Kirby (2013). "Multileaf collimation cardiac shielding in breast radiotherapy: Cardiac doses are reduced, but at what cost?" Clin Oncol (R Coll Radiol) **25**(12): 690-696.

Beard, C. J., L. B. Travis, M. H. Chen, N. D. Arvold, P. L. Nguyen, N. E. Martin, D. A. Kuban, A. K. Ng and K. E. Hoffman (2013). "Outcomes in stage I testicular seminoma: a population-based study of 9193 patients." Cancer **119**(15): 2771-2777.

Bekelman, J. E., A. Shah and S. M. Hahn (2011). "Implications of comparative effectiveness research for radiation oncology." Practical Radiat Oncol **1**(2): 72-80.

Birch, J. M., R. D. Alston, A. M. Kelsey, M. J. Quinn, P. Babb and R. J. Q. McNally (2002). "Classification and incidence of cancers in adolescents and young adults in England 1979-1997." Br J Cancer **87**(11): 1267-1274.

Bleyer, A., R. Barr, B. Hayes-Lattin, D. Thomas, C. Ellis and B. Anderson (2008). "The distinctive biology of cancer in adolescents and young adults." Nat Rev Cancer **8**(4): 288-298.

Bleyer, A., A. Viny and R. Barr (2006). "Cancer in 15- to 29-year-olds by primary site." Oncologist **11**(6): 590-601.

Bluhm, E. C., C. Ronckers, R. J. Hayashi, J. P. Neglia, A. C. Mertens, M. Stovall, A. T. Meadows, P. A. Mitby, J. A. Whitton, S. Hammond, J. D. Barker, S. S. Donaldson, L. L. Robison and P. D. Inskip (2008). "Cause-specific mortality and second cancer incidence after non-Hodgkin lymphoma: A report from the Childhood Cancer Survivor Study." Blood **111**(8): 4014-4021.

Borger, J. H., M. J. Hooning, L. J. Boersma, A. Snijders-Keilholz, B. M. P. Aleman, E. Lintzen, S. van Brussel, P.-P. van der Toorn, M. Alwhouhayb and F. E. van Leeuwen (2007). "Cardiotoxic effects of tangential breast irradiation in early breast cancer patients: The role of irradiated heart volume." Int J Radiat Oncol Biol Phys **69**(4): 1131-1138.

Bouchardy, C., E. Rapiti, M. Usel, S. B. Majno, G. Vlastos, S. Benhamou, R. Miralbell, I. Neyroud-Caspar, H. M. Verkooijen and V. Vinh-Hung (2009). "Excess of cardiovascular mortality among node-negative breast cancer patients irradiated for inner-quadrant tumors." Ann Oncol.

Bouillon, K., N. Haddy, S. Delaloge, J.-R. Garbay, J.-P. Garsi, P. Brindel, A. Mousannif, M. G. Le, M. Labbe, R. Arriagada, E. Jougla, J. Chavaudra, I. Diallo, C. Rubino and F. de Vathaire (2011). "Long-term cardiovascular mortality after radiotherapy for breast cancer." J Am Coll Cardiol **57**(4): 445-452.

Bovelli, D., G. Plataniotis, F. Roila and O. b. o. t. E. G. W. Group (2010). "Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines." Ann Oncol **21**(suppl 5): v277-v282.

Breslow, N. E. and N. E. Day (1987). "Statistical methods in cancer research. Volume II--the design and analysis of cohort studies." IARC Sci Publ(82): 1-406.

Brewster, D. H., D. Clark, L. Hopkins, J. Bauer, S. H. Wild, A. B. Edgar and W. Hamish Wallace (2013). "Subsequent mortality experience in five-year survivors of childhood, adolescent and young adult cancer in Scotland: A population based, retrospective cohort study." Eur J Cancer.

Brewster, D. H., D. Clark, L. Hopkins, J. Bauer, S. H. Wild, A. B. Edgar and W. Hamish Wallace (2013). "Subsequent mortality experience in five-year survivors of childhood, adolescent and young adult cancer in Scotland: A population based, retrospective cohort study." European Journal of Cancer **49**(15): 3274-3283.

Brewster, D. H., D. Clark, L. Hopkins, J. Bauer, S. H. Wild, A. B. Edgar and W. H. Wallace (2014). "Subsequent hospitalisation experience of 5-year survivors of childhood, adolescent, and young adult cancer in Scotland: a population based, retrospective cohort study." Br J Cancer **110**(5): 1342-1350.

Brown, L. M., B. E. Chen, R. M. Pfeiffer, C. Schairer, P. Hall, H. Storm, E. Pukkala, F. Langmark, M. Kaijser, M. Andersson, H. Joensuu, S. D. Fossa and L. B. Travis (2007). "Risk of second non-hematological malignancies among 376,825 breast cancer survivors." Breast Cancer Res Treat **106**(3): 439-451.

Burke, M. E., K. Albritton and N. Marina (2007). "Challenges in the recruitment of adolescents and young adults to cancer clinical trials." Cancer **110**(11): 2385-2393.

Cancer Research UK. (2014). "CancerStats: All cancers combined - Survival." Retrieved 02/09/2014.

Cancer Research UK. (2014). "CancerStats: Breast cancer - Survival." Retrieved 02/09/2014.

Cancer Research UK. (2014). "CancerStats: Teenage and young adult cancer." Retrieved 02/09/2014.

Cancer Research UK. (2014). "CancerStats: Testicular cancer." Retrieved 02/09/2014.

Cardous-Ubbink, M. C., R. C. Heinen, N. E. Langeveld, P. J. Bakker, P. A. Voute, H. N. Caron and F. E. van Leeuwen (2004). "Long-term cause-specific mortality among five-year survivors of childhood cancer." Pediatr Blood Cancer **42**(7): 563-573.

Castellino, S. M., A. M. Geiger, A. C. Mertens, W. M. Leisenring, J. A. Tooze, P. Goodman, M. Stovall, L. L. Robison and M. M. Hudson (2011). "Morbidity and mortality in long-term survivors of Hodgkin lymphoma: A report from the Childhood Cancer Survivor Study." Blood **117**(6): 1806-1816.

Chakma, J., G. H. Sun, J. D. Steinberg, S. M. Sammut and R. Jagsi (2014). "Asia's ascent — Global trends in biomedical R&D expenditures." N Engl J Med **370**(1): 3-6.

Coccia, P. F., J. Altman, S. Bhatia, S. C. Borinstein, J. Flynn, S. George, R. Goldsby, R. Hayashi, M. S. Huang, R. H. Johnson, L. K. Beaupin, M. P. Link, K. C. Oeffinger, K. M. Orr, A. S. Pappo, D. Reed, H. L. Spraker, D. A. Thomas, M. von Mehren, D. S. Wechsler, K. F. Whelan, B. J. Zebrack, H. Sundar and D. A. Shead (2012). "Adolescent and young adult oncology. Clinical practice guidelines in oncology." J Natl Compr Canc Netw **10**(9): 1112-1150.

Corn, B. W., B. J. Trock and R. L. Goodman (1990). "Irradiation-related ischemic heart disease." J Clin Oncol **8**(4): 741-750.

Correa, C. R., H. I. Litt, W.-T. Hwang, V. A. Ferrari, L. J. Solin and E. E. Harris (2007). "Coronary artery findings after left-sided compared with right-sided radiation treatment for early-stage breast cancer." J Clin Oncol **25**(21): 3031-3037.

Coviello, V. and M. Boggess (2004). "Cumulative incidence estimation in the presence of competing risks." Stata Journal **4**(2): 103-112.

Croucher, C., J. S. Whelan, H. Møller and E. A. Davies (2009). "Trends in the incidence and survival of cancer in teenagers and young adults: Regional analysis for South East England 1960–2002." Clin Oncol **21**(5): 417-424.

Cutter, D. J., C. W. Taylor, K. Rahimi, P. McGale, V. Ferreira and S. C. Darby (2010). Effects of radiation therapy on the cardiovascular system. Cancer and the Heart. M. S. Ewer and E. T. Yeh, BC Decker.

Cuzick, J., H. Stewart, R. Peto, M. Baum, B. Fisher, H. Host, J. P. Lythgoe, G. Ribeiro, H. Scheurlen and A. Wallgren (1987). "Overview of randomized trials of postoperative adjuvant radiotherapy in breast cancer." Cancer Treat Rep **71**(1): 15-29.

Cuzick, J., H. Stewart, L. Rutqvist, J. Houghton, R. Edwards, C. Redmond, R. Peto, M. Baum, B. Fisher and H. Host (1994). "Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy." J Clin Oncol **12**(3): 447-453.

Darby, S. C., M. Ewertz, P. McGale, A. M. Bennet, U. Blom-Goldman, D. Brønnum, C. Correa, D. Cutter, G. Gagliardi, B. Gigante, M.-B. Jensen, A. Nisbet, R. Peto, K. Rahimi, C. Taylor and P. Hall (2013). "Risk of ischemic heart disease in women after radiotherapy for breast cancer." N Engl J Med **368**(11): 987-998.

Darby, S. C., P. McGale, R. Peto, F. Granath, P. Hall and A. Ekbom (2003). "Mortality from cardiovascular disease more than 10 years after radiotherapy for breast cancer: Nationwide cohort study of 90 000 Swedish women." BMJ **326**(7383): 256-257.

Darby, S. C., P. McGale, C. W. Taylor and R. Peto (2005). "Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: Prospective cohort study of about 300 000 women in US SEER cancer registries." Lancet Oncol **6**(8): 557-565.

Desandes, E., B. Lacour, A. Belot, F. Molinie, P. Delafosse, B. Tretarre, M. Velten, E. A. Sauleau, A. S. Woronoff, A. V. Guizard, O. Ganry, S. Bara, P. Grosclaude, X. Troussard, V. Bouvier, L. Brugieres and J. Clavel (2013). "Cancer incidence and survival in adolescents and young adults in France, 2000-2008." Pediatr Hematol Oncol **30**(4): 291-306.

Deutsch, M., S. R. Land, M. Begovic, H. S. Wieand, N. Wolmark and B. Fisher (2003). "The incidence of lung carcinoma after surgery for breast carcinoma with and without postoperative radiotherapy." Cancer **98**(7): 1362-1368.

Devis, T. and C. Rooney (1999). "Death certification and the epidemiologist." Health Stat Q **01**: 21-33.

Doyle, J. J., A. I. Neugut, J. S. Jacobson, J. Wang, R. McBride, A. Grann, V. R. Grann and D. Hershman (2007). "Radiation therapy, cardiac risk factors, and cardiac toxicity in early-stage breast cancer patients." Int J Radiat Oncol Biol Phys **68**(1): 82-93.

Early Breast Cancer Trialists' Collaborative Group (2000). "Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: An overview of the randomised trials." Lancet **355**: 1757-1770.

Early Breast Cancer Trialists' Collaborative Group (2005). "Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials." Lancet **365**(9472): 1687-1717.

Early Breast Cancer Trialists' Collaborative Group (2005). "Effects of radiotherapy and of

differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials." Lancet **366**(9503): 2087-2106.

Early Breast Cancer Trialists' Collaborative Group (2011). "Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: Meta-analysis of individual patient data for 10 801 women in 17 randomised trials." Lancet **378**(9804): 1707-1716.

Early Breast Cancer Trialists' Collaborative Group (2014). "Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: Meta-analysis of individual patient data for 8135 women in 22 randomised trials." Lancet.

Early Breast Cancer Trialists' Collaborative Group (2007). Long term toxicity of radiation therapy. In: 2006 Update of the Early Breast Cancer Trialists' Collaborative group overview of radiation therapy for early breast cancer. . American Society of Clinical Oncology Annual Meeting, Chicago.

Fern, L., S. Davies, T. Eden, R. Feltbower, R. Grant, M. Hawkins, I. Lewis, E. Loucaides, C. Rowntree, S. Stenning and J. Whelan (2008). "Rates of inclusion of teenagers and young adults in England into National Cancer Research Network clinical trials: report from the National Cancer Research Institute (NCRI) Teenage and Young Adult Clinical Studies Development Group." Br J Cancer **99**(12): 1967-1974.

Fernandez, C. V. and R. D. Barr (2006). "Adolescents and young adults with cancer: An orphaned population." Paediatr Child Health **11**(2): 103-106.

Fisher, B., S. Anderson, J. Bryant, R. Margolese, M. Deutsch, E. Fisher, J. Jeong and N. Wolmark (2002). "Twenty-year follow-up of a randomised trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer." N Engl J Med **347**: 1233 - 1241.

Floyd, J. D., D. T. Nguyen, R. L. Lobins, Q. Bashir, D. C. Doll and M. C. Perry (2005). "Cardiotoxicity of cancer therapy." J Clin Oncol **23**(30): 7685-7696.

Ford, M. B., A. J. Sigurdson, E. S. Petrulis, C. S. Ng, B. Kemp, C. Cooksley, M. McNeese, B. J. Selwyn, M. R. Spitz and M. L. Bondy (2003). "Effects of smoking and radiotherapy on lung carcinoma in breast carcinoma survivors." Cancer **98**(7): 1457-1464.

Forman D., F. Bray, D. H. Brewster, C. Gombe Mbalawa, B. Kohler, M. Piñeros, E. Steliarova-Foucher, R. Swaminathan and J. Ferlay eds (2013). "Cancer Incidence in Five Continents, Vol. X" (electronic version) Lyon, IARC. http://ci5.iarc.fr last accessed on [07/03/2015].

Fossa, S. D., N. Aass, S. Harvei and S. Tretli (2004). "Increased mortality rates in young and middle-aged patients with malignant germ cell tumours." Br J Cancer **90**(3): 607-612.

Fossa, S. D., E. Gilbert, G. M. Dores, J. Chen, K. A. McGlynn, S. Schonfeld, H. Storm, P. Hall, E. Holowaty, A. Andersen, H. Joensuu, M. Andersson, M. Kaijser, M. Gospodarowicz, R. Cohen, E. Pukkala and L. B. Travis (2007). "Noncancer causes of death in survivors of testicular cancer." J Natl Cancer Inst **99**(7): 533-544.

Fuller, S. A., J. L. Haybittle, R. E. A. Smith and H. J. Dobbs (1992). "Cardiac doses in post-operative breast irradiation." Radiother Oncol **25**(1): 19-24.

Furukawa, K., D. L. Preston, S. Lonn, S. Funamoto, S. Yonehara, T. Matsuo, H. Egawa, S. Tokuoka, K. Ozasa, F. Kasagi, K. Kodama and K. Mabuchi (2010). "Radiation and smoking effects on lung cancer incidence among atomic bomb survivors." Radiat Res **174**(1): 72-82.

Gilbert, E. S., M. Stovall, M. Gospodarowicz, F. E. Van Leeuwen, M. Andersson, B. Glimelius, T. Joensuu, C. F. Lynch, R. E. Curtis, E. Holowaty, H. Storm, E. Pukkala, M. B. van't Veer, J. F. Fraumeni, J. D. Boice, Jr., E. A. Clarke and L. B. Travis (2003). "Lung cancer after treatment for Hodgkin's disease: Focus on radiation effects." Radiat Res **159**(2): 161-173.

Giordano, S. H., Y.-F. Kuo, J. L. Freeman, T. A. Buchholz, G. N. Hortobagyi and J. S. Goodwin (2005). "Risk of cardiac death after adjuvant radiotherapy for breast cancer." J Natl Cancer Inst **97**(6): 419-424.

Giordano, S. H., Y. F. Kuo, Z. Duan, G. N. Hortobagyi, J. Freeman and J. S. Goodwin (2008). "Limits of observational data in determining outcomes from cancer therapy." Cancer **112**(11): 2456-2466.

Green, D. M., A. Hyland, C. S. Chung, M. A. Zevon and B. C. Hall (1999). "Cancer and cardiac mortality among 15-year survivors of cancer diagnosed during childhood or adolescence." J Clin Oncol **17**(10): 3207-3215.

Gutt, R., C. R. Correa, W.-T. Hwang, L. J. Solin, H. I. Litt, V. A. Ferrari and E. E. Harris (2008). "Cardiac morbidity and mortality after breast conservation treatment in patients with early-stage breast cancer and preexisting cardiac disease." Clin Breast Cancer **8**(5): 443-448.

Gyenes, G. (1998). "Radiation-induced ischemic heart disease in breast cancer -- A review." Acta Oncol **37**(3): 241-246.

Hancock, S. L., M. A. Tucker and R. T. Hoppe (1993). "Factors affecting late mortality from heart disease after treatment of Hodgkin's disease." JAMA **270**(16): 1949-1955.

Harris, E. E. R., C. Correa, W.-T. Hwang, J. Liao, H. I. Litt, V. A. Ferrari and L. J. Solin (2006). "Late cardiac mortality and morbidity in early-stage breast cancer patients after breast-conservation treatment." J Clin Oncol **24**(25): 4100-4106.

Haupt, R., M. G. Valsecchi, D. Silvestri, P. De Lorenzo, S. Napoli, G. Masera, B. Terracini and M. Jankovic (2000). "Early and late deaths after elective end of therapies for childhood cancer in Italy." Int J Cancer **86**(3): 393-398.

Hawkins, M. M., E. R. Lancashire, D. L. Winter, C. Frobisher, R. C. Reulen, A. J. Taylor, M. C. G. Stevens and M. E. M. Jenney (2008). "The British Childhood Cancer Survivor Study: Objectives, methods, population structure, response rates and initial descriptive information." Pediatr Blood Cancer **50**: 1018-1025.

Haybittle, J. L., D. Brinkley, J. Houghton, R. P. A'Hern and M. Baum (1989). "Postoperative radiotherapy and late mortality: Evidence from the Cancer Research Campaign trial for early breast cancer." BMJ **298**(6688): 1611-1614.

Heidenreich, P. A. and J. R. Kapoor (2009). "Radiation induced heart disease." Heart **95**(3): 252-258.

Henson, K. E., P. McGale, C. Taylor and S. C. Darby (2013). "Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer." Br J Cancer **108**(1): 179-182.

Hojris, I., M. Overgaard, J. J. Christensen and J. Overgaard (1999). "Morbidity and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: Analysis of DBCG 82b and 82c randomised trials. Radiotherapy Committee of the Danish Breast Cancer Cooperative Group." Lancet **354**(9188): 1425-1430.

Hooning, M. J., A. Botma, B. M. Aleman, M. H. Baaijens, H. Bartelink, J. G. Klijn, C. W. Taylor and F. E. van Leeuwen (2007). "Long-term risk of cardiovascular disease in 10-year survivors of breast cancer." J Natl Cancer Inst **99**(5): 365-375.

Hoppe, R. T. (1997). "Hodgkin's disease: Complications of therapy and excess mortality." Ann Oncol **8**(suppl 1): S115-S118.

Høst, H., I. O. Brennhovd and M. Loeb (1986). "Postoperative radiotherapy in breast cancer—Long-term results from the Oslo study." Int J Radiat Oncol Biol Phys **12**(5): 727-732.

Howe, G. R. (1995). "Lung cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with lung cancer mortality in the Atomic Bomb survivors study." Radiat Res **142**(3): 295-304.

Hudson, M. M., C. A. Poquette, J. Lee, C. A. Greenwald, A. Shah, X. Luo, E. I. Thompson, J. A. Wilimas, L. E. Kun and W. M. Crist (1998). "Increased mortality after successful treatment for Hodgkin's disease." J Clin Oncol **16**(11): 3592-3600.

Hull, M. C., C. G. Morris, C. J. Pepine and N. P. Mendenhall (2003). "Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin Lymphoma treated with radiation therapy." JAMA **290**(21): 2831-2837.

Huyghe, E., T. Matsuda and P. Thonneau (2003). "Increasing incidence of testicular cancer worldwide: a review." J Urol **170**(1): 5-11.

Inskip, P. D., M. Stovall and J. T. Flannery (1994). "Lung cancer risk and radiation dose among women treated for breast cancer." J Natl Cancer Inst **86**(13): 983-988.

Institute of Medicine (2010). A national cancer clinical trials system for the 21st century: reinvigorating the NCI Cooperative Group program, The National Academies Press.

Intensity Modulated Radiation Therapy Collaborative Working Group (2001). "Intensity-modulated radiotherapy: Current status and issues of interest." Int J Radiat Oncol Biol Phys **51**(4): 880-914.

Jacobson, J. A., D. N. Danforth, K. H. Cowan, T. d'Angelo, S. M. Steinberg, L. Pierce, M. E. Lippman, A. S. Lichter, E. Glatstein and P. Okunieff (1995). "Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer." N Engl J Med **332**(14): 907-911.

Jagsi, R. (2014). "Progress and controversies: radiation therapy for invasive breast cancer." CA Cancer J Clin **64**(2): 135-152.

Jagsi, R., P. Abrahamse, S. T. Hawley, J. J. Graff, A. S. Hamilton and S. J. Katz (2012). "Underascertainment of radiotherapy receipt in Surveillance, Epidemiology, and End Results registry data." Cancer **118**(2): 333-341.

Jagsi, R., P. Abrahamse, M. Morrow, S. T. Hawley, J. J. Griggs, J. J. Graff, A. S. Hamilton and S. J. Katz (2010). "Patterns and correlates of adjuvant radiotherapy receipt after lumpectomy and after mastectomy for breast cancer." J Clin Oncol **28**(14): 2396-2403.

Jagsi, R., J. E. Bekelman, A. Chen, R. C. Chen, K. Hoffman, Y.-C. Tina Shih, B. D. Smith and J. B. Yu (2014). "Considerations for observational research using large data sets in radiation oncology." Int J Radiat Oncol Biol Phys **90**(1): 11-24.

Jagsi, R., K. A. Griffith, T. Koelling, R. Roberts and L. J. Pierce (2007). "Rates of myocardial infarction and coronary artery disease and risk factors in patients treated with radiation therapy for early-stage breast cancer." Cancer **109**(4): 650-657.

Jagsi, R., J. Moran, R. Marsh, K. Masi, K. A. Griffith and L. J. Pierce (2010). "Evaluation of four techniques using intensity-modulated radiation therapy for comprehensive locoregional irradiation of breast cancer." Int J Radiat Oncol Biol Phys **78**(5): 1594-1603.

Janjan, N. A., M. T. Gillin, J. Prows, S. Arnold, G. Haasler, M. K. Thorsen, R. Jennings and J. F. Wilson (1989). "Dose to the cardiac vascular and conduction systems in primary breast irradiation." Med Dosim **14**(2): 81-87.

Jones, J. M. and G. G. Ribeiro (1989). "Mortality patterns over 34 years of breast cancer patients in a clinical trial of post-operative radiotherapy." Clin Radiol **40**(2): 204-208.

Kaufman, E. L., J. S. Jacobson, D. L. Hershman, M. Desai and A. I. Neugut (2008). "Effect of breast cancer radiotherapy and cigarette smoking on risk of second primary lung cancer." J Clin Oncol **26**(3): 392-398.

Kero, A., L. Jarvela, M. Arola, N. Malila, L. Madanat-Harjuoja, J. Matomaki and P. Lahteenmaki (2014). "Late mortality among 5-year survivors of early onset cancer: A population-based register study." Int J Cancer.

Kero, A. E., L. S. Jarvela, M. Arola, N. Malila, L. M. Madanat-Harjuoja, J. Matomaki and P. M. Lahteenmaki (2014). "Cardiovascular morbidity in long-term survivors of early-onset cancer: A population-based study." Int J Cancer **134**(3): 664-673.

Korn, E. L. and B. Freidlin (2012). "Methodology for comparative effectiveness research: Potential and limitations." J Clin Oncol **30**(34): 4185-4187.

Landier, W., S. Bhatia, D. A. Eshelman, K. J. Forte, T. Sweeney, A. L. Hester, J. Darling, F. D. Armstrong, J. Blatt, L. S. Constine, C. R. Freeman, D. L. Friedman, D. M. Green, N. Marina, A. T. Meadows, J. P. Neglia, K. C. Oeffinger, L. L. Robison, K. S. Ruccione, C. A. Sklar and M. M. Hudson (2004). "Development of risk-based guidelines for pediatric cancer survivors: the Children's

Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline." J Clin Oncol **22**(24): 4979-4990.

Lavey, R. S., N. L. Eby and L. R. Prosnitz (1990). "Impact of radiation therapy and/or chemotherapy on the risk for a second malignancy after breast cancer." Cancer **66**(5): 874-881.

Lawless, S. C., P. Verma, D. M. Green and M. C. Mahoney (2007). "Mortality experiences among 15+ year survivors of childhood and adolescent cancers." Pediatr Blood Cancer **48**(3): 333-338.

Lewington, S., R. Clarke, N. Qizilbash, R. Peto and R. Collins (2002). "Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies." Lancet **360**(9349): 1903-1913.

Lorigan, P., R. Califano, C. Faivre-Finn, A. Howell and N. Thatcher (2010). "Lung cancer after treatment for breast cancer." Lancet Oncol **11**(12): 1184-1192.

Lyman, G. H. and M. Levine (2012). "Comparative effectiveness research in oncology: An overview." J Clin Oncol **30**(34): 4181-4184.

MacArthur, A. C., J. J. Spinelli, P. C. Rogers, K. J. Goddard, Z. U. Abanto and M. L. McBride (2007). "Mortality among 5-year survivors of cancer diagnosed during childhood or adolescence in British Columbia, Canada." Pediatr Blood Cancer **48**(4): 460-467.

Magne, N., C. Chargari, D. Macdermed, R. Conforti, L. Vedrine, J. P. Spano and D. Khayat (2010). "Tomorrow's targeted therapies in breast cancer patients: What is the risk for increased radiation-induced cardiac toxicity?" Crit Rev Oncol Hematol.

Malin, J. L., K. L. Kahn, J. Adams, L. Kwan, M. Laouri and P. A. Ganz (2002). "Validity of cancer registry data for measuring the quality of breast cancer care." J Natl Cancer Inst **94**(11): 835-844.

Marhin, W., E. Wai and S. Tyldesley (2007). "Impact of fraction size on cardiac mortality in women treated with tangential radiotherapy for localised breast cancer." Int J Radiat Oncol Biol Phys **69**(2): 483-489.

Marini, G., S. Murray, A. Goldhirsch, R. D. Gelber, M. Castiglione-Gertsch, K. N. Price, M. H. Tattersall, C. M. Rudenstam, J. Collins, J. Lindtner, F. Cavalli, H. Cortes-Funes, A. Gudgeon, J. F. Forbes, E. Galligioni, A. S. Coates and H. J. Senn (1996). "The effect of adjuvant prednisone combined with CMF on patterns of relapse and occurrence of second malignancies in patients with breast cancer. International (Ludwig) Breast Cancer Study Group." Ann Oncol **7**(3): 245-250.

Mayer, R., L. Handl-Zeller, F. Quehenberger, J. Hammer, W. Rhomberg, K. Brinda-Raitmayr, B. Forthuber, R. Freund, B. Günczler, G. Kametriser, M. Metz, W. Raunik, I. Wedrich and R. Pötter (2007). "Austrian breast cancer Patterns-of-Care studies PCS93 and PCS01 versus PCS85 to identify changes in national practice." Strahlenther Onkol **183**(4): 170-176.

McGale, P. and S. C. Darby (2005). "Low doses of ionizing radiation and circulatory diseases: A systematic review of the published epidemiological evidence." Radiat Res **163**(3): 247-257.

McGale, P. and S. C. Darby (2008). "Commentary: A dose-response relationship for radiation-induced heart disease--current issues and future prospects." Int J Epidemiol **37**(3): 518-523.

McGale, P., S. C. Darby, P. Hall, J. Adolfsson, N.-O. Bengtsson, A. M. Bennet, T. Fornander, B. Gigante, M.-B. Jensen, R. Peto, K. Rahimi, C. W. Taylor and M. Ewertz (2011). "Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden." Radiother Oncol **100**(2): 167-175.

Merril, W. (2014, Jun 10, 2014). "Radiation-induced lung injury." Retrieved 08/09/2014, from http://www.uptodate.com/contents/radiation-induced-lung-injury?source=search_result&search=radiation+induced+lung+cancer&selectedTitle=1~150.

Mertens, A. C., Q. Liu, J. P. Neglia, K. Wasilewski, W. Leisenring, G. T. Armstrong, L. L. Robison and Y. Yasui (2008). "Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study." J Natl Cancer Inst **100**(19): 1368-1379.

Mertens, A. C., Y. Yasui, J. P. Neglia, J. D. Potter, M. E. Nesbit Jr, K. Ruccione, W. A. Smithson and L. L. Robison (2001). "Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study." J Clin Oncol **19**(13): 3163-3172.

Meyer, A.-M., S. B. Wheeler, M. Weinberger, R. C. Chen and W. R. Carpenter (2014). "An overview of methods for comparative effectiveness research." Semin Radiat Oncol **24**(1): 5-13.

Mitchell, A. E., D. L. Scarcella, G. L. Rigutto, V. J. Thursfield, G. G. Giles, M. Sexton and D. M. Ashley (2004). "Cancer in adolescents and young adults: treatment and outcome in Victoria." Med J Aust **180**(2): 59-62.

Moller, T. R., S. Garwicz, L. Barlow, J. Falck Winther, E. Glattre, G. Olafsdottir, J. H. Olsen, R. Perfekt, A. Ritvanen, R. Sankila and H. Tulinius (2001). "Decreasing late mortality among five-year survivors of cancer in childhood and adolescence: A population-based study in the Nordic countries." J Clin Oncol **19**(13): 3173-3181.

Monsuez, J. J., J. C. Charniot, N. Vignat and J. Y. Artigou (2010). "Cardiac side-effects of cancer chemotherapy." Int J Cardiol **144**(1): 3-15.

Mulrooney, D. A., M. W. Yeazel, T. Kawashima, A. C. Mertens, P. Mitby, M. Stovall, S. S. Donaldson, D. M. Green, C. A. Sklar, L. L. Robison and W. Leisenring (2009). "Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: Retrospective analysis of the Childhood Cancer Survivor Study cohort." BMJ **339**.

Nalbantov, G., B. Kietselaer, K. Vandecasteele, C. Oberije, M. Berbee, E. Troost, A. M. Dingemans, A. van Baardwijk, K. Smits, A. Dekker, J. Bussink, D. De Ruysscher, Y. Lievens and P. Lambin (2013). "Cardiac comorbidity is an independent risk factor for radiation-induced lung toxicity in lung cancer patients." Radiother Oncol **109**(1): 100-106.

National Cancer Research Institute (2008). "NCRI Strategic Plan 2008-2013."

National Institute for Health and Clinical Excellence (2005). "Guidance on Cancer Services - Improving Outcomes in Children and Young People with Cancer. ISBN: 1-84629-067-8 ".

National Institute for Health and Clinical Excellence (2011). "Hypertension: Clinical management of primary hypertension in adults (update)." Clinical guideline 127 http://guidance.nice.org.uk/CG127.

Neugut, A. I., W. C. Lee, T. Murray, E. Robinson, K. Karwoski and G. J. Kutcher (1993). "Lung cancer after radiation therapy for breast cancer." Cancer **71**(10): 3054-3057.

Neugut, A. I., T. Murray, J. Santos, H. Amols, M. K. Hayes, J. T. Flannery and E. Robinson (1994). "Increased risk of lung cancer after breast cancer radiation therapy in cigarette smokers." Cancer **73**(6): 1615-1620.

Ng, A. K., M. P. Bernardo, E. Weller, K. H. Backstrand, B. Silver, K. C. Marcus, N. J. Tarbell, J. Friedberg, G. P. Canellos and P. M. Mauch (2002). "Long-term survival and competing causes of death in patients with early-stage Hodgkin's disease treated at age 50 or younger." J Clin Oncol **20**(8): 2101-2108.

Ng, J., I. Shuryak, Y. Xu, K. S. Clifford Chao, D. J. Brenner and R. J. Burri (2012). "Predicting the risk of secondary lung malignancies associated with whole-breast radiation therapy." Int J Radiat Oncol Biol Phys **83**(4): 1101-1106.

Nichols, M., N. Townsend, P. Scarborough and M. Rayner (2014). "Cardiovascular disease in Europe 2014: epidemiological update." Eur Heart J.

Nissen, H. D. and A. L. Appelt (2013). "Improved heart, lung and target dose with deep inspiration breath hold in a large clinical series of breast cancer patients." Radiother Oncol **106**(1): 28-32.

Nixon, A. J., J. Manola, R. Gelman, B. Bornstein, A. Abner, S. Hetelekidis, A. Recht and J. R. Harris (1998). "No long-term increase in cardiac-related mortality after breast-conserving surgery and radiation therapy using modern techniques." J Clin Oncol **16**(4): 1374-1379.

Obedian, E., D. B. Fischer and B. G. Haffty (2000). "Second malignancies after treatment of early-stage breast cancer: Lumpectomy and radiation therapy versus mastectomy." J Clin Oncol **18**(12): 2406-2412.

Overgaard, M., P. S. Hansen, J. Overgaard, C. Rose, M. Andersson, F. Bach, M. Kjaer, C. C. Gadeberg, H. T. Mouridsen, M.-B. Jensen and K. Zedeler (1997). "Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy." N Engl J Med **337**(14): 949-955.

Overgaard, M., M. B. Jensen, J. Overgaard, P. S. Hansen, C. Rose, M. Andersson, C. Kamby, M. Kjaer, C. C. Gadeberg, B. B. Rasmussen, M. Blichert-Toft and H. T. Mouridsen (1999). "Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial." Lancet **353**(9165): 1641-1648.

Ozasa, K., Y. Shimizu, A. Suyama, F. Kasagi, M. Soda, E. J. Grant, R. Sakata, H. Sugiyama and K. Kodama (2012). "Studies of the mortality of atomic bomb survivors, report 14, 1950-2003: An overview of cancer and noncancer diseases." Radiat Res **177**: 229-243.

Paszat, L. F., W. J. Mackillop, P. A. Groome, C. Boyd, K. Schulze and E. Holowaty (1998). "Mortality from myocardial infarction after adjuvant radiotherapy for breast cancer in the Surveillance, Epidemiology, and End Results cancer registries." J Clin Oncol **16**(8): 2625-2631.

Paszat, L. F., W. J. Mackillop, P. A. Groome, K. Schulze and E. Holowaty (1999). "Mortality from

myocardial infarction following postlumpectomy radiotherapy for breast cancer: A population-based study in Ontario, Canada." Int J Radiat Oncol Biol Phys **43**(4): 755-762.

Paszat, L. F., K. A. Vallis, V. M. Benk, P. A. Groome, W. J. Mackillop and A. Wielgosz (2007). "A population-based case-cohort study of the risk of myocardial infarction following radiation therapy for breast cancer." Radiother Oncol **82**(3): 294-300.

Patt, D. A., J. S. Goodwin, Y. F. Kuo, J. L. Freeman, D. D. Zhang, T. A. Buchholz, G. N. Hortobagyi and S. H. Giordano (2005). "Cardiac morbidity of adjuvant radiotherapy for breast cancer." J Clin Oncol **23**(30): 7475-7482.

Pearce, M. S., L. Parker, K. P. Windebank, S. J. Cotterill and A. W. Craft (2005). "Cancer in adolescents and young adults aged 15–24 years: A report from the North of England young person's malignant disease registry, UK." Pediatr Blood Cancer **45**(5): 687-693.

Peto, R., A. D. Lopez and et al (2010). "Mortality from smoking in developed countries 1950-2010 (http://www.ctsu.ox.ac.uk/research/mega-studies/mortality-from-smoking-in-developed-countries-1950-2010)."

Pinder, M. C., Z. Duan, J. S. Goodwin, G. N. Hortobagyi and S. H. Giordano (2007). "Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer." J Clin Oncol **25**(25): 3808-3815.

Pirie, K., R. Peto, G. K. Reeves, J. Green and V. Beral (2013). "The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK." The Lancet **381**(9861): 133-141.

Pollock, B. H. and J. M. Birch (2008). "Registration and classification of adolescent and young adult cancer cases." Pediatr Blood Cancer **50**(S5): 1090-1093.

Prasad, P. K., L. B. Signorello, D. L. Friedman, J. D. Boice, Jr. and E. Pukkala (2012). "Long-term non-cancer mortality in pediatric and young adult cancer survivors in Finland." Pediatr Blood Cancer **58**(3): 421-427.

Preston, D. L., Y. Shimizu, D. A. Pierce, A. Suyama and K. Mabuchi (2003). "Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950–1997." Radiat Res **160**(4): 381-407.

Prochazka, M., F. Granath, A. Ekbom, P. G. Shields and P. Hall (2002). "Lung cancer risks in women with previous breast cancer." Eur J Cancer **38**(11): 1520-1525.

Prochazka, M., P. Hall, G. Gagliardi, F. Granath, B. N. Nilsson, P. G. Shields, M. Tennis and K. Czene (2005). "Ionizing radiation and tobacco use increases the risk of a subsequent lung carcinoma in women with breast cancer: Case-only design." J Clin Oncol **23**(30): 7467-7474.

Ragaz, J., I. A. Olivotto, J. J. Spinelli, N. Phillips, S. M. Jackson, K. S. Wilson, M. A. Knowling, C. M. Coppin, L. Weir, K. Gelmon, N. Le, R. Durand, A. J. Coldman and M. Manji (2005). "Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomised trial." J Natl Cancer Inst **97**(2): 116-126.

Rayter, Z. (2008). History of breast cancer therapy. Medical Therapy of Breast Cancer. Z. Rayter and J. Mansi, Cambridge University Press.

Recht, A., S. B. Edge, L. J. Solin, D. S. Robinson, A. Estabrook, R. E. Fine, G. F. Fleming, S. Formenti, C. Hudis, J. J. Kirshner, D. A. Krause, R. R. Kuske, A. S. Langer, G. W. Sledge, T. J. Whelan, D. G. Pfister and f. t. A. S. o. C. Oncology (2001). "Postmastectomy radiotherapy: Clinical practice guidelines of the American Society of Clinical Oncology." J Clin Oncol **19**(5): 1539-1569.

Reulen, R. C., D. L. Winter, C. Frobisher, E. R. Lancashire, C. A. Stiller, M. E. M. Jenney, R. Skinner, M. C. Stevens and M. Hawkins (2010). "Long-term cause-specific mortality among survivors of childhood cancer." JAMA **304**(2): 172-179.

Roychoudhuri, R., D. Robinson, V. Putcha, J. Cuzick, S. Darby and H. Moller (2007). "Increased cardiovascular mortality more than fifteen years after radiotherapy for breast cancer: a population-based study." BMC Cancer **7**: 9.

Rubino, C., F. de Vathaire, A. Shamsaldin, M. Labbe and M. G. Le (2003). "Radiation dose, chemotherapy, hormonal treatment and risk of second cancer after breast cancer treatment." Br J Cancer **89**(5): 840-846.

Rugbjerg, K., L. Mellemkjaer, J. D. Boice, L. Kober, M. Ewertz and J. H. Olsen (2014). "Cardiovascular disease in survivors of adolescent and young adult cancer: A Danish cohort study, 1943-2009." J Natl Cancer Inst **106**(6).

Rutqvist, L. E. and H. Johansson (1990). "Mortality by laterality of the primary tumour among 55,000 breast cancer patients from the Swedish Cancer Registry." Br J Cancer **61**(6): 866-868.

Rutqvist, L. E., I. Lax, T. Fornander and H. Johansson (1992). "Cardiovascular mortality in a randomised trial of adjuvant radiation therapy versus surgery alone in primary breast cancer." Int J Radiat Oncol Biol Phys **22**(5): 887-896.

Rutqvist, L. E., A. Liedberg, N. Hammar and K. Dalberg (1998). "Myocardial infarction among women with early-stage breast cancer treated with conservative surgery and breast irradiation." Int J Radiat Oncol Biol Phys **40**(2): 359-363.

Schonfeld, S. J., R. E. Curtis, W. F. Anderson and A. Berrington de Gonzalez (2012). "The risk of a second primary lung cancer after a first invasive breast cancer according to estrogen receptor status." Cancer Causes Control **23**(10): 1721-1728.

Schubert, L. K., V. Gondi, E. Sengbusch, D. C. Westerly, E. T. Soisson, B. R. Paliwal, T. R. Mackie, M. P. Mehta, R. R. Patel, W. A. Tomé and G. M. Cannon (2011). "Dosimetric comparison of left-sided whole breast irradiation with 3DCRT, forward-planned IMRT, inverse-planned IMRT, helical tomotherapy, and topotherapy." Radiother Oncol **100**(2): 241-246.

Schultz-Hector, S. and K.-R. Trott (2007). "Radiation-induced cardiovascular diseases: Is the epidemiologic evidence compatible with the radiobiologic data?" Int J Radiat Oncol Biol Phys **67**(1): 10-18.

Scottish Intercollegiate Guidelines Network "76 Long term follow up of survivors of childhood cancer - A national clinical guidline. http://www.sign.ac.uk ".

Shank, B., J. Moughan, J. Owen, F. Wilson and G. E. Hanks (2000). "The 1993-94 patterns of care process survey for breast irradiation after breast-conserving surgery-comparison with the 1992 standard for breast conservation treatment." Int J Radiat Oncol Biol Phys **48**(5): 1291-1299.

Shapiro, C. L. and A. Recht (2001). "Side effects of adjuvant treatment of breast cancer." N Engl J Med **344**(26): 1997-2008.

Shimizu, Y., K. Kodama, N. Nishi, F. Kasagi, A. Suyama, M. Soda, E. J. Grant, H. Sugiyama, R. Sakata, H. Moriwaki, M. Hayashi, M. Konda and R. E. Shore (2010). "Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950-2003." BMJ **340**: b5349.

Skinner, R., W. H. Wallace and G. A. Lewitt "Therapy Based Long Term Follow Up (2nd Edition) - Practice Statement 2005. ." United Kingdom Children's Cancer Study Group - Late Effects Group (LEG)

Smith, L. A., V. R. Cornelius, C. J. Plummer, G. Levitt, M. Verrill, P. Canney and A. Jones (2010). "Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials." BMC Cancer **10**: 337.

Solin, L. J., B. L. Fowble, K. L. Martz, R. L. Goodman and G. E. Hanks (1990). "Results of the 1983 patterns of care process survey for definitive breast irradiation." Int J Radiat Oncol Biol Phys **20**: 105-111.

Soulos, P. R., J. B. Yu, K. B. Roberts, A. C. Raldow, J. Herrin, J. B. Long and C. P. Gross (2012). "Assessing the impact of a Cooperative Group Trial on breast cancer care in the Medicare population." J Clin Oncol **30**(14): 1601-1607.

Staffurth, J. (2010). "A review of the clinical evidence for intensity-modulated radiotherapy." Clin Oncol (R Coll Radiol) **22**(8): 643-657.

Stewart, J. R. and L. F. Fajardo (1984). "Radiation-induced heart disease: an update." Prog Cardiovasc Dis **27**(3): 173-194.

Stock, W., M. La, B. Sanford, C. D. Bloomfield, J. W. Vardiman, P. Gaynon, R. A. Larson and J. Nachman (2008). "What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies." Blood **112**(5): 1646-1654.

Swerdlow, A. J., C. D. Higgins, P. Smith, D. Cunningham, B. W. Hancock, A. Horwich, P. J. Hoskin, A. Lister, J. A. Radford, A. Z. Rohatiner and D. C. Linch (2007). "Myocardial infarction mortality risk after treatment for Hodgkin disease: A collaborative British cohort study." J Natl Cancer Inst **99**(3): 206-214.

Taghian, A., R. Jagsi, A. Makris, S. Goldberg, E. Ceilley, L. Grignon and S. Powell (2004). "Results of a survery regarding irradiation of internal mammary chain in patients with breast cancer: Practice is culture driver rather than evidence based." Int J Radiat Oncol Biol Phys **60**(3): 706-714.

Taylor, C. W. (2008). Breast cancer radiotherapy and heart disease. DPhil, University of Oxford.

Taylor, C. W., P. McGale and S. C. Darby (2006). "Cardiac risks of breast-cancer radiotherapy: A contemporary view." Clin Oncol (R Coll Radiol) **18**(3): 236-246.

Taylor, C. W., A. Nisbet, P. McGale and S. C. Darby (2007). "Cardiac exposures in breast cancer radiotherapy: 1950s–1990s." Int J Radiat Oncol Biol Phys **69**(5): 1484-1495.

Taylor, C. W., J. M. Povall, P. McGale, A. Nisbet, D. Dodwell, J. T. Smith and S. C. Darby (2008). "Cardiac dose from tangential breast cancer radiotherapy in the year 2006." Int J Radiat Oncol Biol Phys **72**(2): 501-507.

Tonorezos, E. S. and K. C. Oeffinger (2011). "Research challenges in adolescent and young adult cancer survivor research." Cancer **117**(S10): 2295-2300.

Travis, L. B. (1995). "Re: Lung cancer risk and radiation dose among women treated for breast cancer." J Natl Cancer Inst **87**(1): 60-61.

Travis, L. B., M. Gospodarowicz, R. E. Curtis, E. A. Clarke, M. Andersson, B. Glimelius, T. Joensuu, C. F. Lynch, F. E. van Leeuwen, E. Holowaty, H. Storm, I. Glimelius, E. Pukkala, M. Stovall, J. F. Fraumeni, Jr., J. D. Boice, Jr. and E. Gilbert (2002). "Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease." J Natl Cancer Inst **94**(3): 182-192.

Travis, L. B., A. K. Ng, J. M. Allan, C.-H. Pui, A. R. Kennedy, X. G. Xu, J. A. Purdy, K. Applegate, J. Yahalom, L. S. Constine, E. S. Gilbert and J. D. Boice (2012). "Second malignant neoplasms and cardiovascular disease following radiotherapy." J Natl Cancer Inst **104**(5): 357-370.

United Nations Scientific Committee on the Effects of Atomic Radiation (2008). Sources of ionizing radiation, UNSCEAR 2008 report Vol. I, United Nationas.

Usvasalo, A., R. Raty, S. Knuutila, K. Vettenranta, A. Harila-Saari, E. Jantunen, M. Kauppila, P. Koistinen, K. Parto, P. Riikonen, T. T. Salmi, R. Silvennoinen, E. Elonen and U. M. Saarinen-Pihkala (2008). "Acute lymphoblastic leukemia in adolescents and young adults in Finland." Haematologica **93**(8): 1161-1168.

Vallis, K. A., M. Pintilie, N. Chong, E. Holowaty, P. S. Douglas, P. Kirkbride and A. Wielgosz (2002). "Assessment of coronary heart disease morbidity and mortality after radiation therapy for early breast cancer." J Clin Oncol **20**(4): 1036-1042.

van den Belt-Dusebout, A. W., J. Nuver, R. de Wit, J. A. Gietema, W. W. ten Bokkel Huinink, P. T. Rodrigus, E. C. Schimmel, B. M. Aleman and F. E. van Leeuwen (2006). "Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer." J Clin Oncol **24**(3): 467-475.

van der Horst, M., J. F. Winther and J. H. Olsen (2006). "Cancer incidence in the age range 0-34 years: historical and actual status in Denmark." Int J Cancer **118**(11): 2816-2826.

van Laar, M., R. G. Feltbower, C. P. Gale, D. T. Bowen, S. E. Oliver and A. Glaser (2014). "Cardiovascular sequelae in long-term survivors of young peoples' cancer: A linked cohort study." Br J Cancer **110**(5): 1338-1341.

Vandenbroucke, J. (2004). "When are observational studies as credible as randomised trials?" Lancet **363**(9422): 1728-1731.

VanderWalde, A. M., C. L. Sun, L. Laddaran, L. Francisco, S. Armenian, J. Berano-Teh, F. L. Wong, L. Popplewell, G. Somlo, A. S. Stein, A. Nademanee, A. Krishnan, N. Kogut, S. J. Forman and S. Bhatia (2013). "Conditional survival and cause-specific mortality after autologous hematopoietic cell transplantation for hematological malignancies." Leukemia **27**(5): 1139-1145.

Veldeman, L., I. Madani, F. Hulstaert, G. De Meerleer, M. Mareel and W. De Neve (2008). "Evidence behind use of intensity-modulated radiotherapy: A systematic review of comparative clinical studies." Lancet Oncol **9**(4): 367-375.

Verrill, M. (2009). "Chemotherapy for early-stage breast cancer: a brief history." Br J Cancer **101**(S1): S2-S5.

Walker, G. V., S. H. Giordano, M. Williams, J. Jiang, J. Niu, J. MacKinnon, P. Anderson, B. Wohler, A. H. Sinclair, F. P. Boscoe, M. J. Schymura, T. A. Buchholz and B. D. Smith (2013). "Muddy water? Variation in reporting receipt of breast cancer radiation therapy by population-based tumor registries." Int J Radiat Oncol Biol Phys **86**(4): 686-693.

Whelan, J. S. and L. A. Fern (2008). "Poor accrual of teenagers and young adults into clinical trials in the UK." Lancet Oncol **9**(4): 306-307.

Woodward, E., M. Jessop, A. Glaser and D. Stark (2011). "Late effects in survivors of teenage and young adult cancer: Does age matter?" Ann Oncol **22**(12): 2561-2568.

Woodward, W. A., E. A. Strom, M. D. McNeese, G. H. Perkins, E. L. Outlaw, G. N. Hortobagyi, A. U. Buzdar and T. A. Buchholz (2003). "Cardiovascular death and second non–breast cancer malignancy after postmastectomy radiation and doxorubicin-based chemotherapy." Int J Radiat Oncol Biol Phys **57**(2): 327-335.

World Health Organization (2010). Gender, Women and the Tobacco Epidemic.

Yeh, E. T. and C. L. Bickford (2009). "Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management." J Am Coll Cardiol **53**(24): 2231-2247.

Yu, J. B., C. P. Gross, L. D. Wilson and B. D. Smith (2009). "NCI SEER public-use data: applications and limitations in oncology research." Oncology **23**(3): 288-295.

Zagars, G. K., M. T. Ballo, A. K. Lee and S. S. Strom (2004). "Mortality after cure of testicular seminoma." J Clin Oncol **22**(4): 640-647.

APPENDICES

Appendix A (for Chapter 1)

A.1 Age Standardised Incidence Rates in England and Wales for Individuals Diagnosed with Cancer Aged 15-39 by First Primary Tumour Group from Cancer Incidence in Five Continents Volume X[10]

Cancer	Males		Females	
	Cases	Age Standardised Rate per 100,000	Cases	Age Standardised Rate per 100,000
Lip (C00)	27	0	9	0
Tongue (C01-02)	173	0.3	123	0.2
Mouth (C03-06)	100	0.2	73	0.1
Salivary glands (C07-08)	112	0.2	162	0.3
Tonsil (C09)	62	0.1	39	0.1
Other oropharynx (C10)	6	0	3	0
Nasopharynx (C11)	100	0.2	57	0.1
Hypopharynx (C12-13)	11	0	2	0
Pharynx unspecified (C14)	15	0	6	0
Oesophagus (C15)	152	0.3	53	0.1
Stomach (C16)	223	0.4	215	0.4
Small intestine (C17)	68	0.1	50	0.1
Colon (C18)	711	1.4	688	1.3
Rectum (C19-20)	386	0.7	346	0.6
Anus (C21)	64	0.1	74	0.1
Liver (C22)	160	0.3	95	0.2
Gallbladder etc. (C23-24)	29	0.1	23	0
Pancreas (C25)	119	0.2	127	0.2
Nose, sinuses etc. (C30-31)	53	0.1	51	0.1
Larynx (C32)	45	0.1	35	0.1
Lung (incl. trachea and bronchus) (C33-34)	404	0.7	356	0.6
Other thoracic organs (C37-38)	120	0.2	46	0.1
Bone (C40-41)	482	1.1	317	0.7
Melanoma of skin (C43)	2387	4.6	4293	8.4
Other skin (C44)	3373	6.1	4200	7.5
Mesothelioma (C45)	19	0	15	0
Kaposi sarcoma (C46)	243	0.4	62	0.1
Connective and soft tissue (C47+C49)	563	1.2	448	0.9
Breast (C50)	29	0	9369	15.9
Penis (C60)	89	0.2		
Prostate (C61)	44	0.1		
Testis (C62)	5614	11.7		
Other male genital organs (C63)	24	0.1		

[10] http://ci5.iarc.fr/CI5-X/Pages/summary_table_pop_sel.aspx

Vulva (C51)			207	0.4
Vagina (C52)			50	0.1
Cervix uteri (C53)			4497	8.6
Corpus uteri (C54)			388	0.7
Uterus unspecified (C55)			38	0.1
Ovary (C56)			1886	3.7
Other female genital organs (C57)			15	0
Placenta (C58)			39	0.1
Kidney (C64)	410	0.7	315	0.6
Renal pelvis (C65)	12	0	3	0
Ureter (C66)	3	0	4	0
Bladder (C67)	466	0.8	180	0.3
Other urinary organs (C68)	4	0	2	0
Eye (C69)	75	0.1	82	0.2
Brain, nervous system (C70-72)	1392	2.8	941	1.9
Thyroid (C73)	493	1	1864	3.7
Adrenal gland (C74)	37	0.1	40	0.1
Other endocrine (C75)	99	0.2	36	0.1
Hodgkin lymphoma (C81)	1627	3.5	1422	3.3
Non-Hodgkin lymphoma (C82-85,C96)	1743	3.5	1094	2.2
Immunoproliferative diseases (C88)	6	0	3	0
Multiple myeloma (C90)	131	0.2	76	0.1
Lymphoid leukaemia (C91)	478	1.1	253	0.6
Myeloid leukaemia (C92-94)	727	1.5	617	1.3
Leukaemia unspecified (C95)	31	0.1	19	0
Myeloproliferative disorders	28	0.1	19	0
Myelodysplastic syndromes	12	0	8	0
Other and unspecified	466	0.9	434	0.8
All sites	**24247**	**47.9**	**35869**	**67.5**
All sites but skin	**20874**	**41.8**	**31669**	**60**

A.2 Summary of studies of 5-year Survival from TYA Cancer by First Primary Tumour Group

Study	Population	Calendar Period of Diagnosis	Number of survivors	Subgroup	All cancers	5-year survival (%) subdivided by FPT groups														
						Leukaemia	Lymphoma		Head & neck	Breast Cancer	Bone tumour	STS	Thyroid	Lung	Cervix & uterus	CNS	Germ cell	Carcinomas	Melanoma	NMSC	GU	GI tract	Ovary
							HL	NHL															
Desandes et al (2013)	France	2000-04	1,022 adolescents and 1,396 YAs	--	--	67.3		92.1	--	--	50.0	69.7	99.2	--	--	67.3	88.7	--	--	--	--	--	--
Aben et al (2012)	Netherlands Cancer Registry, Age 15-29	1989-09	23,161	15-19	76.2		91.7	74.1	92.5				-						90.9	-			
				20-24	80.8	--	92.4	71.6	75.6	--	--	--	95.3	--	--	--	--	--	86.4	91.7	--	--	--
				25-29	80.9		89.0	70.9	80.1				95.4						87.9	90.7			
Carreira et al (2012)	Portugal, aged 15-24	1997-06	1,223	15-29	77.2	47.8	89.9		-	-	67.5	51.9		-	-	56.4	--	--	--	--	--	--	--
				20-24	81.3	57.1	85.6		72.2	68.0	56.5	48.7		60.0	92.3	83.1							
Furlong et al (2012)	Ontario, Canada 15-29 years	1990-01	10,075	15-19	80																		
				20-24	85	58	85		--	--		69	--	--	--	67	93	86	93	--	--	--	--
				25-29	84																		
Gatta et al (2009)	EUROCARE Subgroup of adolescents only (15-24 years)	1995-02	30,187	--	--	--	93.1	74.4	--	85.5	61.8	67.5	99.5	72.1	85.7 (cervix only)	--	96.9	--	92.2	--	--	--	83.3
Pulte et al (2009)	SEER aged 15-24 with ALL, AML, CML, HL or NHL	1981-05	9,863	2001-05	--		94.8	78.4	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
van Gaal et al (2009)	Netherlands, aged 12-24	1989-03	1,118	--	80.8	60.4	87.0		--	--	61.3	68.4	--	--	--	65.5	92.3	87.1	95.0	--	--	--	--
Birch et al (2008)	England, 13-24 years old	1979-01	31,876	13-16	65	47	82		74	70	48	58		64	60 87	68		70	89				
				17-20	70	42	81		72	75	46	51	--	56	78	61	--	73	84	--	--	--	--
				21-24	74	40	82		80	58	54	55		51	(cervix only)	53		72	85				
Desandes (2007)	Aged 15-19 US: SEER Europe: 10 refs	Europe: 1988-97 US: 1985-99	--	15-19: Eur	73	44	81		--	--	48	67	--	--	--	70	87	88	--	--	--	--	--
				15-19: US	78	48	86				62	66				76	91	90					
Clavel et al (2006)	Hodgkin survivors, European-wide, aged 0-19	1978-97	4,230	15-19	--	--		89	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Folts et al (2006)	Adolescents: 16-21 years YAs: 22-45 years British Columbia, Canada	1981-04	256 adolescents 890 YAs	16-19	--	--	94	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
				22-45			95																
Stiller et al (2006)	European data, age 15-19	1978-97	15,399	--	--	44 (40-48)	89	64	--	--	48	67	99	--	--	70 (	90	--	88	98	--	--	--

Study	Population	Calendar Period of Diagnosis	Number of survivors	Subgroup	All cancers	5-year survival (%) subdivided by FPT groups																
						Leukaemia	Lymphoma		Head & neck	Breast Cancer	Bone tumour	STS	Thyroid	Lung	Cervix & uterus	CNS	Germ cell	Carcino mas	Melano ma	NMSC	GU	GI tract	Ovary
							HL	NHL															
Pearce et al (2005)	Northern England, age <25	1968-97	2,329	15-19 20-24	57 63				--	--	--	--	--	--	--	--	--	--	--	--	--	--
Gatta et al (2003)	EUROCARE	1990-94	15,101	--	--	--	89	67.8	--	67.5	56.7	56.7	98.7	59.6	82.0 (cervix only)	66.1	90	--	89.4	--	--	--	83.0
Pearce et al (2003)	Northern England, aged <25	1968-98	200	--	--	--		--	--	--	--	--	--	--	--	--	--	--		70	--	--	--
Wilkinson et al (2001)	Yorkshire, Aged 15-24	1985-94	1,097	--	75.2	--		--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Stiller et al (1999)	England and Wales with acute leukaemia	1984-94	879	15-19 20-24 25-29	--	**ALL:** 49 38 34 AML: 42 41 43		--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

A.3 References for Sections A.1 and A.2

Aben, K. K., C. van Gaal, N. A. van Gils, W. T. van der Graaf and G. A. Zielhuis (2012). "Cancer in adolescents and young adults (15–29 years): A population-based study in the Netherlands 1989–2009." Acta Oncologica **51**(7): 922-933.

Alston, R. D., M. Geraci, T. O. Eden, A. Moran, S. Rowan and J. M. Birch (2008). "Changes in cancer incidence in teenagers and young adults (ages 13 to 24 years) in England 1979-2003." Cancer **113**(10): 2807-2815.

Alston, R. D., S. Rowan, T. O. Eden, A. Moran and J. M. Birch (2007). "Cancer incidence patterns by region and socioeconomic deprivation in teenagers and young adults in England." Br J Cancer **96**(11): 1760-1766.

Arora, R. S., R. D. Alston, T. O. B. Eden, A. Moran, M. Geraci, C. O'Hara and J. M. Birch (2012). "Cancer at ages 15–29 years: The contrasting incidence in India and England." Pediatric Blood & Cancer **58**(1): 55-60.

Birch, J. M., D. Pang, R. D. Alston, S. Rowan, M. Geraci, A. Moran and T. O. Eden (2008). "Survival from cancer in teenagers and young adults in England, 1979-2003." Br J Cancer **99**(5): 830-835.

Birch, J. M., R. D. Alston, M. Quinn and A. M. Kelsey (2003). "Incidence of malignant disease by morphological type, in young persons aged 12–24 years in England, 1979–1997." European Journal of Cancer **39**(18): 2622-2631.

Bleyer, A., A. Viny and R. Barr (2006). "Cancer in 15- to 29-Year-Olds by Primary Site." The Oncologist **11**(6): 590-601.

Carreira, H., L. Antunes, C. Castro, N. Lunet and M. J. Bento (2012). "Cancer incidence and survival (1997-2006) among adolescents and young adults in the north of Portugal." Pediatr Hematol Oncol **29**(7): 663-676.

Clavel, J., E. Steliarova-Foucher, C. Berger, S. Danon and Z. Valerianova (2006). "Hodgkin's disease incidence and survival in European children and adolescents (1978–1997): Report from the Automated Cancer Information System project." European Journal of Cancer **42**(13): 2037-2049.

Cotterill, S. J., L. Parker, A. J. Malcolm, M. Reid, L. More and A. W. Craft (2000). "Incidence and survival for cancer in children and young adults in the North of England, 1968-1995: a report from the Northern Region Young Persons' Malignant Disease Registry." Br J Cancer **83**(3): 397-403.

Croucher, C., J. S. Whelan, H. Møller and E. A. Davies (2009). "Trends in the Incidence and Survival of Cancer in Teenagers and Young Adults: Regional Analysis for South East England 1960–2002." Clinical Oncology **21**(5): 417-424.

Desandes, E., B. Lacour, A. Belot, F. Molinie, P. Delafosse, B. Tretarre, M. Velten, E. A. Sauleau, A. S. Woronoff, A. V. Guizard, O. Ganry, S. Bara, P. Grosclaude, X. Troussard, V. Bouvier, L. Brugieres and J. Clavel (2013). "Cancer incidence and survival in adolescents and young adults in france, 2000-2008." Pediatr Hematol Oncol **30**(4): 291-306.

Desandes, E. (2007). "Survival from adolescent cancer." Cancer Treatment Reviews **33**(7): 609-615.

Desandes, E., B. Lacour, D. Sommelet, A. Buemi, A. Danzon, P. Delafosse, P. Grosclaude, J. Mace-Lesech, N. Raverdy-Bourdon, B. Tretarre, M. Velten and L. Brugieres (2004). "Cancer incidence among adolescents in France." Pediatric Blood & Cancer **43**(7): 742-748.

Foltz, L. M., K. W. Song and J. M. Connors (2006). "Hodgkin's Lymphoma in Adolescents." Journal of Clinical Oncology **24**(16): 2520-2526.

Furlong, W., C. Rae, M. L. Greenberg and R. D. Barr (2012). "Surveillance and survival among adolescents and young adults with cancer in Ontario, Canada." International Journal of Cancer **131**(11): 2660-2667.

Gatta, G., G. Zigon, R. Capocaccia, J. W. Coebergh, E. Desandes, P. Kaatsch, G. Pastore, R. Peris-Bonet and C. A. Stiller (2009). "Survival of European children and young adults with cancer diagnosed 1995-2002." Eur J Cancer **45**(6): 992-1005.

Gatta, G., R. Capocaccia, R. De Angelis, C. Stiller and J. W. Coebergh (2003). "Cancer survival in European adolescents and young adults." European Journal of Cancer **39**(18): 2600-2610.

Li, J., T. D. Thompson, J. W. Miller, L. A. Pollack and S. L. Stewart (2008). "Cancer Incidence Among Children and Adolescents in the United States, 2001–2003." Pediatrics **121**(6): e1470-e1477.

Magnanti, B. L., M. T. Dorak, L. Parker, A. W. Craft, P. W. James and R. J. McNally (2008). "Sex-specific incidence and temporal trends in solid tumours in young people from Northern England, 1968-2005." BMC Cancer **8**: 89.

Nicholson, B. D., S. V. Picton, P. Chumas, S. Dixit, M. van Laar, C. Loughrey, G. O'Reilly, D. P. Stark and R. G. Feltbower (2013). "Changes in the patterns of care of central nervous system tumours among 16-24 year olds and the effect on survival in Yorkshire between 1990 and 2009." Clin Oncol (R Coll Radiol) **25**(3): 205-214.

Pearce, M. S., L. Parker, K. P. Windebank, S. J. Cotterill and A. W. Craft (2005). "Cancer in adolescents and young adults aged 15–24 years: A report from the North of England young person's malignant disease registry, UK." Pediatric Blood & Cancer **45**(5): 687-693.

Pearce, M. S., L. Parker, S. J. Cotterill, P. M. Gordon and A. W. Craft (2003). "Skin cancer in children and young adults: 28 years' experience from the Northern Region Young Person's Malignant Disease Registry, UK." Melanoma Res **13**(4): 421-426.

Pulte, D., A. Gondos and H. Brenner (2009). "Trends in survival after diagnosis with hematologic malignancy in adolescence or young adulthood in the United States, 1981-2005." Cancer **115**(21): 4973-4979.

Stiller, C. A., E. Desandes, S. E. Danon, I. Izarzugaza, A. Ratiu, Z. Vassileva-Valerianova and E. Steliarova-Foucher (2006). "Cancer incidence and survival in European adolescents (1978–1997). Report from the Automated Childhood Cancer Information System project." European Journal of Cancer **42**(13): 2006-2018.

Stiller, C. A., S. Benjamin, R. A. Cartwright, J. V. Clough, D. W. Gorst, M. E. Kroll, J. R. Ross, K. Wheatley, J. A. Whittaker, P. R. Taylor and S. J. Proctor (1999). "Patterns of care and survival for

adolescents and young adults with acute leukaemia--a population-based study." Br J Cancer **79**(3-4): 658-665.

van der Horst, M., J. F. Winther and J. H. Olsen (2006). "Cancer incidence in the age range 0-34 years: historical and actual status in Denmark." Int J Cancer **118**(11): 2816-2826.

van Gaal, J. C., E. Bastiaannet, M. Schaapveld, R. Otter, J. C. Kluin-Nelemans, E. S. de Bont and W. T. van der Graaf (2009). "Cancer in adolescents and young adults in north Netherlands (1989-2003): increased incidence, stable survival and high incidence of second primary tumours." Ann Oncol **20**(2): 365-373.

van Laar, M., P. A. McKinney, R. C. Parslow, A. Glaser, S. E. Kinsey, I. J. Lewis, S. V. Picton, M. Richards, G. Shenton, D. Stark, P. Norman and R. G. Feltbower (2010). "Cancer incidence among the south Asian and non-south Asian population under 30 years of age in Yorkshire, UK." Br J Cancer **103**(9): 1448-1452.

Weir, H. K., L. D. Marrett, V. Cokkinides, J. Barnholtz-Sloan, P. Patel, E. Tai, A. Jemal, J. Li, J. Kim and D. U. Ekwueme (2011). "Melanoma in adolescents and young adults (ages 15-39 years): United States, 1999-2006." J Am Acad Dermatol **65**(5 Suppl 1): S38-49.

Wilkinson, J. R., R. G. Feltbower, I. J. Lewis, R. C. Parslow and P. A. McKinney (2001). "Survival from adolescent cancer in Yorkshire, UK." Eur J Cancer **37**(7): 903-911.

Wu, X.-C., V. W. Chen, B. Steele, S. Roffers, J. B. Klotz, C. N. Correa and S. E. Carozza (2003). "Cancer incidence in adolescents and young adults in the United States, 1992–1997." Journal of Adolescent Health **32**(6): 405-415.

Appendix B (for Chapter 2)

B.1 Registry Rules for Recording Radiotherapy

The study protocol requested registries to distinguish, if possible, between women who actually received radiotherapy and those for whom it was indicated but not necessarily received. It was also requested that the registry indicate the convention for recording radiotherapy. Not all registries supplied this information, but the information that was supplied is presented in Table B-1.

Country	Registry	Recording Convention or Extra Information
Australia	New South Wales Central Cancer Registry	Proportion of patients receiving RT has decreased since 1999, and registry suspect this is a notification issue rather than a true effect
Canada	Alberta Cancer Registry	Patient initially treated with RT as part of initial planned treatment
Canada	British Columbia Cancer Registry	RT recorded if given as part of initial planned treatment
Canada	Ontario Cancer Registry	RT recorded if patient is likely to have received radiotherapy
China	Tianjin Cancer Registry	All patients were diagnosed by Tianjin Cancer Hospital but not given radiotherapy by there, so radiotherapy status is unclear
Finland	Finnish Cancer Registry	Registry specific whether RT was started 0-4 months, >4 months or unknown time started
Germany	Bremen Cancer Registry	If there was a fitting notification on or within 6 months after first diagnosis from radiotherapist then radiotherapy was assumed yes, but it is not sure in some cases whether RT was administered to breast or other body regions
Iceland	Icelandic Cancer Registry	RT administered for index breast cancer within 6 months of diagnosis
Italy	Lombardy Cancer Registry & Sondrio Cancer Registry	RT only recorded as Yes if actually given. Women who didn't receive any radiotherapy are not distinguished from those whom it was indicated but not actually received
Italy	Parma Province Cancer Registry	RT recorded within 6 months from diagnosis, including complementary of palliative therapy
Italy	Piedmont Cancer Registry	Radiotherapy information retrieved with a record-linkage with cancer registry data and radiotherapy regional files
Italy	Venetian Tumour Registry	Radiotherapy recorded if given within 6 months from diagnosis to treat the primitive lesion

Japan	Nagasaki Prefectural Cancer Registry	Only included cases with RT
Philippines	Philippine Cancer Society-Manila Cancer Registry	Specified if before or after 6 months, or unknown
Philippines	Department of Health-Rizal Cancer Registry	Specified if before or after 6 months, or unknown
Switzerland	Grisons Cancer Registry Cancer Registry of St. Gall-Appenzell	X-ray therapy given as part of the first course of therapy and within 6 months of diagnosis
UK	West Midlands Cancer Intelligence Unit	Only radiotherapy given to treat the primary breast cancer has been included. The WMCIU is not always notified of radiotherapy given at extra-regional Cancer Centres. This may result in artificially low numbers for trusts sending patients outside of the West Midlands for RT
USA	Connecticut Tumour Registry	RT for the "first course" defined as the four months of the start of the cancer treatment
USA	Surveillance Epidemiology and End Results Program (2008)	Before 1998, radiotherapy was only recorded if administered in the first four months following surgery. The new recording procedure states that it will be recorded it received as part of the first course of treatment, whenever it was administered
US	Puerto Rico Central Cancer Registry	Radiotherapy recorded if it was part of the first course of treatment

Table B-1: Recording conventions for radiotherapy by registry (if supplied).

B.2 Data Description of all the Registries that Supplied Data to COBS

Country	Registry / Contributor	Number of women			Number of incomplete observations ‡	Date diagnosed range	Date last seen range	Cause-specific mortality	
		Total	Deaths	Percent given RT †				Breast cancer	Heart disease
Argentina	Regional Cancer Registry of Buenos Aires	-	-	-	-	-	-	-	-
Australia	New South Wales Central Cancer Registry	82,517	34,759	55 **	31,223	1972 to 2004	1972 to 2004	22,282	2,334
Austria	Carinthian Cancer Registry	4,083	759	66	2,086	1995 to 2005	1995 to 2007	166	0
	Cancer Registry of Salzburg	7,377	2,462	54	748	1962 to 2007	1975 to 2007	1,241	161
	Cancer Registry of Tyrol	5,265	2,111	38	546	1988 to 2003	1988 to 2005	1,385	264
	Cancer Registry of Voralberg	2,993	1,264	47	1,469	1985 to 2003	1985 to 2007	681	120
Brazil *	Brasilian Association of Cancer Registries	354	118	62	11	1992 to 1997	1995 to 2008	118	0
	Universidade Corporativa Amaral Carvalho Jaú	194	46	71	9	2000 to 2004	2000 to 2007	7	1
Canada	Alberta Cancer Registry	23,597	7,684	46	377	1989 to 2004	1989 to 2007	4,644	849
	British Columbia Cancer Registry	31,670	9,115	63	15	1985 to 2004	1985 to 2007	5,207	937
	Ontario Cancer Registry	59,160	22,766	100	0	1982 to 1997	1984 to 2007	17,829	1,767
China	Shanghai Cancer Registry	5,045	133	33	49	2002 to 2006	2002 to 2007	133	0
	Tianjin Cancer Registry	2,740	2,740	63	15	1981 to 2000	1981 to 2006	2,485	79
Costa Rica *	Costa Rica National Tumor Registry	3,073	1,215	37	306	1995 to 2000	1995 to 2006	609	26
Cuba *	Registro Nacional de Cancer de Cuba	440	79	65	39	1985 to 2003	1992 to 2007	0	0
Denmark	Danish Breast Cancer Cooperative Group	71,423	41,465	45	8,594	1977 to 2005	1977 to 2011	23,394	4,385
	Danish Cancer Registry	50,187	47,104	66	1,526	1943 to 1977	1943 to 2001	28,901	5,217
Estonia	Estonian Cancer Registry	12,175	8,510	42	286	1968 to 2000	1968 to 2005	6,074	910

Finland	Finnish Cancer Registry	89,447	44,992	54	5,941	1953 to 2006	1970 to 2006	24,373	7,831
France	Côte d'Or Breast & Gynaecologic Cancer Registry	7,110	2,739	70	669	1982 to 2005	1982 to 2007	1,300	0
	Institut Gustave Roussy	6,777	5,574	74	521	1954 to 1984	1954 to 2005	3,545	317
Germany	Population Based Cancer Registry Bavaria	47,040	5,769	53	13,415	1998 to 2007	1998 to 2007	3,895	249
	Gemeinsames Krebsregister	267,912	146,525	50	49,973	1961 to 2005	1961 to 2007	33,839	4,000
	Bremen Cancer Registry	5,011	746	47	3,007	1979 to 2007	1998 to 2007	507	89
	Saarland Cancer Registry	-	-	-	-	-	-	-	-
	Cancer Registry of Schleswig-Holstein Registerstelle	13,368	1,888	62	2,977	1997 to 2004	1999 to 2007	1,421	165
Iceland *	Icelandic Cancer Registry	2,767	963	35	1,769	1985 to 2006	1985 to 2007	547	66
India *	Rural Cancer Registry Barshi	269	181	28	79	1988 to 2004	1989 to 2007	181	0
	Cancer Institute (WIA), Chennai	515	275	89	3	1986 to 1993	1992 to 2008	254	3
Ireland	Ireland National Cancer Registry	15,498	5,291	42	460	1994 to 2004	1994 to 2006	4,225	219
Israel	Israel National Cancer Registry	47,917	27,584	20	20,225	1960 to 2000	1961 to 2006	9,766	2,335
Italy	Friuli Venezia Giulia Cancer Registry	8,990	2,595	7	8,463	1995 to 2003	1995 to 2005	1,565	329
	Latina Cancer Registry	516	11	99	2	2002 to 2007	2004 to 2007	0	0
	Lombardy Cancer Registry	10,783	5,355	5	7,339	1980 to 2000	1980 to 2005	2,679	350
	National Tumour Institute (Milan)	5,367	1,187	59	439	1999 to 2002	1999 to 2006	764	121
	Modena Cancer Registry	8,556	2,665	33	2,902	1988 to 2005	1982 to 2007	1,431	255
	Parma Province Cancer Registry	3,990	1,051	51	1,669	1994 to 2004	1994 to 2007	641	120
	Piedmont Cancer Registry	3,694	652	60	720	2000 to 2003	2000 to 2007	248	29
	Ragusa Cancer Registry	1,823	736	31	950	1990 to 2003	1990 to 2006	521	73
	Sondrio Cancer Registry	1,315	263	49	118	1997 to 2006	1998 to 2007	172	24
	Tuscany Cancer Registry	16,606	6,181	35	1,118	1985 to 2004	1985 to 2005	3,796	618
	Umbria Cancer Registry	4,617	1,316	47	457	1960 to 2004	1994 to 2006	838	137
	Venetian Tumour Registry	4,587	1,707	40	2,271	1987 to 2001	1987 to 2007	1,109	131
Jamaica *	Jamaica Cancer Registry	1,231	189	18	1,143	1996 to 2006	1997 to 2006	28	2
Japan	Tumour & Tissue Registry Office (Hiroshima)	859	514	12	107	1957 to 2001	1957 to 2007	206	70
	Kanagawa Cancer Centre	2,102	994	23	444	1941 to 1989	1971 to 2007	676	27
	Nagasaki Prefectural Cancer Registry	668	201	100	16	1956 to 2005	1961 to 2005	165	7
Korea *	Korea Central Cancer Registry	52,226	13,315	17	35,106	1993 to 2002	1993 to 2007	9,827	68

Kuwait *	Kuwait Cancer Registry	252	2	71	104	1990 to 1996	1994 to 2006	0	0
Lithuania	Lithuanian Cancer Registry	14,591	6,495	39	2,872	1993 to 2005	1993 to 2007	5,671	426
Netherlands	Eindhoven Cancer Registry	22,779	7,430	61	2,306	1960 to 2004	1961 to 2004	176	60
	Netherlands Cancer Institute	7,221	4,213	87	104	1970 to 1987	1971 to 2004	3,085	271
New Zealand *	University of Otago (NZ national database)	16,383	12,536	12	14,705	1980 to 2004	1962 to 2007	4,969	1,083
Norway	Cancer Registry of Norway	28,038	8,989	35	7,566	1983 to 2004	1983 to 2006	6,246	409
Pakistan	Karachi Cancer Registry	1,511	1,140	39	203	1995 to 2000	1995 to 2007	1,010	68
Peru *	Registro de Cáncer de Trujillo	616	172	20	547	1993 to 2002	1993 to 2006	72	0
Philippines *	Philippine Cancer Society-Manila Cancer Registry	2,227	776	18	1,527	1987 to 2002	1987 to 2006	763	0
	Department of Health-Rizal Cancer Registry	1,621	698	24	261	1987 to 2002	1989 to 2006	676	1
Poland *	Regional Cancer Registry in Gdansk	222	41	100	3	1990 to 2007	2003 to 2007	19	0
Serbia *	Cancer Registry of Vojvodina	12,319	6,763	35	6,063	1985 to 2000	1985 to 2007	6,737	0
Slovakia	National Cancer Registry of Slovak Republic	34,747	18,531	55	4,498	1978 to 2003	1978 to 2006	8,795	154
Slovenia	Cancer Registry of Slovenia	16,414	8,507	34	6,880	1954 to 2004	1983 to 2007	6,236	476
Spain	Institute Catalá d'Oncolgía	1,212	481	58	307	1991 to 1997	1991 to 2005	335	33
	Cancer Registry of Girona	6,199	2,999	34	4,290	1934 to 2006	1977 to 2007	1,999	197
	Navarra Cancer Registry	3,698	1,070	66	187	1990 to 2002	1990 to 2007	705	80
Sweden	Gothenburg Regional Cancer Registry	16,756	5,793	42	2,433	1989 to 2006	1989 to 2007	2,686	710
	Regional Tumour Registry, Linköping	10,739	3,820	53	2,738	1986 to 2003	1986 to 2003	1,820	665
	The Swedish Cancer Registry	31,800	11,956	54	1,047	1976 to 2006	1976 to 2006	5,885	2,015
Switzerland	Geneva Cancer Registry	2,365	1,288	53	1,440	1970 to 2004	1970 to 2005	712	169
	Grisons Cancer Registry	1,826	759	34	18	1989 to 2005	1989 to 2007	429	71
	Cancer Registry of St. Gall-Appenzell	7,090	4,004	28	2,952	1940 to 2005	1980 to 2007	2,263	434
	Ticino Cancer Registry	2,371	608	52	95	1995 to 2004	1996 to 2007	277	40

Thailand *	Khon Kaen Cancer Registry	807	136	14		197	2001 to 2005	2001 to 2007	0	0
	Lampang Regional Cancer Center	1,187	420	16	521		1990 to 2003	1990 to 2006	411	1
	Songkhla Cancer Registry	1,832	492	26	715		1976 to 2007	1976 to 2007	470	0
UK	Eastern Cancer Registration & Information Centre (Cambridge)	52,390	27,534	48	2,053		1941 to 2006	1969 to 2007	10,479	1,070
	Northern and Yorkshire Cancer Registry and Information Service	86,213	45,303	36	27,094		1980 to 2004	1999 to 2006	28,078	1,274
	Scottish Cancer Registry	78,852	42,746	18	51,955		1980 to 2004	1980 to 2006	25,913	4,575
UK	Thames Cancer Registry	168,329	83,893	50	6,335		1960 to 2006	1960 to 2006	60,232	3,102
	West Midlands Cancer Intelligence Unit	79,125	44,761	53	2,777		1977 to 2004	1977 to 2007	30,506	3,099
USA	Connecticut Tumour Registry	28,836	26,328	29	491		1935 to 1972	1935 to 2007	14,174	4,544
	Hawaii Tumour Registry	15,729	5,620	46	78		1973 to 2005	1973 to 2007	2,408	964
	SEER-Medicare (2009)	513,265	205,649	36	17,386		1973 to 2007	1986 to 2010	69,419	43,105
	The Pennsylvania Cancer Registry	2,214	532	100	214		1977 to 2007	1979 to 2007	233	0
	Puerto Rico Central Cancer Registry	21,182	8,059	35	7,060		1987 to 2003	1987 to 2008	4,376	474
	Surveillance Epidemiology and End Results Program (2008)	769,045	175,341	43	32		1973 to 2008	1951 to 2008	84,829	25,213
Zimbabwe *	Zimbabwe National Cancer Registry	517	517	45	78		1990 to 2004	1990 to 2007	499	2

* Country was excluded from cardiac mortality study as it had less than 50 cardiac deaths that meet the eligibility criteria.
† Number of women who were recorded to have received radiotherapy as a percentage of the total number of observations (not only those with valid radiotherapy status).
‡ Incomplete if the following information was not recorded: breast cancer laterality, RT s tatus, vital status, age at diagnosis or date of diagnosis.

B.3 ICD codes for cardiac deaths, fully expanded and categorised

Cause of Death	ICD-5	ICD-6	ICD-7	ICD-8	ICD-9	ICD-10
Cardiac	58a-c, 90a-b, 91a-c, 92-95, 111b-c, 199, 200a(1)	401, 402.1, 410-416, 420-422, 430-434, 440-443	401, 402.1, 410-416, 420-422, 430-434, 440-443	391, 392.0, 393-398, 402, 404, 410-414, 420-429	391, 392.0, 393-398, 402, 404, 410-414, 416, 420-429	I01, I02.0, I05-I09, I11, I13, I20-I25, I27, I30-I52
Cardiomyopathy/CHF	58c, 93a-b, 93c(2-3), 93d, 111b-c, 200a(1)	401.2, 415, 422.0, 422.2, 431, 434.1-2	401.2, 415, 422.0, 422.2, 431, 434.1-2	391.2, 422, 425, 427.0, 427.1, 428, 429.0	391.2, 398.0, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 422, 425, 428, 429.0, 429.1, 429.3	I01.2, I09.0, I11.0, I13.0, I13.2, I40-I43, I50, I51.4-5, I51.7
Valvular HD	92a, 92b(1), 92c	421	421	394.9, 395.9, 396.9, 397.0, 424	424	I34-I39
Rheumatic Valv HD	58b, 92b(2)	401.1, 410-414	401.1, 410-414	391.1, 394.0, 395.0, 396.0, 397.9	391.1, 394-397	I01.1, I05-I08, I09.1
Ischaemic HD	93c(1), 94a, 94b	420, 422.1	420, 422.1	410-414	410-414, 429.7	I20-I25
Arrhythmias	199	433.0-1	433.0-1	427.2-9	426-427	I44-49
Pericardial	58a, 90a-b,	401.0, 432	401.0, 432	391.0, 393, 420, 423	391.0, 393, 420, 423	I01.0, I09.2, I30-I32
Cerebrovascular	83a-c	330-334	330-334	430-438	430-438	I60-I69
Thromboembolic	111a	454, 463-466	454, 463-466	444, 450-453	415, 444, 451-453	I26, I74, I80-I82
Peripheral Vasc	96-100	450-453, 455-456, 460-462	450-453, 455-456, 460-462	440-443, 445-448, 454-456	440-443, 446-448, 454-456	I70-I73, I77-I79, I83-I87
Others	91a-c, 95	401.3, 402.1, 416, 430, 433.2, 434.0, 434.3, 440-443	401.3, 402.1, 416, 430, 433.2, 434.0, 434.3-4, 440-443	391.9, 392.0, 398, 402, 404, 421, 426, 429.9,	391.8-9, 392.0, 398.90, 398.99, 402.00, 402.10, 402.90, 404.00, 404.02, 404.10, 404.12, 404.90, 404.92, 416, 421, 429.2, 429.4-6, 429.8-9	I01.8-9, I09.8-9, I11.9, I13.1, I13.9, I27, I33, I51.0-3, I51.6, I51.8-9, I52

B.4 Detailed Statistical Methodology for COBS Study

B.4.1 Calculation of mortality ratio and associated variance using a weighted average

Unless otherwise stated, the mortality ratios are based on a binomial regression model with four categorical explanatory variables:

$$O_{2jtmnp} \sim Binomial\left(\mathrm{O}_{1\mathrm{jt}} + \mathrm{O}_{2\mathrm{jt}}, \pi_{jtmnp}\right) where\ \pi_{jtmnp} = \frac{P_{2jt}\rho_{tmnp}}{P_{1jt} + P_{2jt}\rho_{tmnp}}$$

and

$$\rho_{tmnp} = exp\left(\mu + \tau_t + \alpha_m + \beta_n + \gamma_p\right)$$

where:

τ_t is a categorical explanatory variable for time since diagnosis varying over categories t

α_m is a categorical explanatory variable for age at radiotherapy varying over categories m

β_n is a categorical explanatory variable for calendar year of radiotherapy varying over categories n

γ_p is a categorical explanatory variable for country of treatment varying over categories p

The baseline category is $\tau_1 = \alpha_1 = \beta_1 = \gamma_1 = 0$

If a mortality ratios is stated to be 'unadjusted', then it has been estimated using binomial regression with stratification only.

The adjusted mortality ratio is obtained by firstly fitting the relevant binomial regression model by maximum likelihood estimation. This leads to maximum likelihood estimates $\hat{\mu}, \widehat{\tau_t}, \widehat{\alpha_m}, \widehat{\beta_n}, \widehat{\gamma_p}$. The constant $\hat{\mu}$ corresponds to the mortality ratio in the baseline category. Therefore the estimates $\widehat{\tau_t}, \widehat{\alpha_m}, \widehat{\beta_n}, \widehat{\gamma_p}$ are all relative to this baseline category. This causes two problems: firstly the baseline category may not necessarily be representative of the data as a whole; secondly the variances of the relative estimates will be unnecessarily large.

In order to derive estimates that are representative of the entire dataset and independent of an arbitrary baseline, an average can be taken of the maximum likelihood estimates over all combinations of the categories of the explanatory variables.

The averaged value for the category t of the explanatory variable τ_t, after adjusting for α_m, β_n and γ_p is:

$$e^{\hat{\tau}_t} = \theta e^{\hat{\tau}_t + \hat{\mu}}$$

where:

$$\theta = \sum_{m=1}^{M} \sum_{n=1}^{N} \sum_{p=1}^{P} w_{mnp} e^{\hat{\alpha}_m + \hat{\beta}_n + \hat{\gamma}_p}$$

with $w_{mnp} = \frac{P_{.mnp}}{P_{....}}$

Thus the adjusted mortality ratio for the variable τ_t is the average of adjusted ratios over all combinations of the categories of categories m, n and p weighted by the corresponding person-years.

In order to calculate the variance of the adjusted mortality ratio, a linear combination of the estimates with their respective variances and covariances is needed.

Let $y = f(x_1, x_2, \dots, x_k)$. Let $d = \begin{bmatrix} \frac{\partial y}{\partial x_1} \\ \dots \\ \frac{\partial y}{\partial x_k} \end{bmatrix}$ i.e. the vector of partial derivatives of y with respect to $x_1, x_2, \dots, x_k$.

Matrix manipulation gives:

$$var(d^T x) = var\left(\sum_i d_i x_i\right) = \sum_i {d_i}^2 var(x_i) + \sum_{i,j} d_i d_j cov(x_i, x_j) = d^T V d$$

where $V = \begin{bmatrix} var(x_1) & cov(x_1,x_2) & & \\ cov(x_1,x_2) & var(x_2) & \dots & \\ \vdots & \vdots & & \\ . & . & & var(x_k) \end{bmatrix}$

The first term in the Taylor expansion of y can be used as an approximation to the function. Therefore, $y \approx d^T x$. This allows an approximation to be used: $var(y) \approx d^T V d$.

The aim is to calculate $var(\tilde{\tau}_t)$ where

$$\tilde{\tau}_t = \ln(\theta) + \hat{\tau}_t + \hat{\mu}$$

and

$$\theta = \sum_{m=1}^{M}\sum_{n=1}^{N}\sum_{p=1}^{P} w_{mnp} e^{\hat{\alpha}_m + \hat{\beta}_n + \hat{\gamma}_p}$$

Applying the argument above, $\tilde{\tau}_t = y = f([\mu, \hat{\tau}_1, \hat{\tau}_2 \dots \hat{\alpha}_1 \dots \hat{\beta}_1 \ \dots \hat{\gamma}_1 \dots]) = \ln(\theta) + \hat{\tau}_t + \hat{\mu}$.

The Taylor series of y must be calculated to be used as an approximation during the variance calculation. The definition of the Taylor series for a function of more than one variable is:

$$T(x_1, x_2, \dots, x_d) = \sum_{n_1=0}^{\infty}\sum_{n_2=0}^{\infty}\dots\sum_{n_d=0}^{\infty} \frac{(x_1 - a_1)^{n_1} \dots (x_d - a_d)^{n_d}}{n_1! \dots n_d!} \left(\frac{\partial^{n_1 + \dots + n_d} f}{\partial {x_1}^{n_1} \dots \partial {x_d}^{n_d}} \right)(a_1, \dots, a_d)$$

As an example, for a function of two variables α and β, the Taylor series to the first order about the point (x, y) is:

$$f(\alpha, \beta) \approx f(x,y) + (\alpha - x)\frac{\partial f}{\partial \alpha}(x,y) \ + \ (\beta - y)\frac{\partial f}{\partial \beta}(x,y)$$

Therefore, the partial derivatives of $\tilde{\tau}_t$ need to be calculated with respect to each term $[\mu, \hat{\tau}_1, \hat{\tau}_2 \dots \hat{\alpha}_1 \dots \hat{\beta}_1 \ \dots \hat{\gamma}_1 \dots]$.

Therefore:

$$\frac{\partial \tilde{\tau}_t}{\partial \tau_u} = \begin{cases} 1 \; if \; t = u \\ 0 \; if \; t \neq u \end{cases}$$

$$\frac{\partial \tilde{\tau}_t}{\partial \mu} = 1$$

$$\frac{\partial \tilde{\tau}_t}{\partial \alpha_u} = \frac{F_{u..}}{F_{...}}$$

$$\frac{\partial \tilde{\tau}_t}{\partial \beta_v} = \frac{F_{.v.}}{F_{...}}$$

$$\frac{\partial \tilde{\tau}_t}{\partial \gamma_w} = \frac{F_{..w}}{F_{...}}$$

where:

$$F_{mnp=} w_{mnp} e^{\hat{\alpha}_m + \hat{\beta}_n + \hat{\gamma}_p}$$

Therefore, $\theta = F_{...}$

As a result:

$$d^T x = \hat{\mu} + \hat{\tau}_t + \frac{1}{\theta} \sum_{m=1}^{M} F_{m..} \hat{\alpha}_m + \frac{1}{\theta} \sum_{n=1}^{N} F_{.n.} \hat{\beta}_n + \frac{1}{\theta} \sum_{p=1}^{P} F_{..p} \hat{\gamma}_p$$

In Stata, the function LINCOM can be used to get the variance of $d^T x$. This approximate standard error on the log scale is then with the exact point estimate of the adjusted mortality ratio to calculate the 95% confidence interval.

B.4.1.1 Heterogeneity and Trend Tests

The heterogeneity test was computed using a likelihood ratio test. The significance of the explanatory variable was tested by comparing the difference between the two nested models, one with the explanatory variable and one without. The test statistic is χ^2_r distributed, where r is the difference between the degrees of freedom of the nested models.

The trend test was performed to investigate what proportion of the chi-squared for heterogeneity is explained as linear trend. The trend test is based on the maximum likelihood approach by constraining a linear fit when fitting a variable as a linear term. Therefore, the explanatory variable of interest is fitted as an ordinal term in the regression, and the significance of the ordinal parameter is tested using a likelihood ratio.

The connection between maximum likelihood estimation and the likelihood ratio test is explained below.

The definition of the likelihood ratio test for composite hypotheses is based on the comparison of two likelihoods.

$$H_0 : \theta \in \Theta_0$$

$$H_1 : \theta \in \Theta_1$$

Then the likelihood ratio test (LRT) statistic is:

$$\Lambda(x) = \frac{\max\{L(\theta|x): \theta \in \Theta_0\}}{\max\{L(\theta|x): \theta \in \Theta\}}$$

where: $\Theta \in \{\Theta_0, \Theta_1\}$

Therefore, the test statistic is based upon the maximum likelihood estimates of θ within a subset of the data.

The LRT can be expressed differently, when examining whether a reduced model provides the same fit as a full model:

$$\Lambda(x) = -2ln\left(\frac{l(\widehat{\theta_r}|x)}{l(\hat{\theta}|x)}\right) = -2\left[L(\widehat{\theta_r}|x) - L(\hat{\theta}|x)\right]$$

where $l(\widehat{\theta_r}|x)$ is the maximum likelihood of the reduced model. For sufficiently large sample size the LR test statistic is ${\chi^2}_r$ distributed.

B.4.1.2 Calculation of Cumulative Mortality Risk

Initially, the death rates for all cause and heart disease must be calculated from the general population. These are used as the basis of the cumulative risk in the unexposed group.

$$dth_r = \frac{number\ of\ deaths\ in\ population}{population\ size}$$

$$hd_{dth_r} = \frac{number\ of\ heart\ disease\ deaths\ in\ population}{population\ size}$$

The relative risk varies based on the age group and follow-up period of interest, and is estimated using grouped logistic regression with an interaction term in the COBS dataset. For example, the cardiac mortality ratio for women diagnosed with breast cancer 50-59 years old in the first 10 years of follow-up is 1.12 (1.01-1.26). Thus, for that period assume the increase in rate in the exposed group is 12%.

$$risk = \begin{cases} 1\ if\ unexposed\ group\ (right-sided) \\ 1.12\ if\ exposed\ group\ (left-sided) \end{cases}$$

For each age group, the $risk$ will vary according to the period of follow-up.

$$a_{ij} = hd_{dth_r} * risk$$

Assume 5 years is the width of the age interval, therefore the age-specific rate is:

$$ta_{ij} = a_{ij} * 5$$

The unexposed group is conditioned on all-cause survival, therefore the cumulative hazard function for the unexposed group is:

$$t_{dead} = dth_r * 5$$

The exposed group is conditioned on heart disease survival in the exposed group, and all-cause (without heart disease) survival in the unexposed group:

$$hd2_{dth_r} = dth_r - hd_{dth_r} + hd_{dth_r} * 1.12$$

Thus, the cumulative hazard function for the exposed is:

$$t_{hd} = hd2_{dth_r} * 5$$

The aim is to generate the probability of surviving the start of the next age group, using the survival probability, defined as:

$$s_{dead} = \begin{pmatrix} \exp(-t_{dead}) if\ unexposed \\ \exp(-t_{hd}) if\ exposed \end{pmatrix}$$

Therefore, the cumulative risk is calculating using the cumulative rate multiplied by the duration:

$$crisk = 100 * (1 - e^{-crate})$$

Where:

$$crate = \sum cta_{ij}$$

$$cta_{ij} = cu_{s_{dead}} * ta_{ij}$$

And:

$$cu_{s_{dead}} = e^{\sum \ln(s_{dead})}$$

The cumulative mortality risk can be interpreted as a measure of disease frequency during a period of time.

Appendix C (for Chapter 3)

Authors	Year	Journal	SEER / SEER-Medicare	Outcome	Quote from results that includes RT+ vs RT-	Quote of abstract conclusion
					Primary result	
Berrington de Gonzalez, A., Curtis, R. E., Gilbert, E., et al	2010	Br J Cancer	SEER	Second cancers	The RRs for radiotherapy were 1.45 (95% confidence interval (CI)=1.33-1.58) for high-dose second cancer sites (1+ Gy: lung, oesophagus, pleura, bone and soft tissue) and 1.09 (1.04-1.15) for contralateral breast cancer (approximately 1 Gy)	Most second solid cancers in breast cancer survivors are not related to radiotherapy.
Berrington de Gonzalez, A., Curtis, R. E., Kry, S. F., et al	2011	Lancet Oncol	SEER	Second cancers	For each of the first cancer sites the RR of developing a second cancer associated with radiotherapy exceeded 1, and varied from 1.08 (95% CI 0.79-1.46) after cancers of the eye and orbit to 1.43 (1.13-1.84) after cancer of the testes.	A relatively small proportion of second cancers are related to radiotherapy in adults, suggesting that most are due to other factors, such as lifestyle or genetics.
Cohen, R. J., Li, L., Citron, W., et al	2012	Int J Radiat Oncol Biol Phys	SEER	OS and CSS	At 5 years, CSS was 97.6% (95% confidence interval [CI]: 97.3%-97.8%) for surgery alone versus 98.3% (95%CI: 94.9%-95.8%) for adjuvant radiation	Although information regarding hormonal therapy usage is not available, the improvement in CSS with the addition of radiation suggests that in healthy, elderly women, adjuvant radiation should be strongly considered as part of their breast cancer treatment.
Doyle, J J., Neugut, A I., Jacobson, J S., et al	2007	Int J Radiat Oncol Biol Phys	SEER-Medicare	MI and ischemia	The RT did not increase the risk of MI.	It appears unlikely that RT would increase the risk of MI in elderly women with breast cancer, regardless of type of surgery, tumour laterality, or history of CRFs or HD, for at least 10 years.
Du, X., Freeman, J. L., Nattinger, A. et al	2002	Breast Cancer Res Treat	SEER-Medicare	Overall survival	Women who received either axillary dissection or radiotherapy experienced similar survivals to those who received both axillary dissection and radiation, while women who received neither treatment experienced poorer survival (hazard ratio = 1.76, 1.23-2.52),	Women who receive neither axillary dissection nor radiation therapy after BCS experience an increased risk of death from breast cancer.
Gao, X, Fisher, S G., Emami, B	2003	Int J Radiat Oncol Biol Phys	SEER	Contralateral breast cancer	Overall, RT was not associated with an increased risk of CBC (RR = 1.04, 95% CI 0.97-1.10) in multivariate analysis.	RT was associated with a very small increased long-term CBC risk. This minimal increase in CBC risk should not affect clinical decision-making in treatment selection for patients with localized invasive breast cancer or ductal carcinoma in situ.
Huang, J., Mackillop, W. J.	2001	Cancer	SEER	Soft tissue sarcoma	The RT cohort demonstrated a higher risk of developing both angiosarcoma (RR: 15.9; 95% CI, 6.6--38.1) and other sarcomas (RR: 2.2; 95% CI, 1.4--3.3) compared with the non-RT cohort,	The risk of soft tissue sarcoma, especially angiosarcoma, was elevated after RT in women with breast carcinoma.

Table cont. on next page

Huang, J., Walker, R., Groome, P. G., et al	2001	Cancer	SEER	Thyroid cancer	When the RT cohort was compared with the non-RT cohort, the RR of thyroid carcinoma was 1.0 (95%CI, 0.7-1.5).	The risk of radiation-associated thyroid carcinoma after initial RT for breast carcinoma was so low as to be undetectable in the current large population-based study. ... However, with 10,895 women having been followed for > 10 years at the time of last follow-up in the current study, these findings should be reassuring to women considering RT for their breast carcinoma.
Joslyn, S. A.	1999	Int J Radiat Oncol Biol Phys	SEER	Overall survival	Statistically significant survival advantages were conferred on women receiving radiation therapy in each 5-year age category from age 35 to 84 years (ranging from p = 0.02 to p < 0.0001).	While the use of radiation therapy following local excision of early-stage breast tumours drops significantly in older age groups, women aged 35-84 years receiving radiation therapy had significant reductions in mortality.
Keating, N. L., Landrum, M. B., Brooks, J. M., et al	2011	Breast Cancer Res Treat	SEER-Medicare	Overall survival	Adjusted survival was greatest among women who had BCS with radiation (median survival = 10.98 years). Compared with this group, mortality was higher among women who had mastectomy without radiation (median survival 10.04 years, adjusted hazard ratio (HR) = 1.19, 95% confidence interval (CI) = 1.14-1.23), mastectomy with radiation (median survival 10.02 years, HR = 1.20, 95% CI = 1.14-1.27), and BCS without radiation (median survival 7.63 years, HR = 1.81, 95% CI = 1.70-1.92).	We found better survival for BCS with radiation versus mastectomy among older early-stage breast cancer patients, with no difference in survival for BCS with radiation versus mastectomy among women representative of those in clinical trials.
Ly, B. H., Vlastos, G., Rapiti, E., et al	2010	Tumori	SEER	Overall survival	The median overall survival of radiotherapy versus none was respectively 16 vs. 13 months without surgery (P = 0.0003), 28 vs. 20 months for breast-conserving surgery patients (P < 0.0001), and 28 vs. 28 months among mastectomy patients (P = 0.895).	Surgery and radiotherapy were associated with a significant survival advantage. We argue that local therapy should be considered even in metastatic disease.
McCammon, R., Finlayson, C., Schwer, A., et al	2008	Cancer	SEER	Overall survival and cause-specific survival	The actuarial 10-year CSS for those who received PMRT versus those who did not receive PMRT was 81.6% versus 79.8%, respectively (P = .38). PMRT was not associated with a CSS benefit in any subgroup, a finding that persisted in multivariate analyses.	This retrospective, population-based analysis demonstrated no increase in CSS with PMRT for women with T3N0 breast cancer, lending further support to the hypothesis that T3N0 disease post-mastectomy represents a favourable subset of locally advanced breast cancer.
Mery, C. M., George, S., Bertagnolli, M. M., et al	2009	Cancer	SEER	Soft tissue sarcoma	RT patients had a higher incidence of all STS (31 vs 22 per 100,000 person-years; HR, 1.5 [95% CI, 1.3-1.8]), AS (HR, 7.6; 95% CI, 4.9-11.9), and malignant fibrous histiocytomas (MFH) (HR, 2.5; 95% CI, 1.6-3.9)	RT was found to increase the risk for STS, in particular AS and MFH.
Neta, G., Anderson, W. F., Gilbert, E., et al	2012	Breast Cancer Res Treat	SEER	Contralateral breast cancer	The overall RR (and 95% confidence interval (CI)) of radiotherapy-related CBC was 1.11 (1.05-1.16).	We did not find clear evidence that radiation-related risk varies by histology or ER status, but our findings, which were the first to examine this question, were suggestive of possible differences by ER status that may merit further investigation.

Table cont. on next page

Neugut, A. I., Lee, W. C., Murray, T., et al	1993	Cancer	SEER	Lung cancer	It was found that the risk of lung cancer overall was increased in women who underwent irradiation compared with those who were not irradiated 10 years after the initial breast cancer diagnosis with a relative risk of 2.0 (95% confidence interval, 1.0-4.3).	It was concluded that RT for breast cancer may increase the risk of lung cancer after a latency period of 10 years.
Schootman, M., Jeffe, D. B., Gillanders, W. E., et al	2007	Breast Cancer Res Treat	SEER	Overall survival and cause-specific survival	After adjustment for propensity scores and radiotherapy misclassification, women who did not receive radiotherapy had 2.2 times greater risk of cause-specific and 1.7 times greater risk of all-cause mortality	Unlike the small survival benefit of radiotherapy after first primary breast cancer, omission of radiotherapy after metachronous contralateral breast cancer significantly increased the risk of cause-specific and all-cause mortality.
Smith, B. D., Gross, C. P., Smith, G. L., et al	2006	J Natl Cancer Inst	SEER-Medicare	Ipsilateral BC and/or subsequent mastectomy	Radiation therapy, compared with no radiation therapy, was associated with a lower risk of the combined outcome (hazard ratio = 0.19, 95% confidence interval = 0.14 to 0.28).	For older women with early breast cancer, radiation therapy was associated with a lower risk of a second ipsilateral breast cancer and subsequent mastectomy
Smith, B. D., Haffty, B. G., Hurria, A., et al	2006	Journal of Clinical Oncology	SEER-Medicare	Overall survival	For low- and intermediate-risk patients, PMRT was not associated with survival. For high-risk patients, PMRT was associated with a significant improvement in survival (hazard ratio, 0.85; 95% CI, 0.75 to 0.97; P = .02)	PMRT is associated with improved survival for older women with high-risk breast cancer
Smith, B. D., Smith, G. L., Haffty, B. G.	2005	J Clin Oncol	SEER	Overall survival	After adjusting for covariates, PMRT use was not associated with mortality (hazard ratio [HR] = 0.96; 95% CI, 0.90 to 1.03).	For women with T1-2 breast cancer, PMRT is associated with a 15% to 20% relative reduction in mortality for patients with seven or more involved regional lymph nodes.
Smith, G. L., Smith, B. D., Giordano, S. H., et al	2008	Cancer	SEER-Medicare	Hypothyroidism	The 5-year incidence of hypothyroidism was identical (14%) in irradiated patients with 4+LN, 0 LN, and nonirradiated patients (P=.52).	Although supraclavicular irradiation does not appear to amplify risks, further studies on the role of routine thyroid function monitoring in all breast cancer patients regardless of treatment status may be warranted, given the excess risks compared with the general population.
Vinh-Hung, V., Burzykowski, T., Van de Steene, J., et al	2002	Radiother Oncol	SEER	Overall survival	Radiation was associated with a reduced mortality after breast-conserving surgery in node negative patients (hazard ratio 0.757; 95% confidence interval 0.709-0.809; using total mastectomy without radiation as reference) and in node positive patients (hazard ratio 0.777; 0.717-0.842), and after total mastectomy in node positive patients (hazard ratio 0.885; 0.815-0.961). Radiation was associated with an increased hazard ratio of 1.271 (1.080-1.496) after total mastectomy in node negative patients	The available data indicate that post-surgery radiation provides a survival advantage irrespective of the type of surgery in node positive patients. Likewise, survival advantage was observed with post-surgery radiation and breast-conserving procedure in node negative patients.
Vinh-Hung, V., Voordeckers, M., Van de Steene, J., et al	2003	Radiother Oncol	SEER	Overall survival	Omission of radiotherapy as compared to delivery of radiotherapy was associated with an overall increased mortality hazard ratio of 1.346 (95% confidence interval: 1.204-1.504)	Omission of radiotherapy in breast-conserving surgery is found to be independently associated with an increase in mortality.

Table cont. on next page

Voordeckers, M., Vinh-Hung, V., Lamote, J., et al	2009	Strahlenther Onkol	SEER	Overall survival	Patients in the SEER database who did not receive RT had a significantly worse outcome (p < 0.0001).	RT provides a survival benefit in patients with < or = 3 or > or = 4 pN+; the indication for postoperative RT should therefore be adapted in future consensus meetings.
Yan, W., Christos, P., Nori, D., et al	2013	Am J Clin Oncol	SEER	Overall survival and cause-specific survival	No difference in CSS or OS was detected between women treated with or without PMRT.	This SEER database analysis of patients younger than age 50 and with pT3N0 breast cancer showed that PMRT did not significantly affect CSS at 5 years; however, it implied a trend of benefit for patients younger than 40.
Yap, J., Chuba, P. J., Thomas, R., et al	2002	Int J Radiat Oncol Biol Phys	SEER	Secondary sarcoma	The occurrence of sarcoma was low, regardless of whether cases received or did not receive radiation therapy: 3.2 per 1,000 (SE [standard error] = 0.4) and 2.3 per 1,000 (SE = 0.2) cumulative incidence at 15 years post diagnosis, respectively (p = 0.001)	Radiotherapy in the treatment of breast cancer is associated with an increased risk of subsequent sarcoma, but the magnitude of this risk is small
Yu, J. B., Wilson, L. D., Dasgupta, T., et al	2008	Cancer	SEER	Overall survival	Propensity score matched case-control analysis showed no improvement in overall survival with the delivery of PMRT in this group	The use of PMRT for T3N0M0 breast carcinoma after MRM is not associated with an increase in overall survival.
Zablotska, L. B., Chak, A., Das, A., et al	2005	Am J Epidemiol	SEER	Second primary oesophageal cancer	Estimated relative risks of 2.83 (95% confidence interval: 1.35, 5.92) and 2.17 (95% confidence interval: 1.67, 4.02) for squamous cell oesophageal cancer at 5–9 and ≥10 years, respectively, following post-mastectomy radiation therapy	In summary, post-mastectomy radiation therapy moderately increases the risk of squamous cell oesophageal cancer starting 5 years after exposure, which persists after 10 years, with no increase in the risk of adenocarcinoma.
Zablotska, L. B., Neugut, A. I.	2003	Cancer	SEER	Lung cancer	Although no statistically significant elevation in risk for second primary lung carcinoma prior to 10 years was observed, the authors estimated a RR of 2.06 (95% confidence interval [95% CI], 1.53–2.78) and 2.09 (95% CI, 1.50–2.90) for ipsilateral lung carcinoma at 10–14 years and 15+ years after post-mastectomy RT, respectively, whereas no increased risk was observed for the contralateral lung	Post-mastectomy RT was found to provide a moderate increase in risk for ipsilateral lung carcinoma starting 10 years after exposure; this increased risk is reported to persist to at least 20 years. Post-lumpectomy RT does not appear to incur an increased risk.
				Secondary result		
Ademuyiwa, F. O., Groman, A., Hong, C. C., et al	2013	Breast Cancer Res Treat	SEER	Overall survival	**Table 4**: HR (RT+ vs RT-) = 0.79 (0.75-0.83), p<0.0001	-
Agarwal, J., Agarwal, S., Pappas, L., et al	2012	Breast J	SEER	Breast cancer specific survival	Receipt of radiotherapy did not significantly associate with hazard of death (HR 1.03, p = 0.3494).	-
Bush, D., Smith, B., Younger, J., et al	2011	Breast Cancer Res Treat	SEER	Non-breast-cancer survival	Patients not receiving radiotherapy experienced no increase in relative survival.	-
Dawood, S., Ueno, N. T., Valero, V., et al	2012	Ann Oncol	SEER	Inflammatory breast cancer specific survival	Other factors significantly associated with decreased risk of death from IBC included receiving radiation therapy	-

Table cont. on next page

Delgado, D. J., Lin, W. Y., Coffey, M.	1995	P R Health Sci J	SEER	Breast cancer specific survival	For White women: ... radiation/hormonal treatments ... were significant risk factors for breast cancer survival time	-
Gaffney, D. K., Tsodikov, A., Wiggins, C. L.	2003	J Clin Oncol	SEER	Breast cancer specific survival and overall survival	Patients treated by lumpectomy that received RT had a superior OS compared with patients that did not receive RT in both local (HR, 0.52; 95% CI, 0.48 to 0.61; P <.001) and regional (HR, 0.63; 95% CI, 0.56 to 0.72; P <.001) stage disease.	-
Martinez, S. R., Tseng, W. H., Canter, R. J., et al	2012	Cancer	SEER	Overall survival	On multivariate analysis, RT was associated with a decreased risk of all-cause (HR, 0.78; 95% CI 0.74-0.83; P < .001) and disease-specific (HR, 0.81; 95% CI, 0.76-0.86; P < .001) mortality	Only black patients had poorer OS and DSS relative to whites. When stratified by type of surgery and use of RT, blacks continued to demonstrate poorer survival. This survival disparity is unlikely to be because of lack of RT.
Martinez, S. R., Tseng, W. H., Shah, D. R., et al	2012	Med Oncol	SEER	Overall survival and disease-specific survival	Patients not receiving PMRT experienced poorer OS (HR 1.77, CI 1.39-2.25; P < 0.001) and DSS (HR 1.62, CI 1.23-2.15; P = 0.001)	-
Royce, M., Bouchardy, C., Rapiti, E., et al	2009	Conference abstract: Cancer Res	SEER	Overall survival	RT was associated with a significant mortality reduction, HR=0.81 (0.75-0.88).	-
Vinh-Hung, V., Burzykowski, T., Van de Steene, J., et al	2005	Tumori	SEER	Overall survival	For each treatment combination, ME-no RT, ME+RT, BCS-no RT, BCS+RT, the mortality hazard ratios were respectively: 1, 1.12, 1.11, 0.78 in T1, 0-3 positive nodes; 2.45, 2.77, 2.71, 1.92 in T2, 4+ nodes; 1.31, 1.38, 1.33, 1.19 in T2, 0-3+ nodes; and 3.41, 2.79, 3.44, 2.40 in T2, 4+ nodes	The analyses found subgroup effects that should be taken into account to interpret treatment results in breast cancer.
Vinh-Hung, V., Truong, P. T., Janni, W., et al	2009	Strahlenther Onkol	SEER	Inflammatory breast cancer specific survival	In this subgroup, use of radiotherapy was associated with a 16% proportional increase in mortality	Improved survival was observed with radiotherapy use in all subgroups, except in women with medial tumours with > 4 ALN+ treated with post-mastectomy radiotherapy
Yu, G. P., Schantz, S. P., Neugut, A. I., et al	2006	Cancer Causes Control	SEER	Second cancers	Additionally, radiotherapy slightly increased the risks of second leukaemia (RR=1.8, 1.2-2.8), and second endometrial (RR=1.3, 1.0-1.6) and breast (RR=1.2, 1.1-1.3) cancers	-

Table C-1: List (including quote from results and conclusion in abstract) of eligible articles that used a comparison of irradiated and unirradiated women from systematic review of studies that used the SEER public-use data set to analyse disease control, toxicity or late heart disease and second malignancy associated with radiotherapy for breast cancer.

Authors	Year	Journal	SEER / SEER-Medicare	Outcome	Quote from results that includes RT+ vs RT-	Quote of abstract conclusion
				Primary outcome		
Abrams, M., Wazer, D.E, Price, L.L. et al.	2012	Int J Radiat Oncol Biol Phys	SEER	Cause specific survival	Patients in the low risk group had a trend toward lower survival with PMRT (HR = 0.59 [0.32-1.08]). Patients in the high-risk group had a trend toward improved survival with PMRT (HR = 2.13 [0.91-4.99]).	-
Albert, J. M., Pan, I., Shih, Y., et al.	2011	Int J Radiat Oncol Biol Phys	SEER-Medicare	Risk of mastectomy	The risk of mastectomy was 4.0% for patients who received RT vs. 9.5% for patients who did not (p<0.001). In adjusted analysis, RT was associated with a lower risk of mastectomy (HR = 0.34; 95% CI, 0.28 - 0.41; p<0.001).	Radiation therapy is of marginal benefit for women aged 70 - 79 with T1 N0 ER+ invasive ductal cancer, but remains of substantial benefit for other patients, particularly women aged 66 - 79 with node-positive or T2 N0 disease. RT should be used selectively for older women based on disease characteristics.
Cohen, R. J., Li, L., Mahmood, U., et al.	2013	Int J Radiat Oncol Biol Phys	SEER	Overall survival and cause-specific survival	The median OS was 5.5 years for those treated with surgery and 7 years for patients treated with surgery and radiation (p < 0.0001).	The eldest women with early stage breast cancer treated with breast conserving therapy have improved survival outcomes compared to those with radiation omitted.
Dai Kubicky, C., Marquez, C. M., Wang, S. J.	2010	Int J Radiat Oncol Biol Phys	SEER	Overall survival	Kaplan-Meier analysis showed OS was better in the PMRT group, compared to no PMRT (8-yr OS of 77% vs. 74%, log-rank p = 0.002).	Our study suggests that PMRT is associated with improvement in OS in patients with T1-2N1 breast cancer.
Dawood, S. S., Dent, R. A., Gupta, S., et al.	2012	J Clin Oncol	SEER	Breast cancer specific survival	In the multivariable model compared to women who were in the no S/R group those who underwent S (HR= 0.59, 95%CI 0.55- 0.62, p<0.0001) and S+R (HR=0.51, 95%CI 0.47-0.55, p<0.0001) had decreased risk of death from breast cancer and those who underwent R (HR=1.13, 95% CI 1.04-1.21, p=0.002) had an increased risk of death from breast cancer.	Our results indicate that S+R of the primary breast tumour among pts with denovo stage IV breast cancer may be associated with a decreased risk of death from breast cancer.
Elmore, L., Deshpande, A., Margenthaler, J. A.	2014	Ann Surg Oncol	SEER	Breast cancer specific survival	Receipt of post-mastectomy adjuvant radiation therapy resulted in lower breast cancer-specific mortality (22.6% versus 43.5%, p<0.0001) and patients were less likely to die during the follow-up period (aHR=0.696, 95% CI: 0.624-0.776) compared to patients who did not receive post-mastectomy adjuvant radiation therapy.	Further, receipt of radiation resulted in over 30% reduction in breast cancer-specific mortality for this sub-group of patients.
Horowitz, D. P., Ng, J., Burri, R. J.	2011	Cancer Res	SEER	Overall survival and cause-specific survival	PMRT was associated with improved OS, 92.8% (95% CI 91.294.4%) versus 88.7% (95% CI 87.7-89.7%), p < 0.001. However, there was no overall CSS benefit to PMRT, p = 0.197.	Patients with intermediate risk breast cancer who received PMRT have improved OS compared to those who did not receive PMRT

Table cont. on next page

Korah, M. P., Sener, S. F., Tripathy, D.	2012	Int J Radiat Oncol Biol Phys	SEER	Overall survival and cause-specific survival	Radiation use was associated with improved CSS (HR: 0.61) and OS (HR: 0.51), p < 0.001.	In this analysis of >25,000 elderly women with small, ER+, N0 breast cancers, RT delivery after BCS appeared to be associated with a reduction in the risk of death.
Korah, M. P., Sener, S. F., Tripathy, D.	2013	Int J Radiat Oncol Biol Phys	SEER	Breast cancer specific survival and overall survival	On subset analysis of patients with 3 lymph node metastasis (n= 2,337), BCSS at 5 yrs was 88% (no PMRT) vs 92% (PMRT), p=0.02. When this group was stratified by T-stage; BCSS at 5 yrs was 93% (T1, no PMRT) vs 95% (T1, PMRT) and 85% (T2, no PMRT) vs 90% (T2, PMRT). PMRT was associated with improved BCSS (adjusted HR: 0.80, p=0.01) and OS (adjusted HR: 0.78, p < 0.01) among patients with a minimum of 3 involved lymph nodes	In this cohort of >15,000 patients with intermediate risk breast cancer, women with minimal axillary nodal disease (N0[i+] or N1mic) had an excellent prognosis, with no evident benefit from the routine use of PMRT. However, in an unfavourable subset of women with at least 3 lymph node metastases, PMRT was associated with a significant reduction in the risk of cancer specific death, with the magnitude of benefit being most pronounced among women with T2 tumours.
Lin, C., Denniston, K. A., Charlton, M. E.	2013	J Clin Oncol	SEER	Late cardiac death	Cox model found RT to be associated with lower probability of CD (HR 0.66, 95% CI 0.62-0.70), after adjusting for age, stage, surgery status and diagnosis year	Patients with left breast cancer who survived 5 years and received RT had a lower risk of cardiac death than those who did not.
Morgan, S. C., Caudrelier, J. M., Clemons, M. J.		Cancer Res	SEER	Overall survival	On univariate analysis, EBRT was associated with improved OS (hazard ratio 0.80, 95% CI 0.74-0.87, p < 0.001). 1-year, 3-year, and 5-year OS was 56.9%, 24.2%, and 10.7% respectively in those receiving EBRT and 44.3%, 16.6%, and 7.2% respectively in those not receiving EBRT.	In a population of women presenting with metastatic breast cancer, all of whom were deemed candidates for surgery to the primary tumour but who did not undergo surgery, receipt of EBRT was associated with improved OS.
Ravi, A., Christos, P. J., Nori, D., et al.	2012	J Clin Oncol	SEER	Cause specific survival	Patients with no radiation therapy had a greater risk of breast cancer death compared to patients with radiation therapy (adjusted HR = 1.40; p = 0.003).	Adjuvant EBRT showed survival benefit in this elderly patient population
Surapaneni, A., Sura, S., Rineer, J., et al.	2012	Int J Radiat Oncol Biol Phys	SEER	Overall survival or disease free survival	Five-year OS for those who received RT was 90.7% compared to 85.2% for those who did not receive RT (p < 0.001); 10 year OS was 70.4% compared to 61.1% (p < 0.001), respectively. Five-year BCSS for those who received RT was 98.5% and 97.8% for those without RT (p = 0.002); 10 year BCSS was 95.9% compared to 92.1% (p = 0.002), respectively.	While this large population based study revealed that the use of RT after lumpectomy appears to be associated with improved OS and a small improvement in BCSS, the inherent biases within the SEER database may have influenced these findings. Given that these women have an overall low recurrence rate, further large prospective studies with very large patient cohorts might be necessary to confirm these results.

Table cont. on next page

Taylor, B. F., Evans, S. B., Roberts, K. B., et al.	2012	Int J Radiat Oncol Biol Phys	SEER	Overall survival and breast cancer specific survival	In multivariate analysis, greater nodal stage, ... No RT (Post-Op RT vs. No RT, HR 0.70, [95% CI 0.63-0.76 p < 0.001]) were associated with worse OS. Comparing Post-Op RT to Pre-Op RT, the 95% CI did not overlap for OS in multivariate analysis [Pre-Op vs. no RT, HR 1.12 [0.83-1.52], but were borderline overlapping in BCSS [Pre-Op vs. No RT, HR 1.18 [0.85-1.64].	Post-Op RT is robustly associated with improved OS and BCSS
Xie, L., Fried, D. V., Bailey, J. E., et al.	2010	Int J Radiat Oncol Biol Phys	SEER	Overall survival	The estimated RT-related OS benefit for women age <50 isz10% at 15 years. The absolute risk of RT-SMN estimated from SEER was =0.5% within 0-10 years post-RT, with minimal age dependence.	RT affords a higher survival rate in the initial 15-years and the risk of SMN is manifest only in those cured of breast cancer
Yan, W., Christos, P., Chao, K., et al.	2011	Int J Radiat Oncol Biol Phys	SEER	Overall survival and cause-specific survival	No difference in CSS or OS was detected for women treated with or without post-operative radiation. Five-year CSS was 89.4% and 91.5% for no PMRT and PMRT groups, respectively (p = 0.44 by log-rank test); 5-year OS was 87.6% and 88.3%, for no PMRT and PMRT groups, respectively (p = 0.34 by log-rank test).	This retrospective SEER data base analysis suggested that no statistical difference in CSS at 5 years was detected in patients with or without PMRT. PMRT may be beneficial in patients younger than age 40 as suggested from a non-significant trend.
Yan, W., Christos, P., Nori, D., et al.	2012	Int J Radiat Oncol Biol Phys	SEER	Breast cancer specific survival	Patients with no radiation therapy had a greater risk of breast cancer death compared to patients with radiation therapy (adjusted HR = 1.40; p = 0.003).	Adjuvant EBRT showed survival benefit in this elderly patient population
Ye, J. C., Yan, W., Christos, P. J., et al.	2013	Int J Radiat Oncol Biol Phys	SEER	Heart disease and second cancer mortality	Compared to the no- XRT group, XRT group was associated with lower overall mortality (p < 0.001, RR 0.69, CI 0.61-0.78), BC mortality (p=0.02, RR 0.75, CI 0.59- 0.95), and cardiac mortality (p < 0.001, RR 0.53, CI 0.44-0.64).	This review of the SEER data suggests that XRT is not associated with increased mortality due to BC, secondary cancer in the chest area, or cardiac conditions, and supports the continued use of BCT in early stage BC.
				Secondary outcome		
Martinez, S. R., Beal, S. H., Chen, S. L., et al.	2010	Clinical and Translational Science	SEER	Overall survival	On multivariate analysis, RT was associated with a decreased risk (HR 0.78, CI 0.74-0.83, p<0.001) and black race an increased risk (HR 1.54, CI 1.42-1.68, p<0.001) of mortality.	Although both black and Hispanic patients receive less RT than their white counterparts, only black patients have poorer OS relative to whites. When stratified by type of surgery and use of RT, blacks continued to demonstrate worse survival relative to whites. This OS disparity is thus unlikely to be due to lack of RT.
Martinez, S. R., Mayadev, J., Canter, R. J., et al.	2011	Clinical and Translational Science	SEER	Overall survival	Patients not receiving RT had an increased risk of all-cause mortality (HR 1.82, CI 1.43-2.32; p < 0.001) and disease-specific mortality (HR 1.69, CI 1.27-2.24; p < 0.001).	Rural status does not appear to be an independent predictor of OS or DSS. Our data indicate that the survival disparity noted among rural BCa patients may be due, in part, to decreased use of RT in rural populations.

Table C-2: List (including quote from results and conclusion in abstract) of eligible conference abstracts that used a comparison of irradiated and unirradiated women from systematic review of studies that used the SEER public-use data set to analyse disease control, toxicity or late heart disease and second malignancy associated with radiotherapy for breast cancer.

Authors	Year	Journal	SEER / SEER-Medicare	Outcome	Quote from results that includes a laterality comparison	Quote of abstract conclusion
Bao, J., Yu, K. D., Jiang, Y. Z., et al.	2014	PLoS ONE	SEER	Breast cancer-specific mortality	Laterality only impacted BCSM in patients with breast cancer located in the central portion (HR, 1.100; P = 0.013, using the right side as the reference).	Laterality is not regarded as a prognostic factor in breast cancer.
Darby, S. C., McGale, P., Taylor, C. W., et al	2005	Lancet Oncol	SEER	Heart disease and lung cancer mortality	The cardiac mortality ratio (left versus right tumour laterality) was 1.20 (95% CI 1.04-1.38) less than 10 years afterwards, 1.42 (1.11-1.82) 10-14 years afterwards, and 1.58 (1.29-1.95) after 15 years or more (trend: 2p=0.03)	US breast cancer radiotherapy regimens of the 1970s and early 1980s appreciably increased mortality from heart disease and lung cancer 10-20 years afterwards with, as yet, little direct evidence on the hazards after more than 20 years.
Giordano, S. H., Kuo, Y. F., Freeman, J. L., et al.	2005	J Natl Cancer Inst	SEER	Heart disease mortality	For women diagnosed in 1973-1979, there was a statistically significant difference in 15-year mortality from ischemic heart disease between patients with left-sided (13.1%, 95% confidence interval [CI] = 11.6 to 14.6) and those with right-sided (10.2%, 95% CI = 8.9 to 11.5) breast cancer (P = .02)	Risk of death from ischemic heart disease associated with radiation for breast cancer has substantially decreased over time.
Henson, K. E., McGale, P., Taylor, C., et al	2013	Br J Cancer	SEER	Heart disease and lung cancer mortality	For women diagnosed with breast cancer during 1973-1982 and given radiotherapy shortly afterwards, the cardiac mortality ratios, left-sided vs right-sided, were 1.19 (1.03-1.38), 1.35 (1.05-1.73), 1.64 (1.26-2.14) and 1.90 (1.52-2.37) at <10, 10-14, 15-19 and 20+ years since diagnosis (2p for trend: <0.001).	In this population, the radiation-related risks were larger in the third decade after exposure than during the first two decades.
Paszat, L. F., Mackillop, W. J., Groome, P. A., et al.	1998	J Clin Oncol	SEER	Fatal myocardial infarction	Among irradiated patients, the relative risk (RR) for fatal MI in women with left-sided breast cancer was 1.17 (95% confidence interval [CI], 1.01 to 1.36), controlling for age, compared with those with right-sided breast cancer.	Adjuvant RT for left-sided breast cancer diagnosed in women younger than 60 years of age is associated with a higher risk for fatal MI 10 to 15 years later compared with adjuvant RT for right-sided cases.
Patt, D. A., Goodwin, J. S., Kuo, Y. F., et al.	2005	J Clin Oncol	SEER-Medicare	Heart disease morbidity	The adjusted hazard ratio for left- versus right-sided breast cancer was 1.05 (95% CI, 0.94 to 1.16) for ischemic heart disease, 1.07 (95% CI, 0.89 to 1.30) for valvular heart disease, 1.07 (95% CI, 0.96 to 1.19) for conduction abnormalities, and 1.05 (95% CI, 0.95 to 1.17) for heart failure.	With up to 15 years of follow-up there were no significant differences in cardiac morbidity after radiation for left- versus right-sided breast cancer.
Valina-Toth, A. L., Zavodnik, T., Seicean, S., et al.	2013	Conference abstract: J Am Coll Cardiol	SEER-Medicare	Cardiac failure	The risk of heart failure was similar in left- vs right-sided breast cancer.	Grouping localization of breast cancer into left- versus right-sided laterality does not appear to affect risk of heart failure.

Table C-3: List (including quote from results and conclusion in abstract) of eligible articles that used a laterality comparison from systematic review of studies that used the SEER public-use data set to analyse disease control, toxicity or late heart disease and second malignancy associated with radiotherapy for breast cancer.

C.1 References for Tables C-1 to C-3

Abrams, M., D. E. Wazer, L. L. Price and K. E. Huber (2012). "Investigation on the benefit of PMRT in women with high risk N0 breast cancer." International Journal of Radiation Oncology Biology Physics **1)**: S245-S246.

Ademuyiwa, F. O., A. Groman, C. C. Hong, A. Miller, S. Kumar, E. Levine, D. Erwin and C. Ambrosone (2013). "Time-trends in survival in young women with breast cancer in a SEER population-based study." Breast Cancer Res Treat **138**(1): 241-248.

Agarwal, J., S. Agarwal, L. Pappas and L. Neumayer (2012). "A population-based study of breast cancer-specific survival following mastectomy and immediate or early-delayed breast reconstruction." Breast Journal **18**(3): 226-232.

Albert, J. M., I. Pan, Y. Shih, T. A. Buchholz, S. H. Giordano and B. D. Smith (2011). "Effectiveness of radiation for prevention of mastectomy in older breast cancer patients treated with breast conserving surgery." International Journal of Radiation Oncology Biology Physics **1)**: S35-S36.

Bao, J., K. D. Yu, Y. Z. Jiang, Z. M. Shao and G. H. Di (2014). "The effect of laterality and primary tumor site on cancer-specific mortality in breast cancer: A seer population-based study." PLoS ONE **9**(4).

Berrington de Gonzalez, A., R. E. Curtis, E. Gilbert, C. D. Berg, S. A. Smith, M. Stovall and E. Ron (2010). "Second solid cancers after radiotherapy for breast cancer in SEER cancer registries." British Journal of Cancer **102**(1): 220-226.

Berrington de Gonzalez, A., R. E. Curtis, S. F. Kry, E. Gilbert, S. Lamart, C. D. Berg, M. Stovall and E. Ron (2011). "Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries." Lancet Oncology **12**(4): 353-360.

Bush, D., B. Smith, J. Younger and J. S. Michaelson (2011). "The non-breast-cancer death rate among breast cancer patients." Breast Cancer Research & Treatment **127**(1): 243-249.

Horowitz, D. P., J. Ng and R. J. Burri (2011). "Survival benefit associated with post-mastectomy radiation for node-positive, intermediate-risk breast cancer patients: Results of a study from the SEER registry data." Cancer Research **3)**.

Cohen, R. J., L. Li, W. Citron, M. Oh, C. Drogula, S. Cheston, C. Bui and S. J. Feigenberg (2012). "Improved survival with adjuvant radiation in elderly women with early-stage breast cancer." International Journal of Radiation Oncology Biology Physics **1)**: S33-S34.

Cohen, R. J., L. Li, U. Mahmood, A. Hanlon, W. Citron, M. Oh, C. Drogula, S. Cheston, N. Sharma and S. J. Feigenberg (2013). "Adjuvant radiation improves breast cancer specific survival in the eldest early-stage breast cancer patients." International Journal of Radiation Oncology Biology Physics **1)**: S232.

Dai Kubicky, C., C. M. Marquez and S. J. Wang (2010). "Postmastectomy radiation therapy (PMRT) and overall survival (OS) of breast cancer patients with T1-2 and 1-3 positive axillary lymph Nodes: A SEER Data Analysis." International Journal of Radiation Oncology Biology Physics **1)**: S205.

Darby, S. C., P. McGale, C. W. Taylor and R. Peto (2005). "Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries." Lancet Oncology **6**(8): 557-565.

Dawood, S., N. T. Ueno, V. Valero, W. A. Woodward, T. A. Buchholz, G. N. Hortobagyi, A. M. Gonzalez-Angulo and M. Cristofanilli (2012). "Identifying factors that impact survival among women with inflammatory breast cancer." Annals of Oncology **23**(4): 870-875.

Dawood, S. S., R. A. Dent, S. Gupta, J. K. Litton, R. Mustafa, J. Cortes, E. A. Mittendorf, M. G. A. Ana and T. A. Buchholz (2012). "Impact of surgery and radiation of the primary among women with de novo stage IV breast cancer." Journal of Clinical Oncology **1)**.

Delgado, D. J., W. Y. Lin and M. Coffey (1995). "The role of Hispanic race/ethnicity and poverty in breast cancer survival." Puerto Rico Health Sciences Journal **14**(2): 103-116.

Doyle, J. J., A. I. Neugut, J. S. Jacobson, J. Wang, R. McBride, A. Grann, V. R. Grann and D. Hershman (2007). "Radiation therapy, cardiac risk factors, and cardiac toxicity in early-stage breast cancer patients." International Journal of Radiation Oncology, Biology, Physics **68**(1): 82-93.

Du, X., J. L. Freeman, A. B. Nattinger and J. S. Goodwin (2002). "Survival of women after breast conserving surgery for early stage breast cancer." Breast Cancer Research & Treatment **72**(1): 23-31.

Elmore, L., A. Deshpande and J. A. Margenthaler (2014). "Which patients benefit from post-mastectomy radiation therapy in the setting of T3 node-negative breast cancer?" Annals of Surgical Oncology **1)**: S58.

Gaffney, D. K., A. Tsodikov and C. L. Wiggins (2003). "Diminished survival in patients with inner versus outer quadrant breast cancers." Journal of Clinical Oncology **21**(3): 467-472.

Gao, X., S. G. Fisher and B. Emami (2003). "Risk of second primary cancer in the contralateral breast in women treated for early-stage breast cancer: a population-based study." International Journal of Radiation Oncology, Biology, Physics **56**(4): 1038-1045.

Giordano, S. H., Y. F. Kuo, J. L. Freeman, T. A. Buchholz, G. N. Hortobagyi and J. S. Goodwin (2005). "Risk of cardiac death after adjuvant radiotherapy for breast cancer." Journal of the National Cancer Institute **97**(6): 419-424.

Henson, K. E., P. McGale, C. Taylor and S. C. Darby (2013). "Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer." British Journal of Cancer **108**(1): 179-182.

Huang, J. and W. J. Mackillop (2001). "Increased risk of soft tissue sarcoma after radiotherapy in women with breast carcinoma." Cancer **92**(1): 172-180.

Huang, J., R. Walker, P. G. Groome, W. Shelley and W. J. Mackillop (2001). "Risk of thyroid carcinoma in a female population after radiotherapy for breast carcinoma." Cancer **92**(6): 1411-1418.

Joslyn, S. A. (1999). "Radiation therapy and patient age in the survival from early-stage breast cancer." International Journal of Radiation Oncology, Biology, Physics **44**(4): 821-826.

Keating, N. L., M. B. Landrum, J. M. Brooks, E. A. Chrischilles, E. P. Winer, K. Wright and R. Volya (2011). "Outcomes following local therapy for early-stage breast cancer in non-trial populations." Breast Cancer Res Treat **125**(3): 803-813.

Korah, M. P., S. F. Sener and D. Tripathy (2012). "Implications of omitting radiation after breast conserving surgery in elderly women with low-risk invasive breast cancer." International Journal of Radiation Oncology Biology Physics **1)**: S34.

Korah, M. P., S. F. Sener and D. Tripathy (2013). "The impact of postmastectomy radiation therapy in intermediate-risk breast cancer patients with limited axillary disease." International Journal of Radiation Oncology Biology Physics **1)**: S230.

Lin, C., K. A. Denniston and M. E. Charlton (2013). "Does radiation therapy increase late cardiac death in patients with left breast cancer?" Journal of Clinical Oncology **1)**.

Ly, B. H., G. Vlastos, E. Rapiti, V. Vinh-Hung and N. P. Nguyen (2010). "Local-regional radiotherapy and surgery is associated with a significant survival advantage in metastatic breast cancer patients." Tumori **96**(6): 947-954.

Martinez, S. R., S. H. Beal, S. L. Chen, R. J. Canter, V. P. Khatri, A. M. Chen and R. J. Bold (2010). "Do radiation use disparities influence survival of patients with advanced breast cancer?" Clinical and Translational Science **3 (2)**: S31-S32.

Martinez, S. R., J. Mayadev, R. J. Canter and P. N. Lara (2011). "Rural-urban survival disparities among breast cancer patients eligible for postmastectomy radiation therapy." Clinical and Translational Science **4 (2)**: 117.

Martinez, S. R., W. H. Tseng, R. J. Canter, A. M. Chen, S. L. Chen and R. J. Bold (2012). "Do radiation use disparities influence survival in patients with advanced breast cancer?" Cancer **118**(1): 196-204.

Martinez, S. R., W. H. Tseng, D. R. Shah, R. J. Canter and R. J. Bold (2012). "Urban and non-urban disparities in the use of post-mastectomy radiation for breast cancer." Med Oncol **29**(3): 1523-1528.

McCammon, R., C. Finlayson, A. Schwer and R. Rabinovitch (2008). "Impact of postmastectomy radiotherapy in T3N0 invasive carcinoma of the breast: a Surveillance, Epidemiology, and End Results database analysis." Cancer **113**(4): 683-689.

Mery, C. M., S. George, M. M. Bertagnolli and C. P. Raut (2009). "Secondary sarcomas after radiotherapy for breast cancer: sustained risk and poor survival." Cancer **115**(18): 4055-4063.

Morgan, S. C., J. M. Caudrelier and M. J. Clemons (2012). "Radiotherapy to the primary tumor is associated with improved survival in stage iv breast cancer." Cancer Research **3)**.

Neta, G., W. F. Anderson, E. Gilbert and A. Berrington (2012). "Variation in the risk of radiation-

related contralateral breast cancer by histology and estrogen receptor expression in SEER." Breast Cancer Research & Treatment **131**(3): 1021-1027.

Neugut, A. I., W. C. Lee, T. Murray, E. Robinson, K. Karwoski and G. J. Kutcher (1993). "Lung cancer after radiation therapy for breast cancer." Cancer **71**(10): 3054-3057.

Patt, D. A., J. S. Goodwin, Y. F. Kuo, J. L. Freeman, D. D. Zhang, T. A. Buchholz, G. N. Hortobagyi and S. H. Giordano (2005). "Cardiac morbidity of adjuvant radiotherapy for breast cancer." Journal of Clinical Oncology **23**(30): 7475-7482.

Paszat, L. F., W. J. Mackillop, P. A. Groome, C. Boyd, K. Schulze and E. Holowaty (1998). "Mortality from myocardial infarction after adjuvant radiotherapy for breast cancer in the surveillance, epidemiology, and end-results cancer registries." Journal of Clinical Oncology **16**(8): 2625-2631.

Ravi, A., P. J. Christos, D. Nori, C. Chao and W. Yan (2012). "Age, hormone receptor status, ethnicity, and adjuvant radiation therapy as predictive factors for cancer-related death in patients age 70 and older with early-stage pT1a,b N0 breast cancer: An NCI-SEER database analysis." Journal of Clinical Oncology **1)**.

Royce, M., C. Bouchardy, E. Rapiti, G. Vlastos, G. Cserni, V. Vinh-Hung, J. Lamote, G. Storme, N. P. Nguyen and P. T. Truong (2009). "Tumor location does not influence the survival effects of radiotherapy in node-negative breast cancer." Cancer Research **S)**.

Schootman, M., D. B. Jeffe, W. E. Gillanders, Y. Yan and R. Aft (2007). "The effects of radiotherapy for the treatment of contralateral breast cancer." Breast Cancer Research & Treatment **103**(1): 77-83.

Smith, B. D., G. L. Smith and B. G. Haffty (2005). "Postmastectomy radiation and mortality in women with T1-2 node-positive breast cancer." Journal of Clinical Oncology **23**(7): 1409-1419.

Smith, B. D., C. P. Gross, G. L. Smith, D. H. Galusha, J. E. Bekelman and B. G. Haffty (2006). "Effectiveness of Radiation Therapy for Older Women With Early Breast Cancer." Journal of the National Cancer Institute **98**(10): 681-690.

Smith, B. D., B. G. Haffty, A. Hurria, D. H. Galusha and C. P. Gross (2006). "Postmastectomy radiation and survival in older women with breast cancer." Journal of Clinical Oncology **24**(30): 4901-4907.

Smith, G. L., B. D. Smith, S. H. Giordano, Y. C. Shih, W. A. Woodward, E. A. Strom, G. H. Perkins, W. Tereffe, T. K. Yu and T. A. Buchholz (2008). "Risk of hypothyroidism in older breast cancer patients treated with radiation." Cancer **112**(6): 1371-1379.

Surapaneni, A., S. Sura, J. Rineer, D. Schwartz, M. Rotman and D. Schreiber (2012). "Effect of radiation on breast cancer specific survival for elderly women with early stage (T1N0 ER+) breast cancer: Review of the seer database." International Journal of Radiation Oncology Biology Physics **1)**: S246.

Taylor, B. F., S. B. Evans, K. B. Roberts and J. B. Yu (2012). "Survival for patients with inflammatory breast cancer receiving mastectomy is associated with radiation sequence and race." International Journal of Radiation Oncology Biology Physics **1)**: S222-S223.

Valina-Toth, A. L., T. Zavodnik, S. Seicean, J. Plana and T. Marwick (2013). "Risk of heart failure in women with breast cancer who received radiotherapy." Journal of the American College of Cardiology **1)**: E581.

Vinh-Hung, V., T. Burzykowski, J. Van de Steene, G. Storme and G. Soete (2002). "Post-surgery radiation in early breast cancer: survival analysis of registry data." Radiotherapy & Oncology **64**(3): 281-290.

Vinh-Hung, V., M. Voordeckers, J. Van de Steene, G. Soete, J. Lamote and G. Storme (2003). "Omission of radiotherapy after breast-conserving surgery: survival impact and time trends." Radiotherapy & Oncology **67**(2): 147-158.

Vinh-Hung, V., T. Burzykowski, J. Van de Steene, M. Voordeckers, J. Lamote and G. Storme (2005). "Statistical interaction in the survival analysis of early breast cancer using registry data: role of breast conserving surgery and radiotherapy." Tumori **91**(1): 9-14.

Vinh-Hung, V., P. T. Truong, W. Janni, N. P. Nguyen, G. Vlastos, G. Cserni, M. E. Royce, W. A. Woodward, D. Promish, P. Tai, G. Soete, S. Balmer-Majno, B. Cutuli, G. Storme and C. Bouchardy (2009). "The Effect of adjuvant radiotherapy on mortality differs according to primary tumor location in women with node-positive breast cancer. [German] Die Wirkung der adjuvanten Strahlentherapie auf das Letalitatsrisiko variiert je nach Tumorsitz bei Patientinnen mit einem nodal positiven Mammakarzinom." Strahlentherapie und Onkologie **185**(3): 161-168.

Voordeckers, M., V. Vinh-Hung, J. Lamote, A. Bretz and G. Storme (2009). "Survival benefit with radiation therapy in node-positive breast carcinoma patients." Strahlentherapie und Onkologie **185**(10): 656-662.

Xie, L., D. V. Fried, J. E. Bailey, R. Chen, N. DeMore, E. L. Jones, J. S. Halle and L. B. Marks (2010). "Does the risk of late radiation-associated malignancy offset the survival benefit of post-lumpectomy/mastectomy radiation for young women? A quantitative study based on seer-data." International Journal of Radiation Oncology Biology Physics **1)**: S621.

Yan, W., P. Christos, K. Chao, D. Nori and A. Ravi (2011). "Post-mastectomy radiation therapy in younger women aged less than 50 with T3N0 invasive breast cancer: Outcomes by receptor status/race/age." International Journal of Radiation Oncology Biology Physics **1)**: S34.

Yan, W., P. Christos, D. Nori, C. K. Chao and A. Ravi (2012). "Age, hormonal receptor status, ethnicity, and adjuvant radiation therapy as predictive factors for cancer-related death in elderly patients aged 70 years and older with early stage PT1A,B No breast cancer: A NCI-SEER database analysis." International Journal of Radiation Oncology Biology Physics **1)**: S34-S35.

Yan, W., P. Christos, D. Nori, K. S. Chao and A. Ravi (2013). "Is there a cause-specific survival benefit of postmastectomy radiation therapy in women younger than age 50 with T3N0 invasive breast cancer? A SEER database analysis: outcomes by receptor status/race/age: analysis using the NCI Surveillance, Epidemiology, and End Results (SEER) database." American Journal of Clinical Oncology **36**(6): 552-557.

Yap, J., P. J. Chuba, R. Thomas, A. Aref, D. Lucas, R. K. Severson and M. Hamre (2002). "Sarcoma as a second malignancy after treatment for breast cancer." International Journal of Radiation Oncology, Biology, Physics **52**(5): 1231-1237.

Ye, J. C., W. Yan, P. J. Christos, D. Nori, K. C. Chao and A. Ravi (2013). "Breast cancer (BC), second cancer, and cardiac mortality in stage T1AN0 BC patients with or without external beam radiation therapy (XRT): NCI seer study." International Journal of Radiation Oncology Biology Physics **1)**: S46.

Yu, G. P., S. P. Schantz, A. I. Neugut and Z. F. Zhang (2006). "Incidences and trends of second cancers in female breast cancer patients: a fixed inception cohort-based analysis (United States)." Cancer Causes Control **17**(4): 411-420.

Yu, J. B., L. D. Wilson, T. Dasgupta, W. A. Castrucci and J. B. Weidhaas (2008). "Postmastectomy radiation therapy for lymph node-negative, locally advanced breast cancer after modified radical mastectomy: analysis of the NCI Surveillance, Epidemiology, and End Results database." Cancer **113**(1): 38-47.

Zablotska, L. B. and A. I. Neugut (2003). "Lung carcinoma after radiation therapy in women treated with lumpectomy or mastectomy for primary breast carcinoma." Cancer **97**(6): 1404-1411.

Zablotska, L. B., A. Chak, A. Das and A. I. Neugut (2005). "Increased Risk of Squamous Cell Esophageal Cancer after Adjuvant Radiation Therapy for Primary Breast Cancer." American Journal of Epidemiology **161**(4): 330-337.

Cause of death	Breast conserving surgery * (10,801 women in 17 trials)				
	Deaths / Women		Logrank O-E‡	Variance of O-E	Ratio of annual death rates RT: No RT
	RT	No RT			
Breast cancer	849 / 5,452	1,051 / 5,349	-85.3	440.3	0.82 (SE 0.04) ¶
All causes	1,536 / 5,452	1,607 / 5,349	-63.2	739.5	0.92 (SE 0.04)
Other causes§	687 / 5,452	556 / 5,349	22.1	299.2	1.08 (SE 0.06)

Cause of death	Mastectomy and axillary dissection † (3,131 node-positive women in 14 trials)				
	Deaths / Women		Logrank O-E	Variance of O-E	Ratio of annual death rates RT: No RT
	RT	No RT			
Breast cancer	832 / 1,550	941 / 1,581	-62.0	367.0	0.84 (SE 0.05)
All causes	1,001 / 1,550	1,073 / 1,581	-52.1	430.4	0.89 (SE 0.05)
Other causes§	169 / 1,550	132 / 1,581	9.9	63.4	1.17 (SE 0.14)

* Results for breast cancer and all causes of death in trials of radiotherapy after breast conserving surgery obtained from Webfigures 3, 12a, 12b, 12c of EBCTCG 2011.

† Results for breast cancer and all causes of death in trials of radiotherapy after mastectomy and axillary dissection calculated from Webfigure 30 of EBCTCG 2014.

‡ SE: standard error

§ Logrank "Observed minus expected".

¶ Results for other causes obtained by subtraction of results for breast cancer from results for all causes. Results for all women for breast cancer, all causes, and other causes (shown in Table 1) calculated by addition of results for women given breast conserving surgery and women given mastectomy and axillary dissection. Results for all women for other specified causes of death calculated by addition from results shown in Figure 1 of EBCTCG 2005

Table C-4: Randomised evidence: death rate ratios in 13,932 women with early breast cancer randomised to receive adjuvant radiotherapy (RT) or not (No RT).

	Number of women		Percentage given RT		Cardiac deaths	Breast cancer deaths
	Left-sided	Right-sided	Left-sided	Right-sided		
Stage						
Localised	181,801	175,402	46	46	13,033	26,563
Regional	102,980	98,688	45	46	7,179	49,722
Surgery						
BCS *	129,374	125,675	78	78	5,022	16,623
Mastectomy	155,407	148,415	19	20	15,190	59,662
Calendar year of diagnosis						
1973-1982	32,857	30,716	22	22	6,565	21,705
1983-1992	49,896	47,662	29	29	6,639	23,119
1993-2002	107,284	103,499	52	53	6,009	25,216
2003-2008	94,744	92,213	55	56	999	6,245
Age at diagnosis						
20-49	79,904	78,308	48	48	1,265	25,681
50-59	74,604	71,740	49	50	3,163	20,215
60-69	71,392	68,366	45	46	6,901	18,169
70-79	58,881	55,676	39	40	8,883	12,220
Race / ethnicity						
White	238,657	230,139	46	46	17,408	63,218
Black	24,207	22,679	45	45	2,011	8,931
Other / unknown	21,917	21,272	46	46	793	4,136
Total	**284,781**	**274,090**	**46**	**46**	**20,212**	**76,285**

* Breast conserving surgery

Table C-5: Patient characteristics of SEER observational cohort used in the methodological discussion as a comparison to randomised data.

Certified cause of death	Number of deaths / Woman-years at risk			
	RT		No RT	
	Breast conserving surgery RT: 197,727 No RT: 57,322*	**Mastectomy ¶** RT: 59,249 No RT: 244,573	**Breast conserving surgery** RT: 197,727 No RT: 57,322	**Mastectomy** RT: 59,249 No RT: 244,573
Breast cancer	11,882 / 66,253†	16,421 / 84,313	4,741 / 20,124	43,241 / 263,157
Other deaths	14,971 / 107,341	7,960 / 80,734	6,130 / 613,085	44,530 / 419,107
Lung cancer‡	962 / 7,438	344 / 4,715	261 / 1,395	1,785 / 18,646
Other cancers	3,544 / 26,090	1,716 / 16,923	1,110 / 6,454	8,508 / 84,936
Heart disease	3,392 / 23,212	2,468 / 25,549	1,630 / 7,844	12,722 / 111,366
Other diseases	5,976 / 42,592	2,603 / 25,850	2,637 / 13,222	17,852 / 168,030
Accidents & violence	409 / 2,470	191 / 1,469	153 / 648	1,095 / 9,017
All causes §	26,853 / 173,594	24,381 / 165,047	10,871 / 5,828	87,771 / 682,265

* Number of women recorded as receiving radiotherapy (RT) or as not receiving radiotherapy (No RT).
† Numbers of deaths/number of woman-years at risk.
‡ Includes only deaths from women with microscopically confirmed lung cancer, identified by cross-matching of recorded deaths to SEER data file of lung cancer registrations.
§ Includes deaths with unknown cause.
¶ Mainly node-negative women

Table C-6: Observational evidence: numbers of deaths and woman-years at risk in 558,871 women registered as having breast cancer and recorded as receiving radiotherapy (RT) or not (No RT) in the SEER public-use data set.

Certified cause of death	Number of deaths / Woman-years at risk			
	RT		No RT	
	Breast conserving surgery RT: 186,571 No RT: 54,146*	**Mastectomy ¶** RT: 40,745 No RT: 151,381	**Breast conserving surgery** RT: 186,571 No RT: 54,146*	**Mastectomy** RT: 40,745 No RT: 151,381
Breast cancer	9,628 / 48,655 †	7,858 / 31,822	4,070 / 15,903	16,715 / 78,215
Other deaths	11,731 / 73,402	2,339 / 12,604	4,811 / 21,804	16,360 / 98,263
Lung cancer‡	771 / 5,144	96 / 616	222 / 1,086	778 / 5,236
Other cancers	2,895 / 18,538	644 / 3,538	919 / 4,702	3,208 / 20,577
Heart disease	2,691 / 16,152	592 / 3,085	1,316 / 5,644	4,422 / 25,343
Other diseases	5,017 / 31,665	928 / 5,013	2,227 / 9,898	7,499 / 44,608
Accidents & violence	357 / 1,903	79 / 352	127 / 475	453 / 2,499
All causes §	21,910 / 125,775	10,402 / 45,499	9,157 / 39,237	33,858 / 181,584

* Number of women recorded as receiving radiotherapy (RT) or as not receiving radiotherapy (No RT).
† Numbers of deaths/number of woman-years at risk.
‡ Includes only deaths from women with microscopically confirmed lung cancer, identified by cross-matching of recorded deaths to SEER data file of lung cancer registrations.
§ Includes deaths with unknown cause.
¶ Mainly node-negative women

Table C-7: Observational evidence: numbers of deaths and woman-years at risk in 432,843 women registered as having breast cancer from 1990 onwards and recorded as receiving radiotherapy (RT) or not (No RT) in the SEER public-use data set.

Appendix D (for Chapter 4)

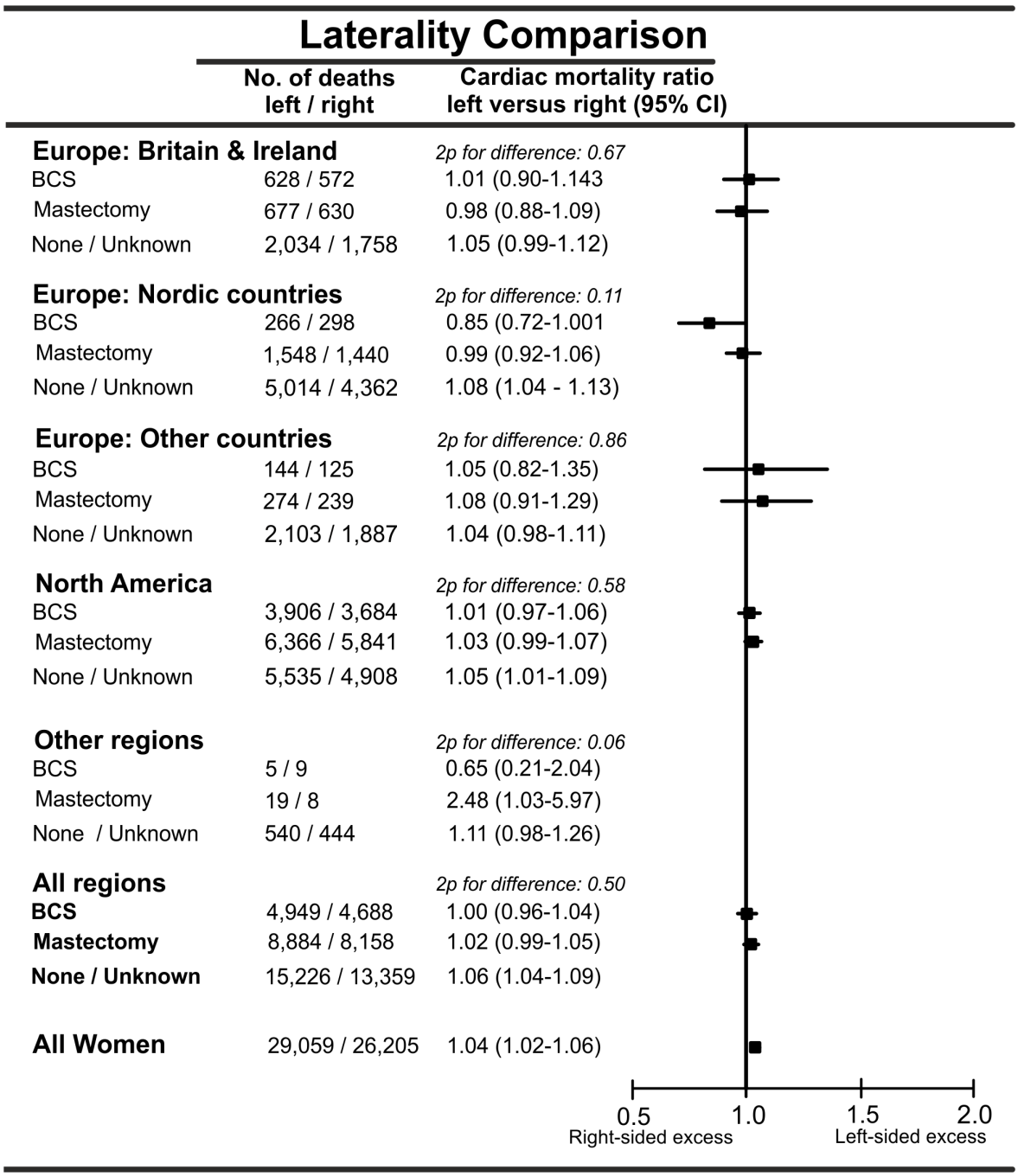


Figure D-1: Cardiac mortality in irradiated and unirradiated women with left-sided breast cancer versus women with right-sided breast cancer subdivided by geographic region.

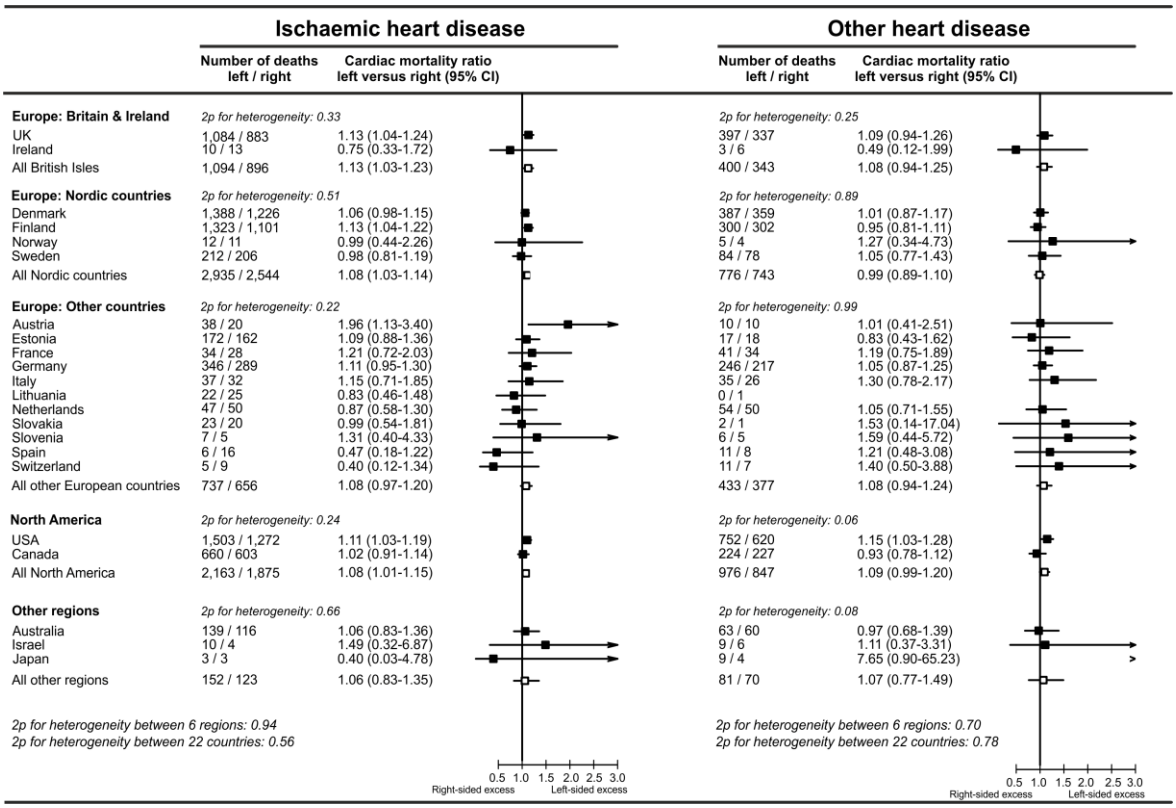


Figure D-2: Mortality from ischaemic heart disease and other types of heart disease in irradiated women with left-sided breast cancer versus irradiated women with right-sided breast cancer subdivided by country.

Women diagnosed with breast cancer aged <60					
	Number of cardiac deaths		Stratification only		Stratification and adjustment for confounding
	Left-sided	Right-sided	Cardiac mortality ratio (95% CI)	Odds ratios of mortality ratios (95% CI)	Odds ratios of mortality ratios (95% CI)
Years since diagnosis					
0-4	523	494	1.01 (0.89-1.14)	1	1
5-14	907	734	1.16 (1.05-1.28)	1.15 (0.97-1.33)	1.18 (0.99-1.37)
15+	2048	1536	1.27 (1.19-1.36)	1.27 (1.09-1.44)	1.36 (1.12-1.59)
				2p for trend=0.0008	*2p for trend=0.0005*
Calendar year of diagnosis					
<1970	1013	801	1.19 (1.08-1.30)	1	1
1970-89	1808	1409	1.22 (1.14-1.31)	1.03 (0.91-1.15)	1.07 (0.93-1.21)
1990+	657	554	1.14 (1.01-1.27)	0.95 (0.81-1.09)	1.15 (0.93-1.38)
				2p for trend=0.62	*2p for trend=0.15*
Region					
Britain & Ireland	316	271	1.10 (0.93-1.29)	0.93 (0.76-1.09)	0.89 (0.73-1.06)
Nordic	1312	1041	1.18 (1.09-1.28)	1.00 (0.89-1.12)	0.97 (0.85-1.09)
Other Europe	457	319	1.34 (1.16-1.54)	1.12 (0.93-1.30)	1.04 (0.87-1.22)
N America	1339	1089	1.19 (1.09-1.28)	1	1
Other regions	54	44	1.17 (0.77-1.80)	0.96 (0.56-1.37)	0.94 (0.54-1.33)
				2p for heterogeneity=0.55	*2p for heterogeneity=0.69*
Chemotherapy					
Yes	196	147	1.43(1.14-1.79)	1.15 (0.88-1.42)	1.21 (0.92-1.50)
No	1273	1003	1.18 (1.09-1.29)	1	1
Unknown	24	14	1.35 (0.68-2.67)	1.00 (0.90-1.11)	1.00 (0.85-1.16)
Not recorded	1985	1600	1.18 (1.10-1.26)	1.15 (0.36-1.93)	1.22 (0.38-2.06)
				2p for difference=0.23	*2p for difference=0.19*
Hormonal therapy					
Yes	227	205	1.03 (0.85-1.25)	0.84 (0.66-1.01)	0.87 (0.68-1.07)
No	1233	941	1.24 (1.14-1.35)	1	1
Unknown	16	4	2.94 (0.97-8.90)	2.41 (-0.27-5.09)	2.51 (-0.29-5.31)
Not recorded	2002	1614	1.18 (1.10-1.26)	0.96 (0.86-1.07)	0.98 (0.82-1.13)
				2p for difference=0.10	*2p for difference=0.10*
Stage					
Localised	1100	918	1.13 (1.03-1.24)	1	1
Regional	1038	798	1.27 (1.15-1.39)	1.12 (0.97-1.26)	1.13 (0.98-1.27)
Metastatic	69	53	1.20 (0.83-1.75)	1.04 (0.65-1.43)	1.15 (0.71-1.60)
DCIS	42	35	1.26 (0.80-1.99)	1.07 (0.58-1.57)	1.09 (0.58-1.60)
Unknown	501	357	1.34 (1.16-1.54)	1.16 (0.97-1.35)	1.12 (0.89-1.35)
Not recorded	728	603	1.12 (1.01-1.25)	1.00 (0.86-1.14)	1.01 (0.86-1.17)
				2p for difference (local vs regional)=0.42	*2p for difference (local vs regional)=0.41*

table cont. on next page

Surgery					
BCS	532	489	1.05 (0.93-1.18)	1	1
Mastectomy	584	481	1.15 (1.02-1.30)	1.10 (0.91-1.29)	1.12 (0.92-1.33)
None	29	33	0.69 (0.39-1.24)	0.74 (0.34-1.14)	0.77 (0.35-1.19)
Unknown	1570	1144	1.30 (1.20-1.40)	1.23 (1.05-1.41)	1.26 (1.05-1.48)
Not recorded	763	617	1.16 (1.04-1.29)	1.11 (0.93-1.29)	1.16 (0.93-1.40)
				2p for difference=0.29	*2p for difference=0.69*
Race / Ethnicity					
White	1786	1397	1.22 (1.14-1.31)	1	1
Black	160	142	1.04 (0.82-1.31)	0.86 (0.66-1.07)	0.91 (0.68-1.14)
Asian / pacific	62	47	1.39 (0.93-2.06)	1.13 (0.69-1.58)	1.15 (0.69-1.61)
Other	39	19	1.58 (0.89-2.81)	1.34 (0.58-2.09)	1.22 (0.51-1.93)
Unknown	250	229	1.02 (0.85-1.22)	0.83 (0.67-0.99)	0.72 (0.48-0.96)
Not recorded	1181	930	1.19 (1.09-1.29)	0.96 (0.85-1.06)	0.93 (0.81-1.05)
				2p between known categories =0.38	*2p between known categories*=0.63

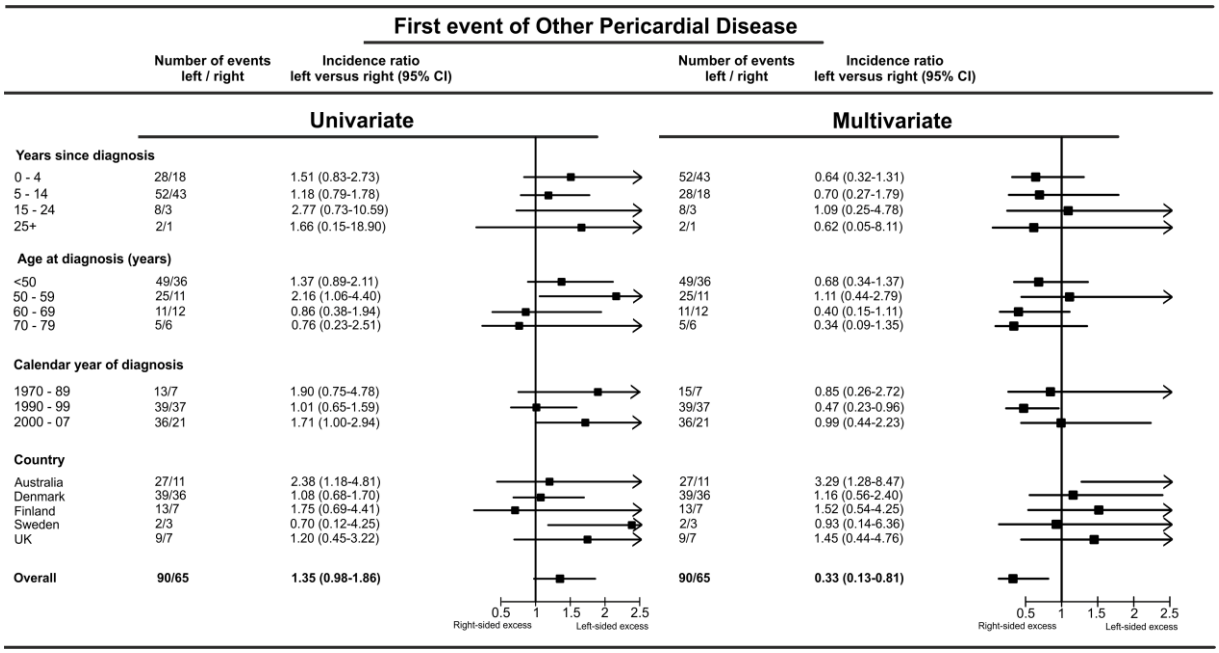
Table D-1: Cardiac mortality in women with left-sided breast cancer versus women with right-sided breast cancer for women diagnosed before age 60 subdivided by various factors.

D.1 Details of cumulative mortality estimate

Age	Cumulative mortality (%) RT+: left	RT+: right
Diagnosed aged 35 years		
35-39	0.007	0.007
40-44	0.039	0.039
45-49	0.187	0.094
50-54	0.453	0.193
55-59	0.749	0.351
60-64	1.265	0.630
65-69	1.833	1.153
70-74	2.952	2.186
75-79	5.364	4.416
Diagnosed aged 45 years		
45-49	0.055	0.055
50-54	0.155	0.155
55-59	0.342	0.315
60-64	0.670	0.595
65-69	1.317	1.122
70-74	2.590	2.161
75-79	4.991	4.407
Diagnosed aged 55 years		
55-59	0.181	0.163
60-64	0.500	0.450
65-69	1.179	0.989
70-74	2.512	2.051
75-79	5.326	4.345
Diagnosed aged 65 years		
65-69	0.583	0.566
70-74	1.740	1.684
75-79	4.257	4.094

Appendix E (for Chapter 5)

E.1 Investigation of significant right-sided excess in first event analysis of other pericardial disease



The estimates calculated using a multivariate model with an additional person-years weighted average and subdivided by years since diagnosis, age, calendar year and country of diagnosis show a right-sided excess in a number of the groupings. There was a right-sided excess in the groups with the largest person-years, for example women aged 60 years or older, when calculated by a univariate model, which was more significant by applying the person-years weighting after the multivariate model. Therefore, the groups with the greatest person-years had the lowest incidence ratio estimates, and resulted in an overall right-sided excess. However, the numbers are so low for this endpoint that the estimates for the subdivisions are mainly due to chance. The multivariate incidence ratio was calculated for wider subgroupings of the patient characteristics: time since 0-14, 15+; age <60, 60+; calendar year: <2000, 2000+, was 0.69 (0.42-1.13), which is more reasonable. However, this estimate was not presented in Chapter 5 to ensure consistency in the calculation of the estimates.

Appendix F (for Chapter 6)

F.1 Details of cumulative mortality estimate

Age	Cumulative mortality (%)	
	RT+: ipsilateral	RT+: contralateral l
	Diagnosed aged 45 years	
45-49	0.082	0.062
50-54	0.261	0.198
55-59	0.730	0.403
60-64	1.366	0.683
65-69	2.009	1.041
70-74	2.710	1.435
75-79	3.527	1.897
	Diagnosed aged 55 years	
55-59	0.321	0.210
60-64	0.758	0.496
65-69	1.612	0.863
70-74	2.538	1.265
75-79	3.746	1.738
	Diagnosed aged 65 years	
65-69	1.001	0.386
70-74	2.088	0.809
75-79	2.715	1.306

Appendix G (for Chapter 7)

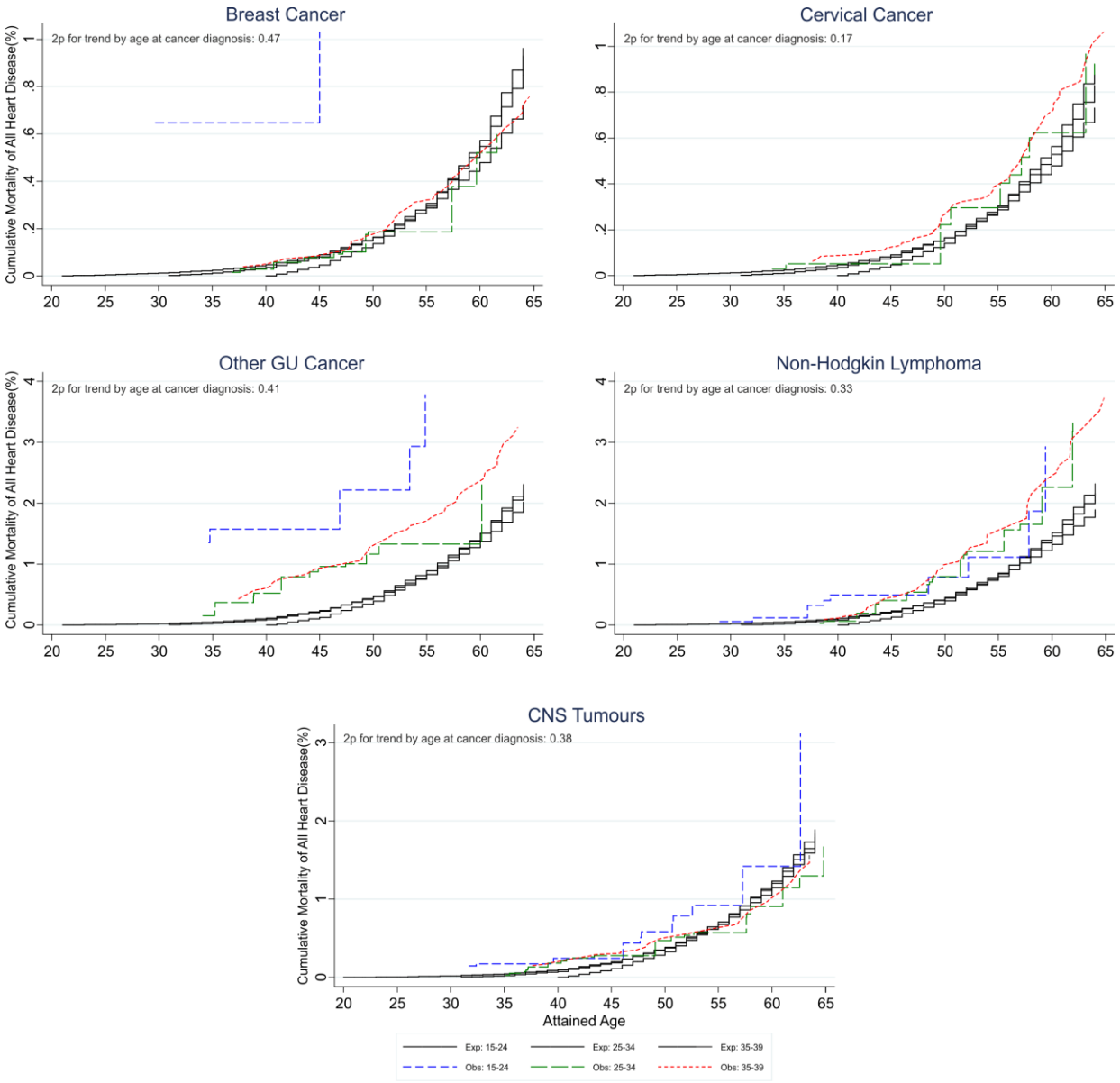


Figure G-1: Cumulative mortality by attained age of all heart disease combined for breast cancer, cervical cancer, other genitourinary, CNS tumours, and non-Hodgkin lymphoma 5-year survivors, subdivided by age at cancer diagnosis and observed versus expected deaths.

G.1 Investigation into potential confounding of SMRs and AERs

Initially, cross-tabulations highlighted correlation between the two measures of follow-up: attained age and years since diagnosis (Table G-1).

Years since diagnosis	Attained Age					
	20 --9	**30 -- 9**	**40 -- 9**	**50 -- 9**	**60 -- 9**	**70 +**
5 -- 9	15	68	213	0	0	0
	3,485	13,328	26,804	0	0	0
	111,881	388,482	578,797	0	0	0
10 -- 14	4	39	191	98	0	0
	1,211	9,118	28,869	11,235	0	0
	22,700	181,381	458,770	155,508	0	0
15 -- 19	0	27	120	244	0	0
	0	3,554	15,379	22,264	0	0
	0	67,781	224,601	295,972	0	0
20 -- 24	0	4	71	238	120	0
	0	791	7,761	18,168	6,338	0
	0	13,254	98,470	220,130	72,272	0
25 -- 29	0	0	37	105	251	0
	0	0	3,482	10,123	14,412	0
	0	0	32,613	95,938	121,686	0
30 +	0	0	9	84	207	182
	0	0	720	6,579	17,925	11,535
	0	0	5,120	40,516	95,113	44,118

Cardiac deaths
5-year survivors
Person-years

Table G-1: Cross tabulation of cardiac deaths, number of 5-years survivors and person-years by attained age and years since diagnosis

Univariable model		All heart disease		IHD		Valvular HD		Cardiomyopathy	
		RR: SMRs	EMR	RR: SMRs	EMR	RR: SMRs	EMR	RR: SMRs	EMR
Gender	Male	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Female	1.1 [1.0,1.2]	0.5 [0.4,0.8]	1.1 [1.0,1.2]	0.5 [0.3,0.8]	1.2 [0.8,1.7]	0.8 [0.4,1.5]	1.1 [0.9,1.4]	0.7 [0.3,1.9]
	2p for heterogeneity:	*0.02*	*0.002*	*0.08*	*0.007*	*0.37*	*0.57*	*0.48*	*0.51*
Age at cancer diagnosis	15-19	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	20-24	0.5 [0.4,0.7]	0.7 [0.5,1.0]	0.6 [0.5,0.9]	1.0 [0.6,1.6]	0.5 [0.2,1.1]	0.8 [0.3,1.8]	0.5 [0.3,1.0]	0.5 [0.2,1.5]
	25-29	0.4 [0.3,0.5]	0.6 [0.4,0.8]	0.4 [0.3,0.6]	0.7 [0.4,1.2]	0.3 [0.1,0.5]	0.5 [0.2,1.2]	0.4 [0.2,0.8]	0.4 [0.1,1.2]
	30-34	0.3 [0.2,0.3]	0.3 [0.2,0.5]	0.3 [0.2,0.4]	0.3 [0.1,0.7]	0.1 [0.06,0.2]	0.2 [0.08,0.7]	0.4 [0.2,0.6]	0.4 [0.1,1.1]
	35-39	0.3 [0.2,0.3]	0.2 [0.1,0.4]	0.3 [0.2,0.4]	0.3 [0.2,0.8]	0.1 [0.05,0.2]	0.3 [0.10,0.7]	0.3 [0.2,0.5]	0.1 [0.0,1.7]
	2p for trend:	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*0.0003*	*<0.0001*	*0.005*
Calendar year of cancer diagnosis	1970-79	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	1980-89	1.1 [1.0,1.2]	0.6 [0.4,1.0]	1.1 [1.0,1.2]	0.8 [0.5,1.4]	0.9 [0.6,1.4]	0.4 [0.2,0.8]	1.1 [0.8,1.5]	0.9 [0.2,4.1]
	1990-99	1.0 [0.9,1.2]	0.3 [0.2,0.5]	1.1 [0.9,1.2]	0.3 [0.1,0.7]	0.8 [0.4,1.4]	0.1 [0.04,0.4]	1.3 [0.9,1.8]	1.0 [0.2,4.3]
	2000+	1.0 [0.8,1.3]	0.1 [0.04,0.4]	1.0 [0.7,1.4]	0.1 [0.0,0.9]	0.5 [0.1,2.1]	0.03 [0.0,4.9]	1.5 [0.9,2.5]	1.1 [0.2,5.5]
	2p for trend:	*0.39*	*<0.0001*	*0.23*	*<0.0001*	*0.22*	*<0.0001*	*0.07*	*0.86*
Attained age (years)	20-39	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	40-49	0.6 [0.5,0.7]	1.3 [0.9,1.8]	0.6 [0.4,0.7]	1.4 [0.9,2.1]	0.9 [0.4,2.0]	1.9 [0.6,6.0]	0.6 [0.4,0.9]	0.8 [0.4,1.7]
	50-59	0.5 [0.4,0.5]	1.4 [0.9,2.2]	0.4 [0.4,0.6]	1.4 [0.8,2.7]	0.9 [0.4,2.0]	5.7 [1.9,17.3]	0.4 [0.3,0.6]	0.2 [0.0,8.5]
	60+	0.4 [0.3,0.5]	1.5 [0.6,3.7]	0.4 [0.3,0.5]	1.2 [0.3,5.7]	0.5 [0.2,1.1]	7.7 [2.2,27.0]	0.4 [0.2,0.5]	-
	2p for trend:	*<0.0001*	*0.10*	*<0.0001*	*0.20*	*0.006*	*<0.0001*	*<0.0001*	*0.06*
First primary cancer	Breast	1.0 [0.8,1.2]	0.7 [0.2,1.9]	1.0 [0.8,1.2]	0.5 [0.2,1.8]	1.1 [0.3,3.5]	1.3 [0.02,69.4]	0.9 [0.4,1.7]	0.2 [0.0,14543]
	NMSC	0.7 [0.5,0.8]	-	0.7 [0.5,0.8]	-	0.4 [0.10,1.6]	-	0.6 [0.3,1.1]	-
	Testicular	0.8 [0.6,1.0]	-	0.8 [0.6,0.9]	-	1.7 [0.6,5.3]	3.9 [0.1,142.9]	0.9 [0.5,1.7]	0.3 [0.0,2149.8]
	Cervix	1.0 [0.8,1.3]	0.7 [0.2,1.9]	1.1 [0.9,1.4]	0.8 [0.3,2.2]	1.4 [0.4,4.6]	1.9 [0.04,83.0]	0.6 [0.3,1.3]	-
	Melanoma	0.4 [0.3,0.5]	-	0.4 [0.3,0.5]	-	0.7 [0.2,3.0]	-	0.6 [0.2,1.3]	-
	Hodgkin	3.1 [2.6,3.7]	9.1 [4.1,20.6]	2.8 [2.3,3.4]	7.6 [3.2,18.1]	10.9 [3.9,30.6]	26.0 [0.8,864.7]	2.8 [1.5,5.2]	9.6 [0.5,201.5]
	CNS tumour	1.2 [0.9,1.5]	1.4 [0.5,3.7]	1.1 [0.9,1.4]	1.2 [0.4,3.5]	1.9 [0.5,6.8]	3.2 [0.08,131.0]	1.2 [0.6,2.6]	1.9 [0.07,57.5]
	Other		1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	NHL	1.4 [1.1,1.7]	2.9 [1.2,7.2]	1.2 [0.9,1.6]	1.9 [0.7,5.6]	1.8 [0.4,7.0]	3.4 [0.07,160.0]	2.5 [1.3,4.9]	9.7 [0.4,211.0]
	Thyroid	0.8 [0.5,1.1]	-	0.6 [0.4,0.9]	-	2.5 [0.6,10.2]	4.8 [0.1,204.1]	0.9 [0.3,2.6]	0.4 [0.0,3328.0]
	Other GU	1.1 [0.9,1.4]	2.6 [1.0,6.8]	1.1 [0.8,1.4]	2.2 [0.8,6.6]	2.0 [0.6,7.0]	7.1 [0.2,277.8]	1.0 [0.5,2.2]	1.3 [0.01,137.1]
	GI	0.7 [0.5,0.9]	-	0.7 [0.5,0.9]	-	1.1 [0.2,5.0]	2.0 [0.02,223.8]	1.0 [0.4,2.4]	1.5 [0.02,136.5]
	Ovary	0.7 [0.4,1.1]	-	0.6 [0.4,1.0]	-	1.5 [0.3,8.3]	2.1 [0.03,168.2]	1.5 [0.6,3.9]	2.5 [0.08,83.9]
	STS	1.0 [0.7,1.4]	0.8 [0.2,4.3]	0.8 [0.5,1.2]	-	1.5 [0.3,8.4]	2.5 [0.03,192.5]	2.9 [1.4,6.0]	10.7 [0.5,238.5]
	Leukaemia	1.5 [1.1,2.2]	2.1 [0.7,6.0]	1.3 [0.8,2.0]	1.3 [0.3,5.1]	1.6 [0.2,14.3]	1.7 [0.01,256.3]	2.9 [1.2,6.9]	8.4 [0.4,199.6]
	Head & Neck	1.0 [0.7,1.3]	1.1 [0.2,6.6]	1.0 [0.7,1.4]	1.3 [0.2,7.2]	0.7 [0.08,6.6]	-	0.9 [0.3,2.6]	-
	Bone Tumour	1.2 [0.7,1.9]	1.2 [0.2,6.5]	1.0 [0.6,1.8]	0.8 [0.07,9.1]	2.4 [0.3,21.4]	3.9 [0.04,340.8]	1.2 [0.3,5.2]	1.5 [0.0,405.3]
	Lung	1.5 [1.1,2.2]	6.4 [2.2,18.6]	1.4 [0.9,2.1]	5.6 [1.7,18.4]	3.5 [0.6,19.2]	15.9 [0.3,786.8]	2.2 [0.7,6.7]	11.6 [0.4,347.1]
	2p for heterogeneity:	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*

Table G-2: Relative risk (RR) and excess mortality ratio (EMR) by potential explanatory factors, estimated using a univariable model (corresponding to Table 7-3, Table 7-8 and Table 7-9).

Multivariable model		All heart disease		IHD		Valvular HD		Cardiomyopathy	
		RR: SMRs	EMR	RR: SMRs	EMR	RR: SMRs	EMR	RR: SMRs	EMR
Gender	Male	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Female	1.4 [1.3,1.6]	0.7 [0.5,0.8]	1.3 [1.1,1.5]	0.5 [0.4,0.7]	2.2 [1.4,3.5]	1.3 [0.7,2.4]	1.7 [1.2,2.3]	1.3 [0.7,2.3]
	2p for heterogeneity:	*<0.0001*	*0.0003*	*0.0001*	*<0.0001*	*0.0004*	*0.37*	*0.001*	*0.46*
Age at cancer diagnosis	15-19	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	20-24	0.6 [0.5,0.8]	0.7 [0.5,1.0]	0.8 [0.5,1.0]	1.1 [0.7,1.9]	0.5 [0.2,1.1]	0.6 [0.2,1.3]	0.7 [0.4,1.3]	0.7 [0.2,2.0]
	25-29	0.6 [0.4,0.7]	0.6 [0.5,0.9]	0.6 [0.5,0.8]	1.0 [0.6,1.7]	0.3 [0.1,0.7]	0.4 [0.1,0.9]	0.7 [0.4,1.3]	0.4 [0.1,1.7]
	30-34	0.5 [0.4,0.6]	0.6 [0.4,0.9]	0.5 [0.4,0.7]	1.0 [0.5,1.7]	0.2 [0.07,0.4]	0.04 [0.0,0.3]	0.8 [0.4,1.5]	1.1 [0.4,3.1]
	35-39	0.5 [0.4,0.6]	0.6 [0.4,0.9]	0.5 [0.4,0.7]	1.1 [0.6,1.9]	0.2 [0.07,0.3]	0.2 [0.06,0.5]	0.7 [0.4,1.3]	0.6 [0.2,2.0]
	2p for trend:	*<0.0001*	*0.01*	*0.0001*	*0.93*	*<0.0001*	*<0.0001*	*0.48*	*0.74*
Calendar year of cancer diagnosis	1970-79	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	1980-89	1.1 [1.0,1.2]	0.6 [0.5,0.8]	1.1 [1.0,1.2]	0.5 [0.4,0.7]	0.9 [0.6,1.4]	0.7 [0.4,1.4]	1.0 [0.7,1.3]	1.0 [0.5,2.3]
	1990-99	1.0 [0.9,1.1]	0.5 [0.3,0.6]	1.0 [0.9,1.2]	0.4 [0.3,0.7]	0.8 [0.4,1.6]	0.5 [0.1,2.0]	1.0 [0.7,1.5]	1.0 [0.4,2.4]
	2000+	0.9 [0.7,1.2]	0.4 [0.3,0.8]	1.0 [0.7,1.3]	0.3 [0.1,0.7]	0.7 [0.2,3.3]	0.9 [0.07,11.0]	1.1 [0.6,1.9]	1.3 [0.4,4.2]
	2p for trend:	*0.95*	*<0.0001*	*0.54*	*<0.0001*	*0.45*	*0.24*	*0.95*	*0.80*
Attained age (years)	20-39	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	40-49	0.8 [0.7,1.0]	2.7 [1.9,3.7]	0.7 [0.5,0.9]	2.2 [1.4,3.4]	1.9 [0.8,4.6]	11.2 [1.9,65.8]	0.7 [0.5,1.1]	1.7 [0.7,4.0]
	50-59	0.7 [0.5,0.8]	4.3 [3.0,6.3]	0.6 [0.5,0.7]	3.1 [1.9,5.1]	2.5 [1.0,6.1]	60.3 [10.3,354.5]	0.5 [0.3,0.8]	2.2 [0.8,6.4]
	60+	0.6 [0.5,0.8]	7.9 [5.1,12.1]	0.6 [0.5,0.8]	5.8 [3.3,10.3]	1.8 [0.7,5.0]	96.8 [13.8,677.2]	0.5 [0.3,0.9]	2.4 [0.5,10.8]
	2p for trend:	*<0.0001*	*<0.0001*	*0.0006*	*<0.0001*	*0.52*	*<0.0001*	*0.008*	*0.16*
First primary cancer	Breast	0.9 [0.7,1.1]	0.9 [0.3,2.1]	0.9 [0.7,1.1]	0.9 [0.1,5.1]	1.0 [0.3,3.2]	-	0.7 [0.4,1.4]	0.2 [0.001,25.0]
	NMSC	0.7 [0.6,0.9]	-	0.7 [0.6,0.9]	-	0.5 [0.1,2.0]	-	0.6 [0.3,1.2]	-
	Testicular	0.9 [0.7,1.1]	-	0.8 [0.6,1.0]	-	2.5 [0.8,8.1]	7.3 [0.4,139.2]	1.0 [0.5,2.0]	-
	Cervix	0.9 [0.7,1.1]	0.7 [0.2,1.9]	1.0 [0.7,1.3]	1.0 [0.2,5.8]	1.1 [0.3,3.7]	-	0.5 [0.2,1.1]	-
	Melanoma	0.4 [0.3,0.5]	-	0.3 [0.2,0.5]	-	0.7 [0.1,2.9]	-	0.5 [0.2,1.2]	-
	Hodgkin	2.9 [2.4,3.5]	9.6 [4.6,20.1]	2.6 [2.1,3.2]	13.6 [3.4,54.3]	9.3 [3.3,26.3]	32.4 [1.9,546.0]	2.7 [1.5,5.0]	6.6 [0.9,48.7]
	CNS tumour	1.1 [0.9,1.4]	1.8 [0.8,4.2]	1.1 [0.8,1.4]	2.0 [0.4,9.5]	1.9 [0.5,6.6]	4.8 [0.2,102.3]	1.2 [0.6,2.4]	1.3 [0.1,12.9]
	Other		1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	NHL	1.4 [1.1,1.8]	3.2 [1.4,7.4]	1.2 [0.9,1.6]	3.0 [0.7,14.2]	2.0 [0.5,8.2]	5.6 [0.2,128.9]	2.6 [1.3,5.1]	5.4 [0.7,40.8]
	Thyroid	0.7 [0.5,1.0]	-	0.6 [0.4,0.9]	-	2.1 [0.5,8.6]	4.9 [0.2,126.6]	0.8 [0.3,2.2]	0.8 [0.04,17.7]
	Other GU	1.2 [1.0,1.6]	2.9 [1.3,6.5]	1.2 [0.9,1.5]	3.5 [0.8,15.4]	2.6 [0.8,8.9]	6.6 [0.3,150.5]	1.1 [0.5,2.5]	1.8 [0.2,17.7]
	GI	0.8 [0.6,1.0]	-	0.7 [0.5,1.0]	-	1.4 [0.3,6.1]	-	1.1 [0.5,2.6]	-
	Ovary	0.6 [0.4,0.9]	-	0.5 [0.3,0.9]	-	1.1 [0.2,6.1]	-	1.1 [0.4,3.0]	1.5 [0.1,19.9]
	STS	1.0 [0.7,1.4]	1.1 [0.3,4.0]	0.8 [0.5,1.1]	-	1.5 [0.3,8.3]	4.4 [0.1,136.3]	2.8 [1.3,5.8]	6.1 [0.7,50.5]
	Leukaemia	1.4 [1.0,2.0]	3.0 [1.1,7.8]	1.2 [0.8,1.8]	3.3 [0.6,18.4]	1.5 [0.2,13.3]	-	2.5 [1.1,6.1]	5.5 [0.6,49.7]
	Head & Neck	1.0 [0.8,1.4]	0.7 [0.1,5.1]	1.1 [0.7,1.5]	-	0.9 [0.1,8.2]	-	0.9 [0.3,2.9]	1.3 [0.06,27.4]
	Bone Tumour	1.0 [0.6,1.6]	1.3 [0.3,6.2]	0.9 [0.5,1.6]	1.6 [0.1,19.4]	1.9 [0.2,16.8]	-	1.1 [0.2,4.7]	-
	Lung	1.7 [1.2,2.5]	5.6 [2.2,14.3]	1.6 [1.0,2.4]	6.2 [1.2,32.8]	4.8 [0.9,26.6]	20.0 [0.8,512.9]	2.6 [0.8,7.9]	8.5 [0.9,77.0]
	2p for heterogeneity:	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*

Table G-3: Relative risk (RR) and excess mortality ratio (EMR) by potential explanatory factors, estimated using a multivariable model including attained age (corresponding to Table 7-3, Table 7-8 and Table 7-9).

Univariable model	Breast cancer		Cervical Cancer		Hodgkin Lymphoma		CNS Tumours		Non-Hodgkin Lymphoma		Other GU	
	RR: SMRs	EMR	RR: SMRs	EMR	RR: SMRs	EMR	RR: SMRs	EMR	RR: SMRs	EMR	RR: SMRs	EMR
Gender												
Male	-	-	-	-	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Female	-	-	-	-	1.7 [1.4,2.1]	0.5 [0.4,0.7]	1.4 [1.0,2.0]	0.9 [0.3,2.6]	1.8 [1.2,2.7]	1.0 [0.5,2.2]	2.4 [1.7,3.3]	6.4 [0.4,113.9]
2p for het	-	-	-	-	*<0.0001*	*<0.0001*	0.04	0.86	0.006	0.98	*<0.0001*	0.007
Age at cancer diagnosis												
15-19	1 (ref)	1 (ref)	-	-	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
20-24	0.1 [0.01,1.6]	0.2 [0.01,2.9]	-	-	0.5 [0.4,0.7]	0.9 [0.6,1.3]	0.6 [0.3,1.6]	0.8 [0.2,4.7]	1.4 [0.4,5.1]	3.3 [0.2,51.9]	0.3 [0.06,1.1]	0.3 [0.04,2.2]
25-29	0.07 [0.01,0.6]	0.1 [0.01,1.2]	0.7 [0.4,1.3]	-	0.4 [0.3,0.5]	1.0 [0.7,1.4]	0.7 [0.3,1.5]	1.5 [0.4,6.1]	1.2 [0.4,4.2]	4.6 [0.3,65.8]	0.2 [0.05,0.6]	0.2 [0.03,1.6]
30-34	0.05 [0.007,0.4]	0.07 [0.008,0.7]	1.2 [0.8,1.6]	1.1 [0.3,3.5]	0.3 [0.2,0.4]	1.3 [0.9,1.9]	0.4 [0.2,0.9]	0.3 [0.006,16.5]	1.2 [0.4,3.9]	7.2 [0.5,96.7]	0.2 [0.05,0.5]	0.3 [0.05,1.4]
35-39	0.04 [0.006,0.3]	0.05 [0.005,0.5]	1 (ref)	1 (ref)	0.3 [0.2,0.4]	1.7 [1.2,2.6]	0.5 [0.2,1.1]	2.0 [0.5,7.7]	0.7 [0.2,2.4]	3.6 [0.2,55.0]	0.1 [0.05,0.5]	0.3 [0.06,1.3]
2p for trend	*0.004*	*0.05*	*0.69*	*0.93*	*<0.0001*	*0.003*	*0.07*	*0.58*	*0.03*	*0.15*	*0.03*	*0.39*
Calendar year of cancer diagnosis												
1970-79	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1980-89	1.5 [1.1,2.0]	3.0 [0.2,39.7]	1.0 [0.7,1.5]	0.5 [0.1,2.1]	0.7 [0.6,0.9]	0.3 [0.2,0.4]	1.2 [0.8,1.8]	1.0 [0.2,4.7]	0.9 [0.6,1.4]	0.4 [0.1,1.2]	1.4 [1.0,2.0]	2.0 [0.3,15.7]
1990-99	1.0 [0.6,1.5]	0.1 [0.0,169.0]	1.0 [0.6,1.6]	0.2 [0.01,2.5]	0.8 [0.6,1.1]	0.2 [0.1,0.3]	1.4 [0.9,2.2]	0.7 [0.1,3.5]	1.3 [0.9,2.1]	0.5 [0.2,1.2]	1.6 [1.0,2.7]	1.3 [0.2,11.6]
2000+	0.7 [0.3,1.9]	-	0.8 [0.2,3.1]	-	1.1 [0.6,2.0]	0.2 [0.08,0.3]	1.4 [0.6,3.4]	0.4 [0.05,4.2]	0.8 [0.3,2.2]	0.07 [0.001,3.7]	4.5 [2.2,8.9]	3.5 [0.4,28.1]
2p for trend	*0.64*	*0.12*	*0.85*	*0.10*	*0.08*	*<0.0001*	*0.15*	*0.35*	*0.54*	*0.03*	*0.0004*	*0.26*
Attained Age (years)												
20-39	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
40-49	0.4 [0.2,1.0]	0.6 [0.2,2.5]	0.8 [0.3,1.9]	1.7 [0.2,12.7]	0.7 [0.5,1.0]	3.1 [2.1,4.6]	0.4 [0.2,0.7]	0.7 [0.2,2.9]	0.7 [0.4,1.4]	2.6 [0.9,7.5]	0.3 [0.1,0.5]	0.6 [0.2,1.5]
50-59	0.3 [0.1,0.7]	0.6 [0.08,4.5]	0.6 [0.3,1.6]	2.3 [0.2,21.2]	0.6 [0.4,0.8]	6.5 [4.4,9.5]	0.5 [0.3,0.8]	2.5 [0.8,7.4]	0.4 [0.2,0.9]	2.2 [0.5,9.8]	0.1 [0.08,0.3]	0.1 [0.001,10.7]
60+	0.3 [0.1,0.7]	1.8 [0.3,12.3]	0.6 [0.2,1.5]	6.9 [0.8,60.8]	0.5 [0.4,0.7]	13.8 [9.1,21.0]	0.4 [0.2,0.7]	3.1 [0.5,19.6]	0.5 [0.2,1.0]	7.9 [2.2,28.7]	0.2 [0.09,0.3]	1.0 [0.2,4.1]
2p for trend	*0.04*	*0.89*	*0.25*	*0.18*	*0.0002*	*<0.0001*	*0.04*	*0.26*	*0.03*	*0.02*	*0.0002*	*0.10*

Table G-4: Relative risk (RR) and excess mortality ratio (EMR) by potential explanatory factors for specific FPT groups, estimated using a univariable model (corresponding to Table 7-5, Table 7-6 and Table 7-7).

Multivariable model	Breast cancer		Cervical Cancer		Hodgkin Lymphoma		CNS Tumours		Non-Hodgkin Lymphoma		Other GU	
	RR: SMRs	EMR	RR: SMRs	EMR	RR: SMRs	EMR	RR: SMRs	EMR	RR: SMRs	EMR	RR: SMRs	EMR
Gender												
Male	-	-	-	-	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Female	-	-	-	-	1.7 [1.4,2.1]	0.5 [0.4,0.7]	1.5 [1.0,2.1]	0.7 [0.3,1.8]	1.9 [1.2,2.8]	0.9 [0.4,1.9]	2.5 [1.8,3.5]	2.4 [0.9,6.2]
2p for het	-	-	-	-	*<0.0001*	*<0.0001*	*0.03*	*0.49*	*0.004*	*0.80*	*<0.0001*	*0.04*
Age at cancer diagnosis												
15-19	1 (ref)	1 (ref)	-	-	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
20-24	0.2 [0.02,1.9]	0.3 [0.02,3.2]	-	-	0.5 [0.4,0.8]	0.6 [0.4,0.9]	0.7 [0.3,1.8]	0.6 [0.1,3.4]	1.5 [0.4,5.6]	2.2 [0.1,37.4]	0.3 [0.08,1.4]	0.3 [0.06,1.8]
25-29	0.1 [0.01,0.8]	0.2 [0.02,1.5]	1 (ref)	-	0.4 [0.3,0.5]	0.5 [0.3,0.7]	0.8 [0.3,1.8]	1.1 [0.2,5.5]	1.4 [0.4,4.8]	2.4 [0.2,30.8]	0.3 [0.07,0.9]	0.3 [0.07,1.4]
30-34	0.08 [0.01,0.6]	0.06 [0.005,0.7]	1.9 [1.0,3.6]	1.0 [0.3,3.3]	0.3 [0.2,0.5]	0.5 [0.3,0.8]	0.5 [0.2,1.2]	0.2 [0.002,17.7]	1.4 [0.4,4.8]	3.6 [0.3,44.7]	0.3 [0.08,0.9]	0.2 [0.05,1.1]
35-39	0.07 [0.01,0.5]	0.06 [0.006,0.6]	1.8 [0.9,3.4]	1 (ref)	0.3 [0.2,0.4]	0.6 [0.4,0.9]	0.7 [0.3,1.5]	0.8 [0.1,5.7]	0.9 [0.3,3.2]	1.9 [0.1,26.8]	0.3 [0.07,0.9]	0.2 [0.04,1.3]
2p for trend	*0.05*	*0.04*	*0.29*	*0.08*	*<0.0001*	*0.01*	*0.40*	*0.87*	*0.18*	*0.70*	*0.28*	*0.19*
Calendar year of cancer diagnosis												
1970-79	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1980-89	1.5 [1.1,2.0]	2.3 [0.6,9.3]	1.0 [0.7,1.4]	0.7 [0.2,2.2]	0.7 [0.6,0.9]	0.4 [0.3,0.6]	1.2 [0.8,1.8]	1.0 [0.3,2.9]	0.9 [0.6,1.4]	0.6 [0.2,1.9]	1.4 [1.0,2.0]	1.9 [0.6,6.0]
1990-99	0.8 [0.5,1.4]	-	0.8 [0.4,1.4]	0.2 [0.03,1.8]	0.8 [0.6,1.1]	0.4 [0.2,0.6]	1.3 [0.8,2.2]	0.9 [0.2,4.1]	1.2 [0.7,2.1]	0.9 [0.3,2.6]	1.4 [0.8,2.4]	1.1 [0.2,4.7]
2000+	0.5 [0.2,1.5]	0.2 [0.005,9.7]	0.5 [0.1,2.2]	-	1.1 [0.6,2.1]	0.4 [0.2,0.9]	1.3 [0.5,3.3]	0.7 [0.09,5.9]	0.6 [0.2,1.9]	0.1 [0.003,5.0]	2.9 [1.3,6.3]	3.2 [0.8,13.6]
2p for trend	*0.74*	*0.04*	*0.29*	*0.05*	*0.09*	*<0.0001*	*0.33*	*0.80*	*0.95*	*0.27*	*0.02*	*0.25*
Attained Age (years)												
20-39	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
40-49	0.5 [0.2,1.4]	1.4 [0.3,6.1]	0.5 [0.2,1.4]	0.9 [0.1,5.7]	1.0 [0.7,1.3]	3.6 [2.3,5.4]	0.5 [0.3,0.9]	1.3 [0.3,6.2]	0.8 [0.4,1.7]	2.5 [0.7,8.5]	0.3 [0.2,0.7]	0.7 [0.2,2.3]
50-59	0.4 [0.2,1.0]	0.6 [0.07,6.0]	0.4 [0.2,1.1]	0.7 [0.08,6.0]	0.8 [0.6,1.2]	6.5 [4.1,10.1]	0.6 [0.3,1.1]	3.9 [0.6,26.5]	0.5 [0.2,1.2]	1.5 [0.3,9.3]	0.2 [0.09,0.4]	0.8 [0.2,3.8]
60+	0.4 [0.2,1.0]	2.5 [0.4,15.7]	0.4 [0.1,1.0]	1.6 [0.2,13.4]	0.8 [0.6,1.2]	12.3 [7.3,20.9]	0.5 [0.2,1.1]	5.5 [0.5,59.3]	0.6 [0.3,1.5]	7.5 [1.6,35.0]	0.2 [0.1,0.5]	2.1 [0.4,9.7]
2p for trend	*0.09*	*0.85*	*0.05*	*0.84*	*0.23*	*<0.0001*	*0.36*	*0.09*	*0.17*	*0.06*	*0.03*	*0.45*

Table G-5: Relative risk (RR) and excess mortality ratio (EMR) by potential explanatory factors for specific FPT groups, estimated using a multivariable model including attained age (corresponding to Table 7-5, Table 7-6 and Table 7-7).

Appendix H: Henson, K. E., P. McGale, C. Taylor and S. C. Darby (2013). "Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer." Br J Cancer 108(1): 179-182.