
**University of Oxford**

# Survivors of adult cancer – their use of primary care services and unmet needs

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Wolfson College, Oxford

A thesis submitted for the degree of Doctor of Philosophy in the University of Oxford

Trinity Term 2011

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## Abstract

The work described in this thesis concerns the use and quality of primary care service use by people living beyond a diagnosis of breast, colorectal and prostate cancer and long-term risks associated with cancer. Firstly, the thesis provides a background for this work, with a definition of long-term survivors as those living at least five years past cancer, and the role of primary care in the care of this population.

The second section describes use of the General Practice Research Database amongst a cohort of cancer survivors compared to a control population. Breast and colorectal cancer survivors consult more frequently than controls up to 10 years post-diagnosis, while prostate survivors continue to see their GP up to 3 times more for at least 15 years. Most survivors receive adequate preventative care and chronic disease monitoring, excepting mammography for long-term breast cancer survivors. Cancer survivors receive more prescriptions for pain relief, anti-depressants and erectile dysfunction, suggesting higher rates of pain, depression and sexual

dysfunction. Breast cancer survivors have an elevated risk of incident heart failure, coronary artery disease and hypothyroidism, while colorectal survivors experience increased risk of dementia and diabetes. All three groups of cancer survivors had higher risks of osteoporosis and second cancers, all-cause, non-cancer and cancer mortality compared to controls.

The third section describes a qualitative study of the primary care usage and unmet needs of 40 long-term survivors of breast, colorectal and prostate cancer. Most respondents did not need active GP involvement. Others had ongoing information and psychological service needs. Some felt that their GPs did not have the right expertise for cancer related issues or were too busy, while others had concerns about continuity of GP care.

Overall, this thesis provides a background on how the increasing numbers of cancer survivors use and experience primary care in the UK, areas of good practice, and areas where care can be improved in the future.

## Acknowledgements

I couldn't have done this without my friends and family, who provided much love and support throughout the time I've been working on this thesis. I want to dedicate this work to my parents, Nina and Mujtaba Khan, who have always encouraged me in my academic pursuits.

I would like to thank Macmillan Cancer Support and Cancer Research UK for funding this project. I hope the results will be of use for future research and policy.

I've been very lucky to have had excellent support and advice from so many people here at Oxford. It's been wonderful to work with my two supervisors and this thesis wouldn't have been possible without them. I don't think I could have asked for anyone nicer or more knowledgeable to work with than Peter Rose, who has taken on the role of supervisor, friend, advisor and ally! Lucy Carpenter's statistical and career advice was exceptional. David Mant has acted as a third supervisor – it's rare to be able to run ideas through with someone as respected and I am very grateful for his time. Having never done a qualitative study before I am indebted to Julie Evans for guiding me through the process of interviewing and analysis, often when I really didn't know what to do! I've very much enjoyed being based at the Department of Primary Care and am sad to be leaving. Thank you to you all.

Finally, I would like to thank the interview participants for their hospitality (the biscuits were much appreciated!), for discussing often very difficult topics and for their time.

# List of abbreviations

| | |
|---|---|
| BMI | Body mass index |
| BNF | British National Formulary |
| CAD | Coronary artery disease |
| CI | Confidence interval |
| COPD | Chronic obstructive pulmonary disease |
| FOB | Faecal occult blood |
| DDD | Defined daily dose |
| ED | Erectile dysfunction |
| EMIS | Egton Medical Information System |
| EMR | Electronic medical record |
| GPRD | General Practice Research Database |
| HbA1c | Glycosylated haemoglobin |
| HR | Hazard ratio |
| HRT | Hormone replacement therapy |
| HTO | Health Talk Online |
| IBD | Irritable bowel disorder |
| ICD | International Classification of Diseases |
| IMD | Index of Multiple Deprivation |
| IQR | Interquartile range |
| IRR | Incidence rate ratio |
| LBC | Living beyond cancer |
| MHRA | Medicines and Healthcare Regulatory Authority |
| MI | Myocardial infarction |
| NCIN | National Cancer Intelligence Network |
| NCSI | National Cancer Survivorship Initiative |
| NHS | National Health Service |
| NHSBCSP | NHS Bowel Cancer Screening Programme |

| | |
|---|---|
| NHSBSP | NHS Breast Screening Programme |
| NICE | National Institute for Health and Clinical Excellence |
| NSAIDs | Non-steroidal anti-inflammatory drugs |
| NYCRIS | Northern and Yorkshire Cancer Registry and Information Service |
| OCIU | Oxford Cancer Intelligence Unit |
| ONS | Office for National Statistics |
| OR | Odds ratio |
| OSOP | One sheet of paper |
| PCRMP | Prostate Cancer Risk Management Programme |
| PPV | Positive predictive value |
| PSA | Prostate specific antigen |
| ROC curve | Receiver operating characteristic curve |
| SOD | Statement of death |
| QOF | Quality and Outcomes Framework |
| TIA | Transient ischaemic attack |
| UTS | Up-to-standard (i.e. the GPRD practice was providing UTS data) |
| WHO | World Health Organization |

# Preface

In 1862, an American collector of antiquities named Edwin Smith purchased an ancient papyrus from an Egyptian man named Mustafa Agha. The papyrus, intended as a surgical textbook, describes 48 cases of traumatic injury. Case 45 is the first known description of cancer. The case describes a bulging tumour on the breast of a man, and to the misfortune of the ancient Egyptians, the suggested treatment was to 'do nothing'.

*From Breasted's translation of the Edwin Smith Surgical Papyrus. New England Journal of Medicine 1932;206:28-9.*

# Chapter 1: Background

## 1.1 Cancer as a public health issue

Cancer is a major source of morbidity in the UK and the world, with 12.7 million new cases each year and 7.6 million deaths worldwide in 2008 (1). In Europe alone, cancer currently represents the second largest cause of death and morbidity, with 3.2 million new cancer diagnoses and 1.7 million cancer deaths (1). One in three people in Europe will develop cancer at some point in their lives, and one in four deaths is attributable to cancer. Cancer affects not only the individuals diagnosed with disease; the burden of illness falls on families, carers, societies and economies as a whole (2).

Cancer is a growing public health problem, and incidence is increasing globally. If current estimates are correct, it is predicted that the incidence of cancer in Europe will increase by 20% by 2020 (3). This rise is largely due to changes in demography in an aging and growing population. The introduction of national cancer screening programmes is also impacting upon national cancer trends in developed economies. Cancer is predominately a disease that occurs in older people, with more than 75% of total cases occurring in men and women aged over 60 at the time of diagnosis (4). As populations grow, much of the increasing cancer burden will occur among elderly men and women.

The aim of this chapter is to provide an overview of the public health implications of cancer and a summary of cancer incidence, survival and prevalence in the UK. The concept of 'cancer survivorship' will be introduced, along with a discussion of the primary

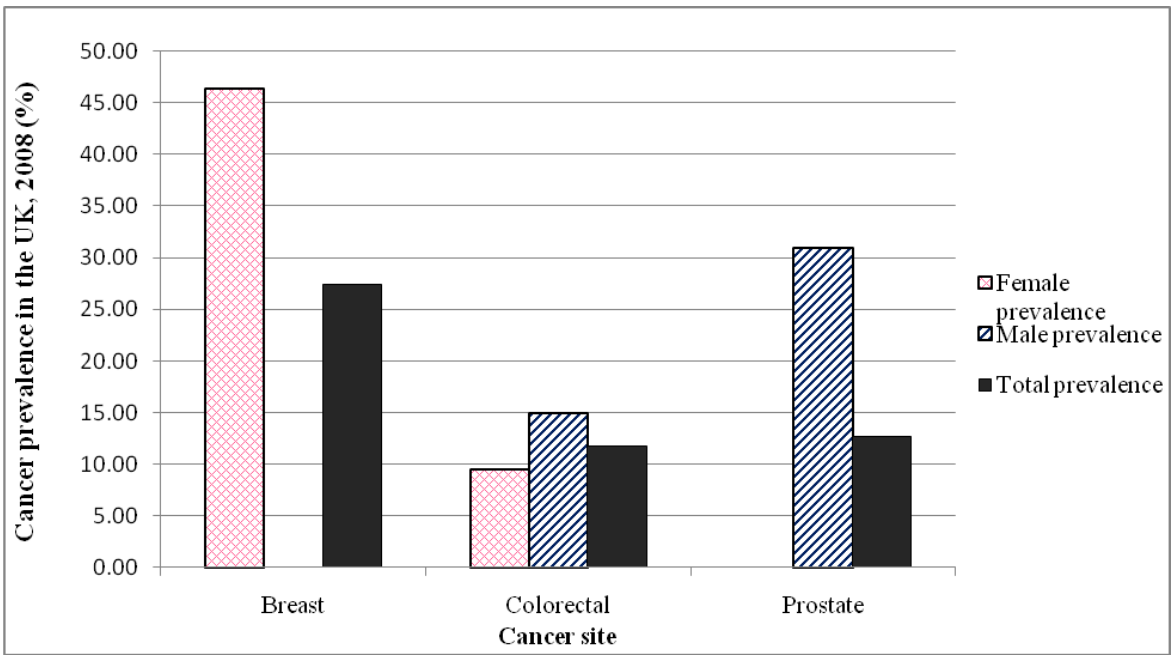
health care of people living beyond cancer in the face of the changing epidemiology of the disease.

## 1.2 Current cancer prevalence estimates in the UK

Once seen as an almost fatal disease half a century ago, cancer has increasingly become a treatable disease with successful patient outcomes. Four types of cancer, breast, lung, colorectal and prostate, make up more than half (53.8%) of all new diagnoses of cancer in the UK (5). Survival rates for most common cancers have been increasing due to improvements in diagnosis and treatment, with an average increase in five year relative survival of 6.1% for breast cancer, 5.6% for colon cancer and 15.9% for prostate cancer every five yearly period since the 1980s (6). As of 2009, half of all cancer patients in the UK will live for at least five years, and many die from causes other than cancer (7).

Recent estimates suggest that there are now 2 million people living past a diagnosis of cancer in UK (8). This figure includes 550,000 breast cancer survivors, 250,000 colon cancer survivors, 215,000 prostate cancer survivors, and 985,000 survivors of other cancer sites. Breast cancer is by far the most prevalent cancer due to its high incidence and relatively good prognosis (Figure 1.1). Colorectal cancer accounts for 10-15% of total cancer prevalence in men and women. Prostate cancer is the most prevalent cancer in men, comprising roughly 31% of the total prevalent cancer cases amongst men in the UK.

**Figure 1.1 - Cancer prevalence in the UK, 2008 - by sex* and total population**




Adapted using data from Maddams et al (8) *Male breast cancer is not represented in this chart as it accounts for less than 1% of all incident breast cancer cases

### 1.2.1 Future projections based on increase in elderly people in the population

Prevalence of cancer is increasing in an aging and growing population; the number of prevalent cases is currently growing by 3.8% per year for men and 2.7% for women. The higher rate in men is driven partly due to the rapidly increasing incidence of prostate cancer (8).

Over half of the population of cancer survivors comprises those who have had breast, colorectal or prostate cancer, and this thesis will focus on these three cancers. The prevalence of cancer survivors in the UK is driven by current incidence and trends in survival for each individual cancer. The next sections describe the trends in cancer epidemiology and risk factors for breast, colorectal and prostate cancer.

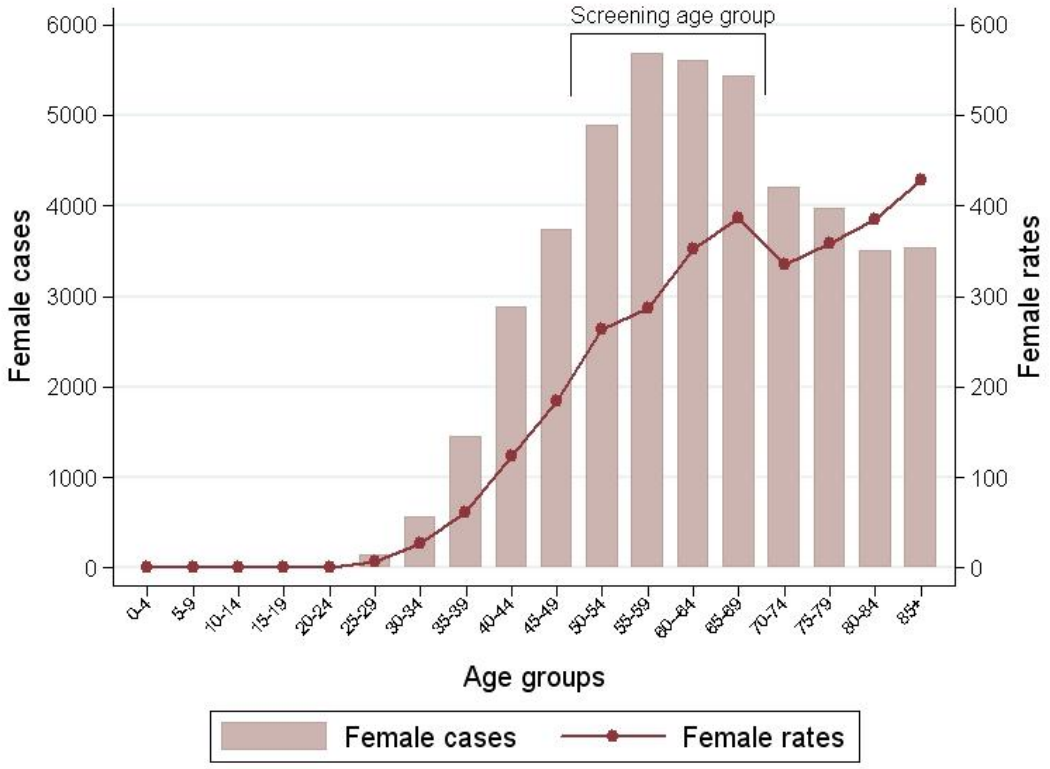
## 1.3 Cancer incidence in the UK

Cancer incidence is the frequency of new cases of cancer in a population over a given period of time. It is usually expressed as a rate – the annual number of new cases per unit of population per year. Incidence rates can be affected by mass or opportunistic screening, improvements in diagnostic techniques and changing completeness of registration.

### 1.3.1 Breast cancer

Breast cancer is the most commonly diagnosed cancer in the UK. Breast cancer is extremely rare in men, with 341 cases diagnosed in men compared to over 45000 diagnosed cases in women in 2006 (Figure 1.2).

**Figure 1.2: Numbers of new cases and age-specific incidence rates 2006, breast cancer (5)***



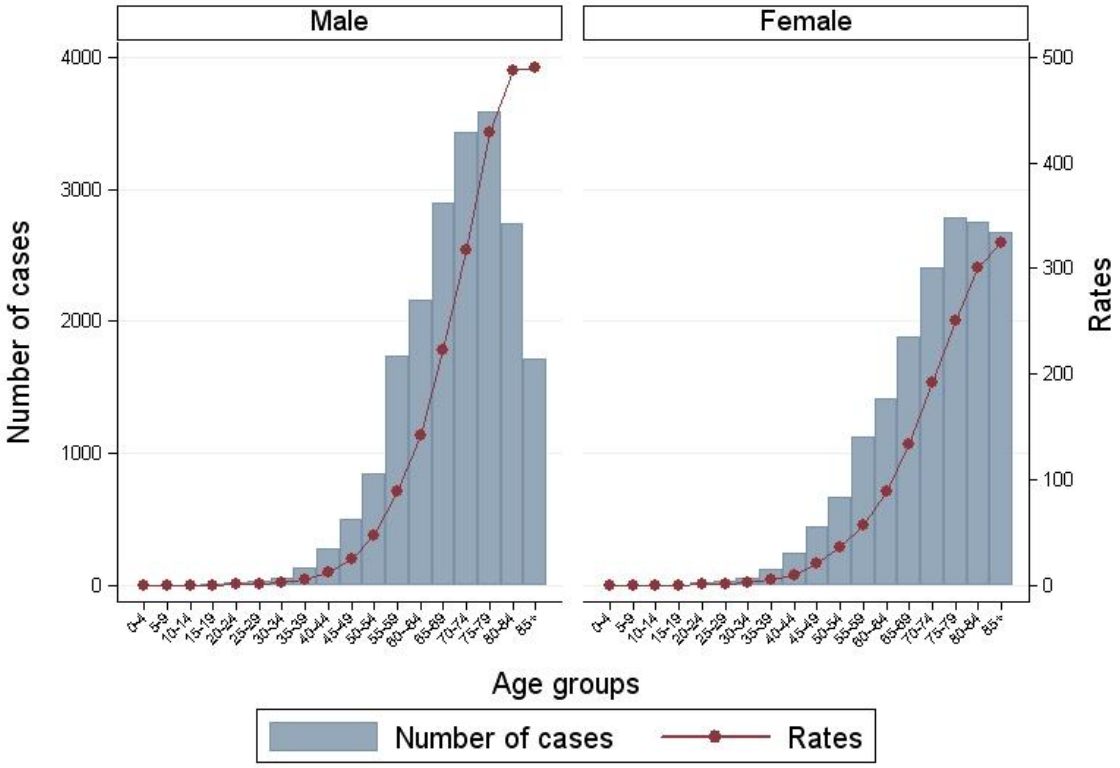

* adapted from the Cancer Research UK Cancerstats webpage

Breast cancer is one of the four cancers covered by the NHS cancer screening programmes, and was the first cancer site covered by an organised population-wide call and recall screening programme. The NHS Breast Screening Programme (NHSBSP) was established in 1988 to screen asymptomatic women aged betwen 50-64 and extended in 2004 to women aged up to 70, and is currently being extended again to include women aged 47-49. Eligible women are currently invited to attend mammographic screening every 3 years; and those aged over 70 may request screening exams. Incidence of breast cancer is correspondingly highest between the ages covered by the NHSBSP (Figure 1.2), and widespread use of mammography screening has resulted in increasing numbers of younger patients and women diagnosed with smaller tumours. The majority of tumours are diagnosed in women aged 50 and over, but breast cancer does occur in younger women. Historical trends show that breast cancer incidence is increasing in the UK and globally; since 1990 there has been an overall increase in incidence of about 0.5% per year above the increase explained by the national screening programme (9).

### 1.3.2 Colorectal cancer

Colorectal cancer is the third most commonly diagnosed cancer in the UK population, with over 36000 new cases diagnosed annually (10). Colorectal cancer affects more men than women, and is predominately diagnosed in older people; 83% of cases occur in people who are 60 years or older (Figure 1.3) (4). The left side of the bowel is affected by cancer more often than the right; tumours in the sigmoid colon, rectosigmoid junction and the rectum account for over half of all cases of colorectal cancer (4).

**Figure 1.3: Numbers of new cases and age-specific incidence rates, by sex, colorectal cancer, UK 2005 (5)***



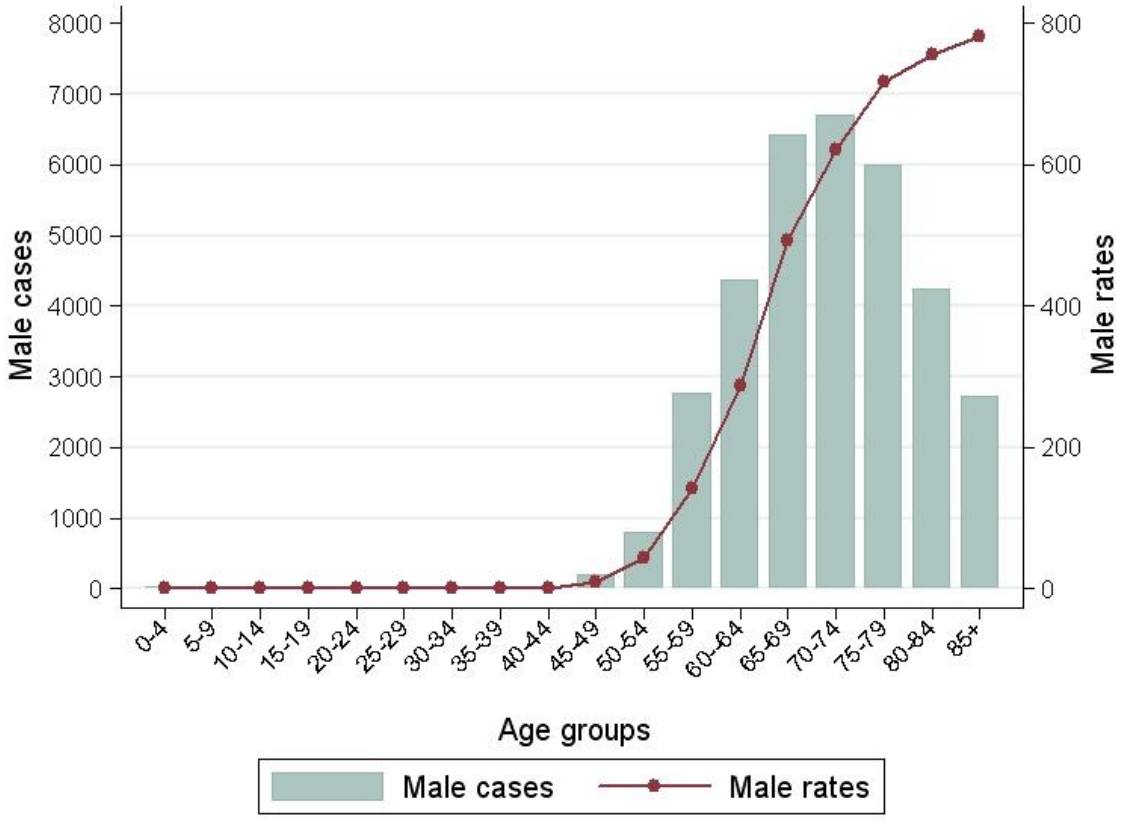

* adapted from the Cancer Research UK Cancerstats webpage

Colorectal cancer was added to the NHS national cancer screening programme in April 2006. The NHS Bowel Cancer Screening Programme (NHSBCSP) operates through programme hubs responsible for sending postal faecal occult blood (FOB) test kits, receiving samples and conducting FOB testing. Men and women aged 60-69 are eligible for screening every two years. Those aged above 70 can request entry into screening, although by 2014 individuals between 70-74 will also be included in routine screening invitations (10). Adoption of colorectal cancer screening is likely to increase the incidence of colorectal cancer in the next decade, with more early and asymptomatic tumours diagnosed in the screening age range.

## 1.3.3 Prostate cancer

Prostate cancer is the most common cancer diagnosed in men in the UK, with over 34000 new cases in 2005 (4). There has been a marked rise in the incidence of prostate cancer in the last decades due to an increase in the uptake of prostate-specific antigen (PSA) testing for prostate cancer screening. This increase has not been associated with an increase in mortality rates. The majority of new cases are diagnosed in men over the age of 50 (Figure 1.4).

**Figure 1.4: Numbers of new cases and age specific incidence rates, prostate cancer, UK 2005 (5)***




* adapted from the Cancer Research UK Cancerstats webpage

Prostate cancer screening is not offered on a population-wide basis in the UK, however, the NHS introduced the Prostate Cancer Risk Management Programme (PCRMP) in 2002.

The PCRMP is an informed choice programme available to men aged between 40-75 in England, which allows men to request PSA testing from their GPs (11).

### 1.3.4 Risk factors for breast, colorectal and prostate cancer

The incidence rates of these three common cancers are mediated by individual risk factors. These include personal characteristics such as age, sex, weight and family history, behaviours such as smoking and alcohol use, and drug factors. Some of the common risk factors for breast, colorectal and prostate cancer are discussed below.

**Breast cancer**

There are several reproductive risk factors associated with risk of developing breast cancer. Early age at menarche has been consistently associated with an increased risk of breast cancer, and has been shown to have an effect on premenopausal breast cancer risk, with a decrease in risk with increasing age of 7% per year (12;13). Parity is also strongly linked with breast cancer risk (12;13). The higher the number of full-term pregnancies, the greater the protection, with a reduction in risk of 7% for each birth after the first. Late menopause increases the risk of breast cancer. There is an approximate 3% increase in breast cancer risk for each year menopause is delayed. Postmenopausal women have a lower risk of breast cancer compared to premenopausal women of the same age (13).

Recent clinical trial and observational data have shown that menopausal hormonal therapy, including combined oestrogen plus progestagen, increases the risk of breast cancer. Risk increases with duration of use, however, risk decreases once women stop hormone replacement therapy (HRT) use as past users have a similar risk to never users (14;15).

A large pooled analysis of international data showed that women currently taking oral contraceptives were 24% more likely to have breast cancer, and women within 10 years of stopping use are at 16% increased risk of having breast cancer. However, there was no significant risk of breast cancer 10 or more years after stopping use of oral contraceptives (16).

Increasing intake of alcohol is associated with an increase in the risk of developing breast cancer, with an increase of 7% in the risk of developing breast cancer with the consumption of each additional 10g/l of alcohol (equivalent to two alcoholic drinks) per day (9).

A pooled analysis from seven prospective cohort studies shows that a high body mass index (BMI) moderately increases the risk of postmenopausal breast cancer (17). Women who had a BMI exceeding 31 $kg/m^2$ had a 26% increased risk of developing breast cancer compared with women with normal range BMI. The same study demonstrated that taller women also have an increased risk of breast cancer (17). However, the authors speculate that height may be a marker for other life course exposures, including childhood nutrition, genetic and environmental factors.

Breast cancer is one of the few cancers to have a higher incidence in the more affluent social classes. This is probably a reflection of other factors including better detection, reproductive history and early nutrition.

**Colorectal cancer**

In contrast to breast cancer, use of HRT is associated with a decreased risk of colorectal cancer in women. A meta-analysis of 18 studies showed that compared with women who had never taken hormonal therapy, post-menopausal women who had ever taken HRT had reduction of 20% in the risk of colon cancer and a 19% decrease in the risk of rectal cancer (18). Several studies have shown an inverse relationship between use of oral contraceptives and risk of colorectal cancer. A pooled analysis showed a combined reduction of 18% in the risk of colorectal cancer amongst women who had ever used an oral contraceptive. Current or recent use of oral contraceptives was associated with an even greater risk reduction of colorectal cancer amongst women (19).

In terms of other pharmacological interventions, long-term use of nonsteroidal anti-inflammatory (NSAIDs) is associated with a significantly lower risk of colorectal cancer in men and women (20;21). The benefit is related to dose; long-term and regular aspirin use of two tablets a day is associated with a 50% reduced risk of colorectal cancer (20).

There has been some evidence linking smoking to risk of colorectal cancer. A recent paper found a 16% increase between former smoking and colorectal cancer, however, there was no evidence for a significant relationship between current smoking and colorectal cancer (22). The authors suggest that further research is needed in this area. The International Agency for Research on Cancer (IARC) concluded that 'there is some evidence from prospective cohort studies and case–control studies that the risk of colorectal cancer is increased among tobacco smokers. However, it is not possible to conclude that the association between tobacco smoking and colorectal cancer is causal.'(23)

A pooled analysis of alcohol use showed that alcohol is also associated with an increased risk of colorectal cancer in both men and women. Compared with non-drinkers, those who consumed more than 45 g/d of alcohol had a 41% increased risk of colorectal cancer (24). While the studies of breast and colorectal cancer have found positive associations, research examining the effects of alcohol intake on prostate cancer is inconsistent.

Two recent meta-analyses demonstrated that obesity is an independent risk factor for colorectal cancer, but the association is greater in men. Risk for colorectal cancer was elevated by 41% amongst men who were obese compared with men of normal weight. Increasing BMI is not as high a risk factor for women; obese women had an 8% higher risk of developing colorectal cancer compared with women with normal range BMI (25;26).

One of the well-studied risk factors for colorectal cancer is diet, specifically, there is consistent evidence that diets with less red and processed meat and more vegetables, fish, milk and fibre are associated with reduced risk of colorectal cancer (27).

Type II diabetes has been associated with an increased risk of colorectal cancer in many studies. A meta-analysis of 15 studies found that compared with no history of diabetes, diabetes was associated with a 30% increased risk of colorectal cancer (28). This may be an underestimate of the true effect as many of the studies in the review did not distinguish between type I and type II diabetes, and type I diabetes may not be related to colorectal cancer (29).

Increased colorectal cancer risk is associated with a history of inflammatory bowel disease (IBD). A population-based study demonstrated that incidence of colon cancer in was more than doubled in patients with Crohn's disease or ulcerative colitis (30). The same study showed an increased risk of rectal cancer only amongst patients with ulcerative colitis. The association between ulcerative colitis and risk of colorectal cancer is supported by a meta-analysis of 116 studies (31).

**Prostate cancer**

After age, the second strongest risk factor is family history, and it is estimated that 5-10% of all prostate cancer cases are familial. Incidence rates suggest that ethnicity is linked with risk of prostate cancer; men of African or Caribbean background have a 2 to 3 times the risk of developing or dying from prostate cancer than white men (32). However, it is unclear what is driving these higher incidence rates; the increased risk may be due to access to health care, differences in nutrition and diet, uptake of screening or genetic differences.

Similarly to colorectal cancer, use of NSAIDs may also decrease the risk of prostate cancer; a recent meta-analysis of 12 studies showed a 10% in risk of developing prostate cancer associated with use of aspirin (33).

Work looking at the link between smoking and prostate cancer risk is conflicting, the international consensus is that there is no evidence for a link between prostate cancer and smoking (23;32).

Most studies have found no significant association between alcohol intake and risk of prostate cancer (32). One meta-analysis found a 19% increased risk of prostate cancer associated with a daily intake of the highest level of alcohol intake (100 g/d) compared with never drinkers (34). A second meta-analysis found that overall, ever alcohol consumption and prostate cancer were not associated (35).

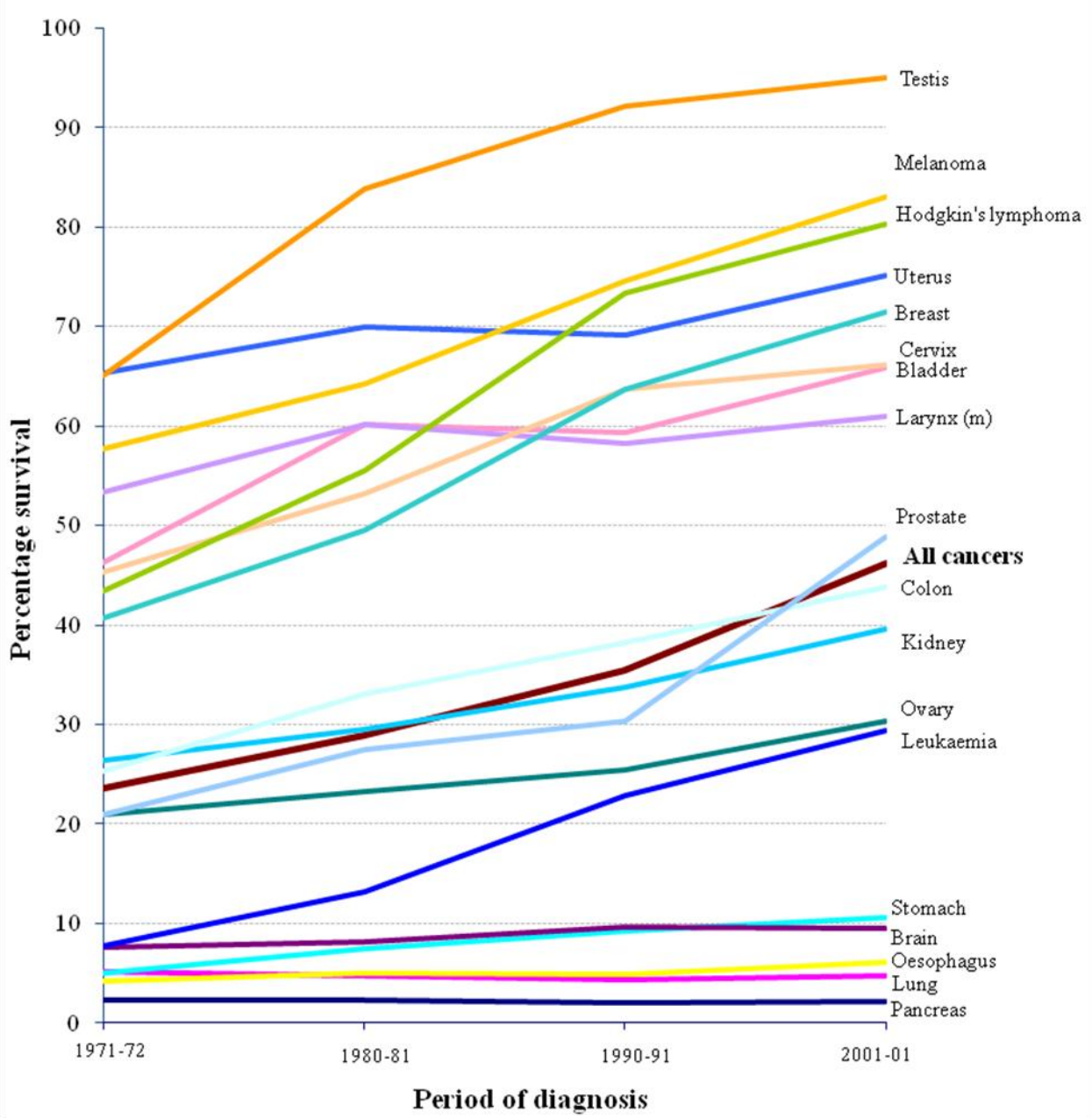
A recent meta-analysis suggests that increasing BMI is associated with small increased risk of prostate cancer. There is a wide literature looking at fat intake and risk of prostate cancer, however, the results are mixed.

Several large epidemiological studies have shown a link between family history and risk of developing prostate cancer. Risk of prostate cancer is positively associated with an increase in the number of relatives with prostate cancer (32).

## 1.4 Historical cancer survival trends

Recent statistics indicate that cancer survivors are living for longer; in the UK, five and ten year survival for most cancers has increased steadily since the 1970s. Survival for some cancers is very high, currently 95% of men diagnosed with testicular cancer will live for at least ten years post-diagnosis (Figure 1.5). However, survival rates for other cancers, including lung, stomach, brain, pancreatic and oesophageal, have remained low for the past 30 years. As the five-year survival rates for all cancers combined have reached 50%, the long-term consequences of living past a cancer diagnosis are becoming more relevant.

**Figure 1.5: Ten year relative survival of adults aged 15-99 years diagnosed with cancer from 1970s onwards (7)**




## 1.4.1 Breast cancer

The estimated five-year survival for women diagnosed with breast cancer in England and Wales has been increasing steadily to 80% in 2001-2003, an average increase of 6.2% for

every 5 years since 1986 (36). Breast cancer survival has improved largely due to early detection through the NHSBCSP and more successful treatments (37).

### 1.4.2 Colon and rectal cancer

Colon cancer is the second most frequently diagnosed cancer in women and third in men. Relative 10-year survival in men and women has increased considerably since the 1980s; five year survival for men rose from 39% in 1986-1990 to 50% in 2001-2006, indicating a 5.6% improvement every five years. Female survival trends follow a very similar pattern (38). Rectal cancer is the fifth most frequent cancer in men and women, and when combined with colon cancer is the third most common malignancy after lung and breast cancer. The introduction of bowel cancer screening across England and Wales is predicted to increase the detection of early stage colon and rectal cancer.

### 1.4.3 Prostate cancer

The increase in detection of prostate cancer associated with PSA testing has not only driven up incidence rates for prostate cancer, but also survival rates through earlier diagnosis of prostate cancer and identification of tumours which may have remained latent in the individual's lifetime (39). The five-year relative survival rate for men has increased rapidly at a rate of almost 16% every five years from 1986-1999. Current estimates from 2001 indicate that survival rates are still improving, but at a less rapid pace (40).

## 1.5 Defining the concept of cancer survivorship

### 1.5.1 Initial descriptions and definitions

The phases of cancer, and the concept of 'survivorship', were first articulated as 'stages of survival' by Fitzhugh Mullans, an American physician diagnosed with cancer in the 1980s

(41), who believed that the simple concept of cure did not capture the long-term experience of cancer. Mullans described the first, or acute, phase of survival in cancer as the time of diagnosis and treatment, which was followed by a phase of extended survival, or remission. Permanent survival, or 'cure', was the last and final stage, when patients can be described as 'survivors'. Survivorship was described by Mullans as an independent phenomenon, with cancer survivors experiencing distinct problems as they moved into the permanent survival stage.

### 1.5.2 Current definitions of cancer survivorship

The original conception of cancer survivorship from Fitzhugh Mullans has been widely interpreted and continues to be an area of some discussion and debate. Two main organizations in the United States use varying descriptions. The Lance Armstrong Foundation, which funds cancer survivorship research and outreach, defines survivorship as 'beginning at diagnosis, the moment your battle with cancer begins. A survivorship experience includes physical, psychological and social as well as practical aspects. Cancer survivorship describes the many experiences and emotions that are part of living life as a cancer survivor'(42). The Office of Cancer Survivorship, which primarily funds cancer survivorship research in the United States, includes families in the definition, stating that 'An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. Family members, friends, and caregivers are also impacted by the survivorship experience and are therefore included in this definition'(43).

Researchers in the United States have developed dynamic paradigms to highlight the multifaceted nature of cancer survivorship. The area of survivorship research is described as one that seeks to identify and control adverse sequelae of cancer and its treatment,

involves management of comorbid conditions, optimization of health through health and lifestyle interventions, defines optimal follow-up and surveillance, explores disparities in survivorship outcomes and explores the impact on the family (44;45). This paradigm shifts the focus of cancer survivorship from solely related to acute physical health following cancer diagnosis to a long-term disease model covering physical, social and psychological health.

### 1.5.3 Development of the UK National Cancer Survivorship Agenda

Although survival for many cancers has improved over time, successive results from the EUROCARE studies have showed that the UK fares poorly when considering survival from many cancers in comparison with other European countries (46). Age-standardized one and five-year survival rates for breast, colorectal and prostate cancer for the UK lag behind the Nordic countries, France, Germany, Spain and Italy (47). The NHS Cancer Plan was published in 2000, in part as a reaction to the poor UK survival rates highlighted in the EUROCARE studies, and provided a 10 year strategy to improve cancer diagnosis, treatment and prevention in England (48). A recent study showed evidence for an acceleration in survival in England from 2001 to 2007, indicating that the Cancer Plan may have had an early and beneficial effect (49). The NHS Cancer Plan was followed by the Cancer Reform Strategy in 2007, which set out targets for the provision of cancer-specific health care for a five year period. The Cancer Reform Strategy included a section on people living with and beyond cancer, and described in detail their unique health care needs. The document also described the development of the National Cancer Survivorship Initiative (NCSI) in partnership with Macmillan Cancer Support and other cancer charities (50). The remit of the NCSI is to 'improve the quality of life and experience of care of

cancer survivors as well as securing the sustainability and efficiency of health care services'.

In the UK, the NCSI has provided the impetus for acknowledging that cancer survivors are a unique and growing group with specific supportive and service needs which need to be addressed. The NCSI Vision document, outlining the first year of the Initiative, has acknowledged that there are different definitions of cancer survivorship, and broadly defines survivorship as 'encompassing those who are undergoing primary treatment, those who are in remission following treatment, those who are cured and those with active or advanced disease' (51). This definition includes those living with cancer and those who have moved beyond the acute stage of the disease.

### 1.5.4 Long-term cancer survivors

The above definitions include patients who may only survive for a short time following a cancer diagnosis. The scope of this thesis is to examine the use of primary care services by cancer survivors. As most short term cancer survivors are likely under the care of their hospital consultant, my focus will be on long-term cancer survivors. These are defined as cancer survivors who are five or more years past diagnosis, and are in the stage of 'permanent survival' described by Mullans (45). In the UK, the majority of cancer survivors are discharged from hospital follow-up to the care of their GP five years post-diagnosis. These long-term cancer survivors, who are alive at least five years past their initial cancer diagnosis, are therefore likely to receive the majority of their health care in a primary care setting.

### 1.5.5 The role of primary care in the care of cancer survivors

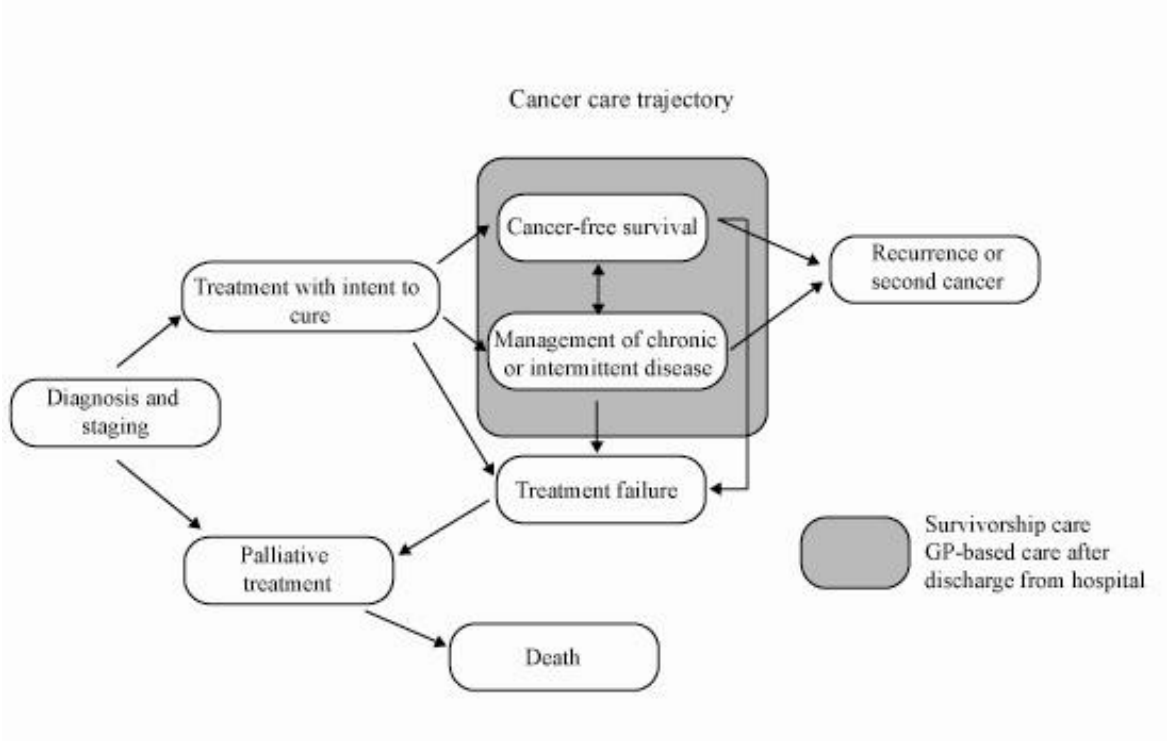
Traditionally, following initial diagnosis and treatment of cancer, services for cancer patients consist of hospital-based outpatient follow up systems to monitor individuals for recurrence or metastatic disease. In health care systems with a strong primary health care base such as the UK, alternative models of cancer follow up involving primary care have been explored. For instance, a UK-based randomized trial of follow up care of breast cancer patients receiving follow-up in primary care compared to breast cancer patients receiving follow-up in hospital demonstrated no increase in time to diagnosis of cancer recurrence or increase in anxiety (52), and patient satisfaction was improved (53). Because primary care based follow up has been shown to be effective, the current trend is moving towards earlier discharge of some cancer patients to primary care. These hospital discharge policies mean that cancer patients in the UK will typically be discharged back to the care of their GP 3-5 years post-diagnosis, and will not see a hospital based consultant on a regularly scheduled basis after five years. Therefore, primary care will be the point of first contact for long-term cancer survivors seeking medical care.

The role of primary care lies in the 'long-term survivorship' phase of care following discharge from hospital follow-up, when cancer survivors need to manage physical, psychosocial and information needs as well as comorbid conditions and late-effects of their cancer treatment (54). Long-term survivors are likely to access primary and community care services for care of chronic conditions as well as health promotion and disease prevention services (55). The challenge of managing survivors' diverse health care needs after treatment will lie with GPs and community nurses who are well positioned and qualified to manage this ever-growing population (56;57).

### 1.5.6 Health care needs specific to long-term cancer survivors

As many as one in every six adults over the age of 65 years in each British primary care practice is a cancer survivor (57). As the number of long-term cancer survivors increases, primary care practitioners need a greater awareness of the specific health needs of this population. Half of cancer survivors have unmet needs relating to ongoing health conditions, including depression, fear of recurrence, secondary effects from the disease and its treatment, and also lack the resources to deal with their emotional needs (58). Specifically, cancer survivors are at increased risk of ill health due to a number of factors, including second cancers due to shared risk factors, and late effects and other comorbidities related to treatment (59-61). The cancer and comprehensive care needs of cancer survivors in the UK lie in the long-term survivorship phase, and in the UK, primary care is responsible for providing this care. The cancer care trajectory, and the role of primary care following treatment in providing management of chronic diseases and monitoring the early signs of cancer recurrence, is shown in Figure 1.6 (57).

**Figure 1.6: Cancer care trajectory and aspects of primary care based survivorship care***




*Adapted from 'From Cancer Patient to Cancer Survivor'(62)

Primary care is well placed to provide care for long-term cancer survivors; GPs have an existing relationship with patients, GPs are directly accessible to patients, and patients can easily be referred back to secondary care cancer consultants when required (63). Prior to starting this thesis, I conducted a systematic review of the literature looking at how long-term survivors of cancer use primary care services. The main finding of the review was that there was very little research, especially outside of the United States, relating to the care of long-term cancer survivors (64).

## 1.6 Aims and objectives of this thesis

In order to address the previous lack of research in this area highlighted by the systematic review, the main aims of this thesis are to examine how survivors of breast, colorectal and prostate cancer use primary care services and to explore their unmet needs for health care in the United Kingdom (64). The focus is on primary care services received by long-term cancer survivors who are alive at least five years post cancer diagnosis.

In order to meet these aims, the principal objectives are threefold:

1. To study the use and quality of primary care services in long-term survivors of each cancer. The following outcomes will be considered:
    a. Primary care consultation rates, patterns and behaviours
    b. Uptake of preventive health services, including cancer screening
    c. Management and monitoring of chronic diseases
    d. Prescribing patterns for relevant drugs

2. To study the risks associated with being a cancer survivor in long-term survivors of each cancer. The following outcomes will be considered:
    a. Incidence of new diagnoses which may be related to cancer treatment
    b. Risk of second cancers
    c. Mortality

3. To investigate the views of long-term cancer survivors on their unmet needs and how these needs might be addressed. This involves:

a. Follow-up the quantitative analysis, and investigate how the results from the quantitative analysis compares with individual patient experiences
b. Explore patient experiences that cannot be described in a quantitative database analysis

I will meet the first and second objectives through three cohort studies of breast, colorectal and prostate cancer survivors registered in a national primary care database. The specific outcomes will be compared between cancer survivors and matched controls. The control population comprises patients without a diagnosis of breast, colorectal or prostate cancer matched to each cancer survivor on the basis of age, sex and general practice. The third objective will be met through a qualitative interview study of 40 long-term survivors of breast, colorectal and prostate cancer at least five years from diagnosis but at different stages of survival.

This research will provide a background to further research in this area with a view to improving the provision of primary care services to long-term survivors of adult cancers in the UK. The three cancers have been selected because they are three of the most common cancers in the United Kingdom with the highest rates of survival and therefore represent a significant proportion of all long-term survivors in primary care. By describing the use of primary care services for each cancer site, I illustrate the issues individual to each cancer to guide provision of services to survivors of each cancer site. Finding overlapping themes for these three cancers will also provide information to guide clinical decision making for cancer survivors in general.

### 1.6.1 Structure of this thesis

The structure of the thesis overlaps the main objectives presented in the previous section. Chapter 2 describes the methods in analysis of the General Practice Research Database (GPRD) to achieve objectives 2 and 3, along with a discussion of the quality of data in the database. Chapter 3 focuses on the use and quality of primary care services amongst a cohort of survivors of breast, colorectal and prostate cancer, while Chapter 4 investigates the risk of long-term effects of cancer and its treatment, second cancers, and all-cause and cause-specific mortality. Moving on from the GPRD analysis, Chapter 5 describes an in-depth qualitative study of cancer survivors' use of primary care services and unmet needs. The thesis ends with a broad discussion of the findings, strengths and limitations, future avenues for research and implications for primary care and policy makers.

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# Chapter 2: A description of the data sources used for the analyses

## 2.1 Introduction

To achieve the first two objectives of this thesis, I used the UK-based General Practice Research Database (GPRD), currently the world's largest anonymised database of primary care records (1). Practices participating in the GPRD record data on clinical diagnoses, test results, prescriptions and referral data on individual patients seen in primary care. This chapter describes in detail the characteristics of the GPRD, quality of diagnostic coding in the database, general methods of the analysis and the development of a comorbidity score applicable for use in the GPRD for the purposes of this thesis.

## 2.2 Use of the General Practice Research Database

This thesis uses data from the UK-based General Practice Research Database (GPRD) to investigate use of primary care services by a cohort of long-term survivors of cancer. As of April 2010, there were 545 practices contributing data to the GPRD, representing data from 4.56 million patients, or 7.4% of the UK population. Practices were originally recruited into the previous version of GPRD (the Value Added Medical Products, or VAMP) on a voluntary basis with the aim of enlisting a representative sample of UK based primary care practices. It is possible for practices to join the GPRD through an application procedure on the GPRD website, and the number of practices in the GPRD is growing annually. Practices are responsible for ensuring that their staff are trained and familiar with the GPRD recording guidelines, which describe how to record diagnoses and referrals onto the patient electronic medical record. Practices are nominally reimbursed at a level of 10 pence per patient per year.

There are several software packages currently in use in British primary care, including the Egton Medical Information System (EMIS), which is the largest supplier in the UK, and Vision. Currently, the GPRD is limited to practices using Vision software, while the QResearch database managed by the University of Nottingham covers a sample of practices using EMIS software. Data collection software for practices involved in the GPRD is incorporated into the Vision system and automatically extracts data from practice computers. These data are routinely uploaded, typically every two weeks, into the GPRD main data warehouse through a secure email. All clinical encounters recorded by each participating practice are potentially available in the GPRD. Historical patient data are also uploaded when each practice joins the GPRD. Patient diagnoses and symptoms are recorded in the patient electronic medical record (EMR) using Read codes, or historically OXMIS codes, two widely used systems based on the International Classification of Diseases (ICD). Although free text entered by practice staff are also uploaded into the GPRD data warehouse, these data are not freely available; GPRD staff must remove all identifiable terms from the free text data (at a cost) before it can be released. Each patient is assigned a unique patient identifier which maintains this anonymity (2).

Historically, the GPRD has been used for studies of pharmacological safety, and as such, has been widely accessed by the pharmaceutical industry and the Medicines and Healthcare Regulatory Authority (MHRA). Recognizing the potential for epidemiological research, a five year Medical Research Council (MRC) scheme to allow free access to GPRD datasets for academic purposes was announced in 2005. The MRC scheme provided academic research groups with free access to GPRD datasets, typically up to 100,000 patients. In 2006, an application to access a GPRD dataset to look at use of primary care services by long-term survivors of cancer was submitted.

### 2.2.1 Dataset specification

Following approval by the GPRD custodians, a dataset containing longitudinal primary care data on a cohort of cancer survivors and a matched control population was provided. A practice-based quality marker, the up-to-standard date (UTS date), is generated for each practice in the GPRD, indicating when data recording by the practice complied with specific quality measures in key areas of data recording. This standard was used to select practices for inclusion to the study (2). The cancer survivors population consisted of all eligible patients in GPRD in up-to-standard practices with a diagnosis of breast, colorectal or prostate cancer as defined by a Read/OXMIS medical diagnosis code. The following criteria were applied to identify the cancer survivors population:

a) Patients with a first ever diagnosis of breast, colorectal or prostate cancer in their electronic medical record from registration to 30 June 2001.
b) Patients with a minimum age of 30 years at the time of cancer diagnosis
c) Breast cancer survivors were restricted to female cases only
d) Patients had to have at least 5 years of survival following their index date of diagnosis with one or more days of UTS follow-up between 1 July 2001 and 31 August 2006.

The control population was randomly selected from the population of GPRD patients based on the following criteria:

a) Patients without a diagnosis of breast, colorectal or prostate cancer ever recorded on the database
b) Controls were matched to each cancer survivor on a 1 to 4 ratio, on the basis of:
    - Age. The control needed to be the same age as the matched exposed.

- Primary care practice. The controls needed to be from the same practice as the cancer survivor.
- Sex. The controls were the same sex as the cancer survivor to which they were matched.

### 2.2.2 Description of dataset

The total dataset contained longitudinal primary care data on 145662 patients, comprising 29244 cancer survivors and 116418 controls. A breakdown of numbers by cancer type and sex is given below in Table 2.1:

**Table 2.1: Cancer survivors and controls population in the GPRD dataset**

| | **Breast** | | **Colorectal** | | **Prostate** | | **Total** |
|---|---|---|---|---|---|---|---|
| | Survivor | Control | Survivor | Control | Survivor | Control | |
| Male | - | - | 2912 | 11515 | 4868 | 19288 | 38583 |
| Female | 18612 | 74284 | 2852 | 11331 | - | - | 107079 |
| **Total** | **18612** | **74284** | **5764** | **22846** | **4868** | **19288** | **145662** |

Mirroring trends in cancer incidence, prevalence and survival, the breast cancer survivors comprised the largest group of cancer survivors in the dataset. There were roughly equal numbers of male and female colorectal cancer survivors. Prostate cancer survivors comprised the smallest group of cancer survivors in this cohort.

There were 410 primary care practices contributing data to the GPRD at the time this dataset was provided. Although the precise location of each practice is anonymised, the GPRD provides information on practice region (Table 2.2).

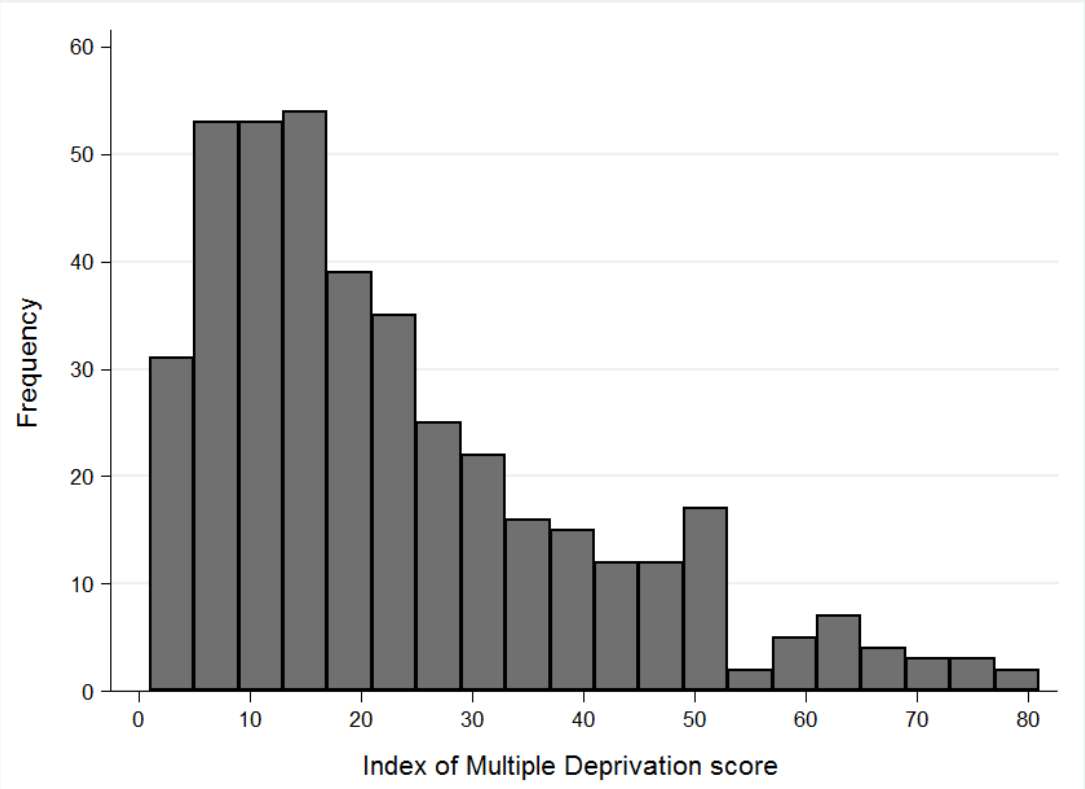
**Table 2.2: Regional spread of the 410 practices included in the GPRD**

| Region (by Strategic Health Authority, 2006) | Number of practices | % |
|---|---|---|
| Eastern Regional Office | 37 | 9.0 |
| London Regional Office | 56 | 13.7 |
| Northern Ireland | 12 | 2.9 |
| Northwest Regional Office | 54 | 13.2 |
| Northern and Yorkshire | 27 | 6.6 |
| Scotland | 22 | 5.4 |
| South East Regional Office | 77 | 18.8 |
| South West Regional Office | 41 | 10.0 |
| Trent Regional Office | 24 | 5.9 |
| Wales | 23 | 5.6 |
| West Midlands Regional Office | 37 | 9.0 |
| **Total** | 410 | 100.0 |

The spread of practices within the GPRD does not reflect the UK population distribution, but does reflect an attempt to representatively include practices from all locations. Although the GPRD does not contain patient-level socioeconomic information to preserve anonymisation, researchers are given access to practice-level socioeconomic data in the form of the Index of Multiple Deprivation (IMD) score. The IMD score is a measure based on several different small area level factors, including income deprivation, employment deprivation, health deprivation, education deprivation, barriers to housing and services, living environment deprivation and crime (3). A distribution of the IMD scores

amongst the 410 practices in the GPRD dataset is shown in Figure 2.1; the higher IMD scores represent the more socially deprived practices. The majority of practices in the study fall in the more affluent IMD regions represented by a lower IMD score. Cancer survivors and controls were matched on the basis of primary care practice, therefore many of the analyses in this study involve comparisons amongst patients in the same practice within the same IMD region.

**Figure 2.1: Histogram of practice level IMD scores**




**Analysis window**

Due to increasing computerization of information in primary care, data quality in the GPRD is best in the most recent years. In order to ensure that the analyses in this thesis were conducted on the best quality data, I specified a three year analysis window from 1 September 2003 to 31 August 2006, which comprised the most recent available data.

Cancer survivors who were diagnosed before the start of the analysis window were followed up through the three year analysis window unless they died or transferred out of the practice. Restricting the dataset to this analysis period meant that some of the cancer survivors and controls in the original dataset provided by the GPRD were excluded, as cancer survivors and their controls may have died prior to the start of the follow-up period on 1 September 2003. The final patient population for any analyses using patients with follow-up data from 1 September onwards is shown in Table 2.3.

**Table 2.3: Patients in GPRD cohort with follow-up in the 2003 to 2006 follow up period**

| | **Breast** | | **Colorectal** | | **Prostate** | |
|---|---|---|---|---|---|---|
| | Survivor | Control | Survivor | Control | Survivor | Control |
| Male | - | - | 2569 | 10178 | 4207 | 16709 |
| Female | 16938 | 67649 | 2499 | 9950 | - | - |
| **Total** | **16938** | **67649** | **5068** | **20128** | **4207** | **16709** |

## 2.2.3 Data linkages

Although the GPRD contains relatively reliable quality data from clinical events in primary care (see Section 2.3, Quality of the data in the GPRD and validity of diagnostic coding), information on diagnoses and treatments conducted in secondary care is limited. Additionally, while it is possible to identify patient deaths from their primary care records, the GPRD does not contain information on cause of death. One of the major aims of this thesis was to undertake linkages between the primary care data in the GPRD and other

national datasets, including those held by the National Cancer Intelligence Network (NCIN) and Office for National Statistics (ONS). The purpose of linking to the NCIN was to gain more information on tumour specific variables and cancer treatment from regional cancer registries, and the ONS linkage was conducted to obtain data on cause of death. Approval to undertake these linkages was provided to the GPRD custodians within the course of this thesis. Data from the GPRD was linked to ONS and NCIN data on the basis of NHS number, sex, date of birth and post code by a trusted third party service which also undertakes data quality and linkage checks.

**National Cancer Intelligence Network**

The first GPRD-linked dataset that I accessed for the purposes of this thesis was the National Cancer Intelligence Unit (NCIN) dataset. The NCIN comprises of 11 cancer registries across the United Kingdom, which are detailed in Table 2.4. Data from the NCIN includes information on tumour site, staging, and limited data on treatment modality (radiotherapy, chemotherapy or surgery) within six months of diagnosis.

**Table 2.4: Cancer registries in the United Kingdom**

| Cancer registry | Geographical coverage | Approximate population coverage |
|---|---|---|
| Eastern Cancer Registry and Information Centre | Norfolk, Suffolk, Cambridgeshire, Essex, Bedfordshire and Hertfordshire | 5.5 million |
| Northern and Yorkshire Cancer Registration and Information Centre | Yorkshire and Northeast of England | 6.6 million |
| North West Cancer Intelligence Service | Cheshire, Greater Manchester, Lancashire, Merseyside and South Cumbria | 6.5 million |
| Oxford Cancer Intelligence Unit | Berkshire, Buckinghamshire, Northamptonshire and Oxfordshire | 2.7 million |
| South West Cancer Intelligence Service | Avon, Cornwall, Devon, Somerset, Gloucestershire, Dorset, Wiltshire and Isles of Scilly and Wight, Hampshire | 6.6 million |
| Thames Cancer Registry | London, Surrey, Sussex and Kent | 12 million |
| Trent Cancer Registry | South Yorkshire, Derbyshire, Nottinghamshire, Lincolnshire, Leicestershire and Rutland | 4.8 million |
| West Midlands Cancer Intelligence Unit | Shropshire, Staffordshire, Birmingham, Herefordshire, Warwickshire, Worcestershire | 5.3 million |
| Northern Ireland Cancer Registry | Northern Ireland | 1.7 million |
| Scottish Cancer Registry | Scotland | 5.1 million |
| Welsh Cancer Intelligence Unit | Wales | 2.9 million |

The amalgamation of hospital-based cancer registries into larger regional registries covering a wider geographical area is a relatively recent development. This has led to a varying level of quality of registration and variations in the amount of information captured at the time of cancer diagnosis. Historically, not all cancer registries have collected information on staging or treatment modality. As a result, the cancer treatment information provided here is incomplete.

**Office for National Statistics**

The second GPRD-linked dataset that I accessed for the purposes of this thesis was from the Office for National Statistics (ONS), which collects data on death registrations in England and Wales, but not from Scotland or Northern Ireland. Information from death certificates are sent to ONS, which compiles statistics on mortality and cause of death, which is not reliably recorded in GPRD patient medical records. For the purposes of this thesis, the ONS data was accessed primarily for information on underlying cause of death, which is defined as 'the disease or injury which initiated the train of morbid events leading directly to death' and coded using ICD-10 (International classification of diseases, 10$^{th}$ Revision) (4). The ONS data had a longer follow-up period than the GPRD follow-up because it was provided at a much later date; the last date of ONS follow up was 1 November 2009.

**Coverage of the linkage scheme**

In 2009, when the GPRD custodians received approval from national information protection authorities (the now defunct Patient Information Advisory Group, or PIAG) to link the database with outside databases such as the NCIN, a request was sent to each practice to gain practice-level consent for the linkage scheme. Not all practices responded,

and a small number of practices did not provide consent for participation. Currently, the GPRD linkage scheme, which encompasses the NCIN and ONS linkage, is limited to 207 of the 410 (50.4%) primary care practices in this GPRD cohort which have consented to external data linkages.

Practices contributing data to the linkage scheme may have slightly different characteristics than the practices that did not agree to linkage. I compared the patient and practice-level characteristics in the ONS linked data, such as age and IMD score to compare whether the patients and practice in the linked practices were different than those that were not linked. Patient level characteristics were comparable, however, the practices available in the GPRD-ONS linkage scheme tended to be slightly more affluent than the unlinked practices (Table 2.5).

Any ONS linked analyses (see Chapter 4, section 4.3.3 cause of death in cancer survivors) include data on 84720 patients from 207 contributing GPRD practices comprising 58.3% of the total patients from the original GPRD cohort. Although patients with linked GPRD-NCIN data have complete data on tumour site, not all patients have complete data on stage or modality of treatment (radiotherapy, chemotherapy or surgery).

**Table 2.5: Patients and practices in the ONS-GPRD linkage scheme compared to those in unlinked practices**

| | Patients and practices in the GPRD linkage scheme | | | | | | Unlinked patients and practices | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Breast | | Colorectal | | Prostate | | Breast | | Colorectal | | Prostate | |
| | Survivor | Control | Survivor | Survivor | Control | Survivor | Survivor | Control | Survivor | Control | Survivor | Control |
| Male | - | - | 1672 | 6609 | 2894 | 11460 | - | - | 1240 | 4906 | 1974 | 7828 |
| Female | 10798 | 43084 | 1651 | 6552 | - | - | 7814 | 31200 | 1201 | 4779 | - | - |
| *Mean age** | 67.6 | 67.6 | 75.2 | 75.0 | 77.0 | 76.8 | 67.8 | 67.8 | 75.4 | 75.2 | 76.8 | 76.9 |
| *Mean years from diagnosis** | | | | | | | | | | | | |
| Years | 10.4 | - | 10.5 | - | 6.1 | - | 10.5 | - | 10.8 | - | 6.4 | - |
| *Charlson comorbidity score>0* | | | | | | | | | | | | |
| n | 4922 | 18222 | 1939 | 6814 | 1889 | 6486 | 3672 | 13162 | 1479 | 5208 | 1300 | 4552 |
| % | 45.6% | 42.3% | 58.4% | 51.8% | 65.3% | 56.6% | 47.0% | 42.2% | 60.5% | 53.8% | 65.9% | 58.2% |

*Practice level Index of Multiple Deprivation (IMD) score ( lower score indicates a higher level of deprivation)*

| | Number of practices | % | Number of practices | % |
|---|---|---|---|---|
| 0† | 31 | 14.9 | 42 | 20.7 |
| 1 | 37 | 17.9 | 33 | 16.3 |
| 2 | 45 | 21.7 | 42 | 20.7 |
| 3 | 47 | 22.7 | 39 | 19.2 |
| 4 | 47 | 22.7 | 47 | 23.2 |
| **Total** | 207 | | 203 | |

## 2.3 Quality of data in the GPRD and validity of diagnostic coding

### 2.3.1 Introduction

One of the main benefits in using automated databases such as the GPRD lies in the ability to access data pertaining to large patient populations across a wide population coverage. Whilst these datasets represent a valuable tool for conducting research, it is important to remember that the data are collected primarily for clinical and routine use, therefore, it was essential to consider the data quality and reliability in the GPRD for the purposes of this thesis.

Each practice contributing data to the GPRD is issued with a set of GPRD Recording Guidelines describing how to record all significant morbidity events in the patient's medical history and consultation events (5). The raw data provided from each practice undergoes extensive 'up-to standard' quality control and validity checks by a research team based at the MHRA before release. Patient-level data are also assessed, with patients considered 'acceptable' for inclusion in the GPRD if recorded details are internally consistent in four areas: age, sex, registration details and event recording (6).

While the global checks conducted by the GPRD team provide an overall evaluation of which practices are providing good quality data meeting certain standards, they do not specifically assess the validity and completeness of individual patient records. Quality of data in disease registers can be assessed by considering two issues. Firstly, is the data accurate; do the codes on the register represent the diagnosis under question, and secondly, is the data complete; in other words, what proportion of all true cases are recorded on the database (7).

In order to assess the quality of the data in the GPRD, I conducted a systematic review of the literature to present a description of the accuracy and completeness of recording in the GPRD. Specifically, I considered both the recording of clinical diagnoses and comparisons between the GPRD and other databases or national statistics. This set of work was written up as a paper and published in the British Journal of General Practice (8). Please see Appendix 1 for a copy of the published paper.

### 2.3.2 Methods

**Literature search**

I searched six electronic databases (MEDLINE, EMBASE, BNI, PsycInfo, HMIC, SSCI) from inception to May 2009, using search terms relating to the GPRD in association with terms synonymous with validity, accuracy, concordance and recording. The full search strategy is provided in the published paper (Appendix 1) (8). With the assistance of a second reviewer (Sian Harrison, or SH) we screened titles and abstracts of all papers in the initial search and excluded citations which did not meet the inclusion criteria. Disagreements at this stage were resolved through discussion, however the full-text paper was ordered when either myself or SH was uncertain about inclusion. I independently assessed the retrieved full-text papers for relevance and inclusion, and hand-searched reference lists of all retrieved papers. Additionally, I also conducted a hand search of the GPRD bibliography provided on the GPRD website (http://www.gprd.com/bibliography) and included any potentially relevant papers in the review process.

**Inclusion criteria**

I included studies with a primary aim of considering the accuracy of recording of data in the GPRD, and studies that looked at accuracy of recording of data as part of a larger study.

Papers written in English and non-English languages were considered for inclusion. Papers which did not look specifically at the GPRD, those which were not original research and papers which did not conduct validation or comparison of information held on the GPRD were excluded, as well as database comparison studies if the study compared prevalence rates over different time periods. Along with SH, I reviewed articles meeting the inclusion criteria and abstracted relevant data on to a standardised data extraction form. A third reviewer (PWR) resolved any uncertainties on the main outcomes.

**Assessment of accuracy and completeness of data**

Consideration of the accuracy of diagnoses was achieved by within papers comparing the GPRD coded data in the electronic patient record against a gold standard. Assessing the completeness of data was achieved by comparing disease prevalence and prescription rates between the GPRD and other national datasets and determining the level of underreporting or over reporting in the GPRD. The results presented in this thesis will only discuss those papers with results relevant to this work. Full results including all papers in this review are reported in the full paper (8).

**Statistical analysis**

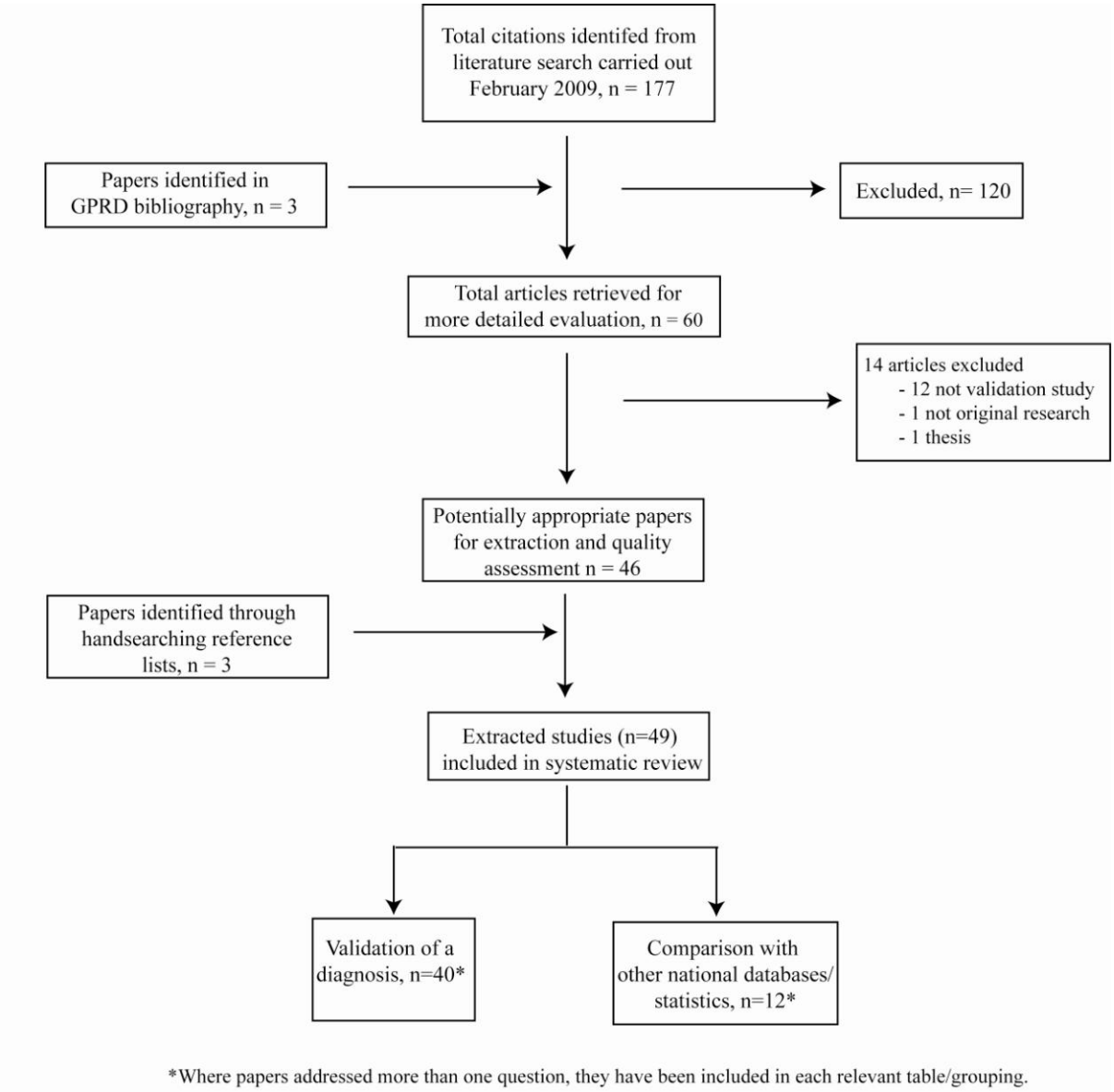
I defined the positive predictive value (PPV) as the proportion of GPRD coded diagnoses validated as true cases against a gold standard (GP questionnaire, medical records or hospital letters). Where the investigators used a GP questionnaire or request for hospital notes, I calculated the percentage validated using the returned questionnaires as the denominator along with binomial exact 95% confidence intervals for each PPV.

## 2.3.3 Results

### Literature search

In total, 47 papers were identified through the literature search and included in this review. I identified three additional papers through hand-searching the reference lists of the final 46 papers (9-11). Therefore, a total of 50 papers entered the review (see Figure 2.2), but only those results relating to this thesis are reported in detail this chapter. The results are presented in these two main groupings: validation of clinical diagnoses and comparisons between GPRD and other national statistics or databases.

**Figure 2.2: Flowchart of search results**




## Papers validating a diagnosis or patient characteristic

A total of 41 papers conducted validation of a diagnosis or patient characteristic coded in the GPRD database. Most of these validation exercises involved sending a questionnaire to the patient's GP (n=20) and conducting independent verification of a diagnosis against hospital letters or medical records in practice (n=16). Some studies involved both sending a GP questionnaire and conducting verification against medical records (n=5).

The majority of the papers report PPVs over 50%, and simply required the patient's GP to confirm the diagnosis on the GPRD database. Of particular relevance to this thesis, only one paper considered the validity of coding for cancer diagnoses. In 1997, Jick et al conducted a study looking at the risk of cancer associated with use of calcium blockers. In their study, the investigators sent out 464 questionnaires to confirm the diagnosis of cancer and 316 (68%) were returned. 15 (5%) were excluded because the cancer was not confirmed. Therefore, the PPV for a cancer diagnosis was 95% (12).

Two studies assessed the completeness of GP recording of diagnoses made by hospital consultants. In these studies, the diagnosis was transcribed from the hospital discharge letter onto the patients electronic medical file in a high proportion (~90%) of cases (13;14).

One paper considered the recording of smoking status in the GPRD (15). Although current smoking is generally well recorded, former smoking is not as well recorded.

Three papers reported results relating to accuracy of the date of diagnoses. There were discrepancies in date recording in 45/95(47%) of dementia cases (16). The differences were generally small, with an interquartile range (IQR) from -7 to 0 weeks. In a study of the validity of inflammatory bowel disease (IBD) recording, the median difference in the first date reported by the GP and the first IBD diagnosis in the electronic record was -8 days (IQR 0 to -81 days). However, for 33 of the 53 patients included in the study, the first recorded diagnosis of IBD in the electronic record was within 30 days of the date reported by the GP (17). The recording of date of acute myocardial infarction (MI) was also generally reliable; only 31/201 (15%) of confirmed cases had a GP-reported date that was inconsistent with the

electronic record. The differences in dates were generally small; 28/31 (90%) of the GP-reported dates were within 15 days of the date in the electronic record (18).

**GPRD compared with other databases or statistics**

Twelve papers compared GPRD database prevalence or consultation rates with other primary care databases or national statistics registers. All compared the GPRD with UK data except for one comparison with a US-based database (19).

Three papers compared GPRD consultation or prevalence rates against the Morbidity Statistics from General Practice 1991-92 (MSGP4), a UK-wide survey of consultation patterns in primary care (20-22). There was good agreement between the GPRD and MSGP4 for eleven common respiratory conditions. However, consultation rates and prevalence of diabetes and musculoskeletal conditions were underestimated in the GPRD compared with MSGP4 (21;22).

Three studies compared the GPRD with the Doctors Independent Network (DIN), a UK based primary care database which has been collecting routine data from over 300 practices distinct from the GPRD since 1989 (23-25). Generally, there was good agreement between the two databases. The six remaining papers compare the GPRD with a variety of other primary and secondary care databases. Three papers report similar rates of disease amongst the GPRD and other databases.

There were some differences between disease coding in the GPRD and other datasets. A comparison of the GPRD and the 1996 General Household Survey suggests that current smoking rates in the GPRD are 79% of the expected rate. The rates for ex-smokers were

substantially underestimated; the GPRD rate for ex-smoking was 29% of what was expected according to the General Household Survey (15).

### 2.3.4 Discussion

This review considered the accuracy and completeness of recording of diagnoses within the GPRD. Most of the diagnoses coded in the GPRD electronic record were well recorded when compared against GP questionnaire responses, medical records held at the GP practice or hospital letters.

Only three papers looked specifically at the differences between the date of onset of disease in the GPRD electronic medical record and the GP-reported date (16-18). Although there were some inconsistencies in date recording, the differences were small and are unlikely to affect the outcomes in this study.

Generally, there is good agreement in disease prevalence rates between the GPRD and other national databases and statistics; however, there were some differences identified in this review. There is no 'gold standard' measure against which data from one database can be compared, or to suggest which database contains the most accurate measure. Discrepancies between two data sources do not necessarily mean that one database is right and one is wrong. There may be geographical differences or disease coding system variability which will lead to systematic differences in disease prevalence or data recording (20). There are two reasons why the GPRD may be systematically different to other datasets. Firstly, not all consultations for chronic diseases need to be recorded in the GPRD; the GPRD recording guidelines state that the GP should make at least one entry in the medical history for each episode of illness or new occurrence of a symptom (5). The requirement to only record the

first instance of disease may partially explain why consultation rates and prevalence of diabetes and chronic musculoskeletal conditions were underestimated in the GPRD compared with other databases (21;22). Secondly, it is important to consider that practices supplying early years of data to the GPRD provided data using an older coding system called OXMIS.

Only one study considered the accuracy of recording of cancer diagnoses in the GPRD. The PPV was high at 95%, suggesting that for the purposes of this thesis I can be confident about the case validity of cancer survivors in the cohort. Additionally, this review suggests that for the purposes of this thesis, I can be confident about the identification of most chronic conditions and major hospital diagnoses within the GPRD. Prescription data are well recorded in the GPRD, because prescriptions for patients are generated directly from the computer and details on drug type and dosage are automatically recorded on computer. Therefore, prescribing data can be used to verify clinical diagnoses, or to capture additional cases. For instance, use of inhalers was used as a proxy for asthma diagnoses (20). However, it is important to be cautious in using drug prescribing as a proxy for disease and ensure that the prescribed drug is specific to the diagnosis of interest.

Smoking status is an important risk factor and potential confounder in any study of cancer survivors, and although current smoking may be recorded well enough for the purposes of epidemiological research, data on former smoking may need to be independently validated (15). The results of this systematic review meant that for the purposes of this thesis, I classified the patients in the cancer survivors cohort as ever or never smokers.

The results of this systematic review helped to develop my understanding of how diagnoses were recorded in the GPRD and assured that the results of the main analyses would be valid. The next section describes how I prepared data from the main GPRD dataset for analysis.

## 2.4 Methods in GPRD data assembly and analysis

This section describes the general methods used for data preparation for the GPRD analysis. A more detailed description of the methods used for each specific outcome will be described in Chapters 3 and 4.

### 2.4.1 Data preparation

**Identify event codes using GPRD dictionaries**

The first step in each analysis was to identify codes which defined the event of interest in the GPRD. The GPRD custodians provided two dictionaries, one for clinical events and one for prescriptions, which contain all potential event codes in the GPRD along with a search engine. For each event, I firstly conducted the initial dictionary searches to find potentially relevant codes which define each event. This initial list of codes was then sent to PWR, and who determined whether or not the codes corresponded to the event of interest. Different types of events are coded in within the GPRD in different ways. A detailed summary of how events are coded is provided below:

**Clinical events**

Clinical events are coded within the GPRD using Read/OXMIS codes. The GPRD custodians provided a medical dictionary which is searchable by text word to identify the relevant Read/OXMIS codes relating to each event. Read codes are hierarchical, so once the top level code for a clinical event was identified it was possible to compile the remaining

secondary codes corresponding to the event. Any additional OXMIS codes, which are not coded in a hierarchical format, were identified through Boolean searches. The search results were over-inclusive at this stage in order to capture as many potentially relevant codes as possible.

**Prescription events**

Prescription events are coded using British National Formulary (BNF) headings (26). The GPRD custodians provided a product dictionary containing information on all prescription drugs. This dictionary was used to identify the relevant drug codes as represented in the GPRD.

**Diagnostic test events**

The GPRD custodians provided a spreadsheet of all 305 test codes corresponding to test events (laboratory examinations, screening and diagnostic tests), which were searched to find tests and investigations relevant to each outcome.

### 2.4.2 Identifying events in the GPRD files using defined codes

There are several sources of information for events in the GPRD, and the data files were provided in the following categories:

**Patient file**

This file contained basic patient demographics, including year of birth, sex, and in addition, most recent smoking status, body mass index and practice registration details on all patients in the cohort.

**Clinical files**

These contain historical medical events, including all of the symptoms, signs and diagnoses entered on the patient's electronic medical record. The data is coded using a Read or OXMIS code. After PWR had checked the Read/OXMIS code list, I produced a final list of codes corresponding to the clinical event which was used to search through all of the clinical files to identify relevant events.

**Therapy files**

The therapy files contain data relating to all prescriptions for drugs and appliances issued by the practices. Again, once the list of drugs relating to the prescribing behaviour of interest had been checked by PWR, I produced a final list of codes corresponding to the prescription event which was used to search through all of the therapy files to identify relevant prescription events.

**Test files**

Test files contain information on tests conducted in primary care (laboratory investigations, screening and diagnostic tests). Tests are coded using test names, and test results are recorded normal, abnormal or as a numeric value with an associated unit.

**Additional clinical detail files**

The additional clinical details include alcohol use, blood pressure data, death administration, diabetes, diet, exercise, height, BMI, maternity data, smoking and weight. There may be more than one line of data for each patient corresponding to each measurement made on different dates. The files are split into the following sub-groups:

1. Blood pressure data: contains data on current and historic blood pressure records
2. Death administration: contains data on death

3. Diabetes data file: contains data entered via the practice based Diabetes Disease Management data area
4. Height data file: contains data relating to the patient's height
5. Weight and BMI file: contains weight data

Information on an event can come from one or more of the above data files. A summary of the sources of information for the main outcomes in this study is provided in Figure 2.3.

**Figure 2.3: Sources of information on GPRD events**

| | | Patient | Clinical | Referral | Therapy | Test | BMI | Status | Blood pressure | Death | Diabetes | Height | Smoking | Weight |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Consultation rates | | ✓ | | | | | | | | | | | |
| | Mortality | ✓ | ✓ | | | | | | | ✓ | | | | |
| | Second cancers | | ✓ | | | | | | | | | | | |
| Monitoring of chronic Disease | BP control | | | | | ✓ | | | ✓ | | | | | |
| | Cholesterol | | | | | ✓ | | | | | | | | |
| | HbA1c | | | | | ✓ | | | | | ✓ | | | |
| Incidence of new diagnoses related to cancer treatment | Heart failure | | ✓ | | | | | | | | | | | |
| | Erectile dysfunction | | ✓ | | | | | | | | | | | |
| | Osteoporosis | | ✓ | | ✓ | | | | | | | | | |
| | Bowel/bladder dysfunction | | ✓ | | | | | | | | | | | |
| | Lymphoedema | | ✓ | | | | | | | | | | | |
| | All prescriptions | | | | ✓ | | | | | | | | | |
| Incidence of comorbid diseases and new diagnoses | Dementia | | ✓ | | | | | | | | | | | |
| | Depression | | ✓ | | | | | | | | | | | |
| | Anxiety | | ✓ | | | | | | | | | | | |
| | Diabetes | | ✓ | | ✓ | | | | | | ✓ | | | |
| | Renal disease | | ✓ | | | | | | | | | | | |
| Uptake of non-cancer preventive care and screening | Flu vaccine | | ✓ | | ✓ | | | | ✓ | | | | | |
| | Bone density scan | | ✓ | | | ✓ | | | | | | | | |
| | BP testing | | ✓ | | | ✓ | | | ✓ | | | | | |
| | Cholesterol | | ✓ | | | ✓ | | | | | | | | |
| Cancer screening | Mammogram | | ✓ | | | ✓ | | | | | | | | |
| | PSA testing | | ✓ | | | ✓ | | | | | | | | |
| | Cervical smear | | ✓ | | | ✓ | | | | | | | | |
| | Hospital referral | | ✓ | ✓ | | | | | | | | | | |
| | BMI | | | | | | ✓ | ✓ | | | | ✓ | | ✓ |
| | Smoking | | | | | | | ✓ | | | | | ✓ | |

**Identifying deaths**

The GPRD dataset specification describes an algorithm for identifying all deaths in the GPRD population. Briefly, a dead patient can be identified three ways in the GPRD:

1. A record of the patient transferring out of the primary care practice with a 'Transfer out reason' specified as 'death'
2. A 'clinical' or 'referral' event with a Read/OXMIS code indicating a death category
3. A record in the death administration area (additional clinical details files)

When a patient dies, the GP should firstly enter a Read/OXMIS code (known as the 'Statement of Death' or 'SoD'), in the patient's medical record indicating that they have died and the date of death.

**Date of death**

GPRD advises that using a 'transfer out reason' of death is the most reliable way of identifying deaths, however, the 'transfer out date' is not necessarily the actual date of death.

In most cases, there is both a 'transfer out date' and a SoD date in the patient's record. In this case, GPRD recommends that the date of the SoD should be used as the date of death when it precedes the 'transfer out date' by an appropriate time interval, specified as 95 days by GPRD researchers.

**Looking for death events in the cancer survivors and controls cohort**

Using the strategies suggested by GPRD to identify deaths in the patient cohort, 12217 deaths were identified amongst the cancer survivors and control cohort (Table 2.6).

**Table 2.6: Breakdown of death, as identified in the GPRD from 2001-2006, by cancer type**

| | Breast | | Colorectal | | Prostate | |
|---|---|---|---|---|---|---|
| | Survivor n=18612 | Control n=74248 | Survivor n=5764 | Control n=22846 | Survivor n=4868 | Control n=19288 |
| Total deaths | 3061 | 2849 | 1316 | 1690 | 1503 | 1798 |
| % | 16.5% | 3.8% | 22.8% | 7.4% | 30.9% | 9.3% |

**Cause of death**

It is difficult to determine the underlying cause of death using the GPRD especially when there were more than one SoD codes, or if there were several Read coded events seemingly leading up to the death. Although cause of death is difficult to ascertain within the GPRD, I accessed linked data from the Office for National Statistics (ONS) which provided information on underlying cause of death for the patients with linked data.

Although this research accessed the GPRD-ONS linkage scheme, which provides further information on death registrations, the linkage scheme only covers roughly 50% of the practices in the GPRD. Therefore, the GPRD was used as the primary source of data for the majority of analyses identifying deaths for the full cohort. The ONS data provided a longer follow-up, with information on deaths and cause of death until 2009. For the analyses on

cause of death (Section 4.3.3, mortality analysis), the analyses were limited to the proportion of practices with linked data, and the GPRD-ONS data linkage was used to both identify death and to investigate cause of death in the cohort.

### 2.4.3 Internal data linkage and cleaning

For each outcome in this thesis, data were extracted from all different sources (i.e. test and clinical files) and merged into one file. This process created a master file containing all of the relevant data for each event. Each patient has a unique identifier in the GPRD, so events from different sources were linked back to the same patient.

Before the outcome analysis, I created a master file that contains individual level information on key patient characteristics. This file included data on: date of birth, sex, type of cancer, case/control status and matched groupings, year of cancer diagnosis, date of death, date of transfer from the practice, smoking status, BMI and a comorbidity score (see Section 2.5 for details). I added this information into each analysis file before proceeding any further, linking patients to their patient characteristics data via the unique patient identifier.

The next step after setting up a final file containing all relevant data for each analysis was to clean the data and look for errors in the raw data. This consisted of several different steps, which included:

**Looking for nonsensical readings and consistency checks**

For each characteristic or result, I considered whether the data was within sensible limits, and looked for measurements outside of these levels. For instance, if a BMI reading was outside of a pre-specified range (15-60 $kg/m^2$), it was recoded as missing. Similar checks were conducted for other data such as age or year of cancer diagnosis.

**Restricting events to the analysis window**

The majority of the analyses involve events during an analysis window of September 1 2003 to August 31 2006 and events outside of this time period were excluded. However, for historical clinical diagnoses of chronic diseases, I considered all of the patient data during and before this analysis window.

**Entry into the study upon achieving five years survival**

The cohort contains data from cancer survivors with less than five years survival at the start of the analysis window on 1 September 2003, but who achieved five years survival within the analysis window. Data on these patients was included in the follow-up, along with data from their matched controls, upon achieving five years survival (Case A in Figure 2.4).

**Censoring patients upon death**

A number of patients died within the analysis window. I censored these patients from the analysis on the date of death, but included data on them for the period before the date of death. The follow-up schematic for patients who died is shown in Figure 2.4. If the patient with cancer was a cancer survivor (case), then I also censored the matched controls corresponding to the case (Case B in Figure 2.4). However, if the patient who died was a control patient, I only censored the follow-up for that one patient on the date of death (Case C in Figure 2.4).

**Censoring patients who develop a second cancer**

Some patients developed cancer during the analysis window. I censored these patients from the analysis on the date of the cancer diagnosis. The follow-up schematic for patients diagnosed with a second cancer is shown in Figure 2.5. If the patient with cancer was a cancer survivor (case), then I also censored the matched controls corresponding to the case

(Case A in Figure 2.5). However, if the patient diagnosed with cancer was a control patient, I only censored the follow-up for that one patient on the date of cancer diagnosis (Case B in Figure 2.5).

**Figure 2.4: Follow up schematic - entry at 5 years survival and death**

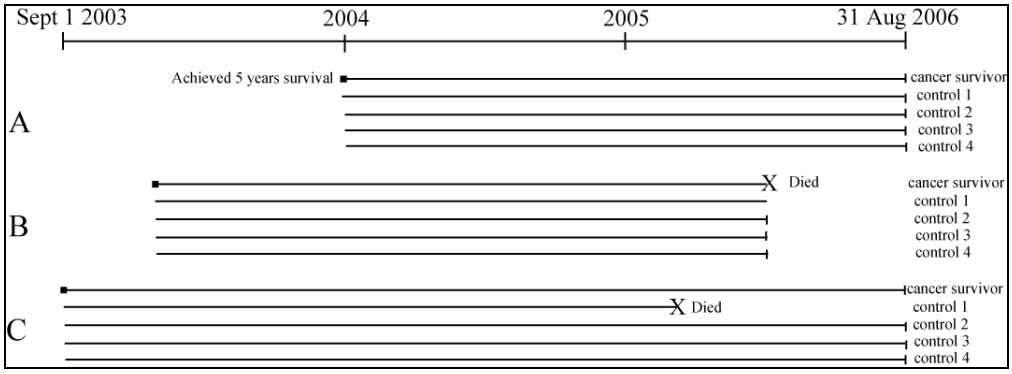
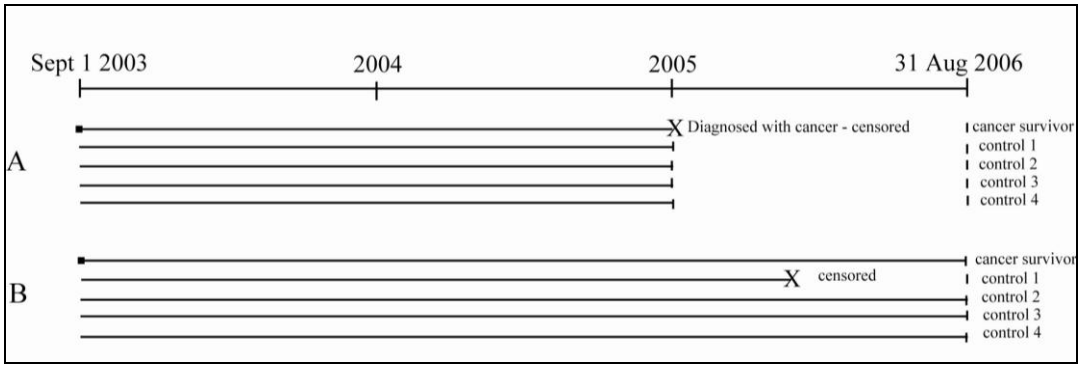



**Figure 2.5: Follow up schematic for second cancers**




## 2.4.4 Data analysis

All statistical analyses in this thesis were conducted using Stata MP, version 10.1.

**Descriptive analyses**

Once all events were identified and set up within an analysis file, I checked through the distributions of each of the variables in the dataset to ensure the data made sense and to gain an understanding of the study population.

**Data reduction and reclassification**

I grouped numerical variables such as BMI according to standard World Health Organization classifications (i.e. <20 $kg/m^2$ = underweight, 20-25 $kg/m^2$ = normal weight, 25-30 $kg/m^2$ = overweight, $\geq$30 $kg/m^2$ = obese) (27). For most of the analyses, age was not recoded as the cases and controls were born in the same year and therefore it was unnecessary to adjust for the effects of age.

**Univariate analysis**

In this study, the explanatory (exposure) variable was always cancer survival status (cancer survivor versus control). For each set of analyses the first step was to examine the association of the outcome with the exposure, for instance, whether rates of mammography (outcome) were associated with being a breast cancer survivor (exposure). The control group (i.e. patients who are not cancer survivors) were always used as the baseline group. If there was a strong relationship (at $\leq$ p=0.05 significance level) between the outcome and history of cancer, a multivariate analysis was conducted. The univariate analysis was conducted using a matched analysis as the dataset is structured as a matched cohort study.

**Choosing confounders and exposure variables to include in the multivariate model**

Univariate analyses were followed by multivariate matched analyses to determine the effect between the cancer survivors status (exposure) and outcome variables. Cases and controls

were matched on the basis of age, sex and GP practice, therefore, these variables were not taken into account in the final multivariate analysis.

For each analysis, I used information from previous literature, clinical advice from PWR, and examples from the literature to guide selection of covariates to include in multivariate analysis (28). In order to adjust for multiple comorbid disease, I translated the Charlson comorbidity score for use in Read/OXMIS coded databases like the GPRD (see Section 2.4 for details). The analyses in this thesis do not use stepwise regression techniques.

**Multivariate analysis**

The final step in the analysis was a multivariate analysis looking at the effect of the exposure on the outcome, taking into account any confounders and matched groups when relevant.

In collaboration with my clinical supervisor (PWR) and prior to looking at any results, we specified a list of interactions a priori to examine in the final models. We pre-specified looking at interactions amongst subgroups of patients who died during the analysis window. These patients might be treated differently in the period before death, for instance, they may not receive screening and preventive care, or GPs may code diagnoses differently if they know the patient is nearing death.

A summary of the methods in the GPRD analysis is shown in Figure 2.6.

### 2.4.5 Appropriateness of database selection and methods

Although this study uses the GPRD to achieve the main objectives, it is important to consider the potential alternatives to the choice of this database and the methods I intend to use.

The GPRD is not the only primary care database in the United Kingdom; there are two other main UK based databases. The Health Improvement Network (THIN) is a medical research database of roughly 450 practices also using Vision software, and is similar in its characteristics to the GPRD (29). The third national database is QResearch, covering 602 practices using EMIS practice software (30). However, while the GPRD-MRC licensing agreement allowed for free access for the purposes of academic research, QResearch is provided at a minimum cost of £10,000 per dataset, and THIN access amounts to £190,000 over a four year period or per dataset. As these datasets are very similar in the method of data collection from patient electronic medical records and information provided, it was a pragmatic decision to use the GPRD as a free resource to explore the use of primary care services by cancer survivors.

Some of the questions in this thesis could have been answered using practice audits or questionnaire-based methodology, for instance, to gain patient-reported data on use of primary care services. However, the national coverage of the GPRD, its large size and the low cost means that it covers a population-based, representative population which may not be accessible via survey methodology where a low response rate could lead to bias. Again, the GPRD was the most practical and lowest cost alternative for this thesis.

### 2.4.6 Assessment of approaches to handling missing data

Exposure variables in the GPRD such as smoking are well recorded, however there is some missing data relating to patient characteristics such as smoking status and body mass index (BMI). In order to determine the best way to deal with missing data in the GPRD, I undertook an analysis comparing three different approaches to dealing with missing data. A methodological paper published in 1995 by Greenland et al used a similar approach (31).

The example used here was the risk of incident diabetes amongst colorectal survivors and controls in the GPRD.

**Summary of data**

There are a total of 5068 colorectal cancer survivors and 20128 colorectal controls in this data set with one or more day of follow-up after 2003. The missing data are: BMI (3764 missing a reading, or 16.4%), smoking status (973 missing smoking status, or 4.2%). These two pieces of information are potentially important covariates, as they increase the risk of developing diabetes.

**Missing data analyses**

The simplest approach for dealing with missing data is complete case analysis which simply discards observations with any missing data. This generally makes the assumption that the data are missing completely at random (MCAR) (32).

The second option considered was multiple imputation, which works by filling in the missing values with imputed values based on the observed data. The imputation method involves cycling through all of the variables, imputing and modelling each conditional on the other variables. The imputed values are predicted values from the regression models, with the appropriate random error included (33). This step creates a set of 'complete' data sets of imputed data with appropriate random error included. The analysis is then run separately on each data set, and the results are combined across data sets by using Bayesian multiple imputation combining rules.

The final option I considered was use of a missing category indicator. This method involves creating a missing category for variables with missing values, and then using this category in

The final option I considered was use of a missing category indicator. This method involves creating a missing category for variables with missing values, and then using this category in multivariate analyses. However, the problem with this approach is that the 'missing' category is a mix of actual levels of the variable. This category can yield confounded results in case control studies if the variable is a confounder, and can lead to biased estimates of the overall effect of the main exposure variable (34).

**Results of missing data analyses**

Each of the three methods to deal with the missing BMI and smoking data resulted in similar incidence rate ratios for the risk of developing incident diabetes amongst colorectal cancer survivors, using the colorectal controls as the baseline population (Table 2.7).

**Table 2.7: Results from three different approaches to missing BMI and smoking data, risk of incident diabetes amongst colorectal cancer survivors**

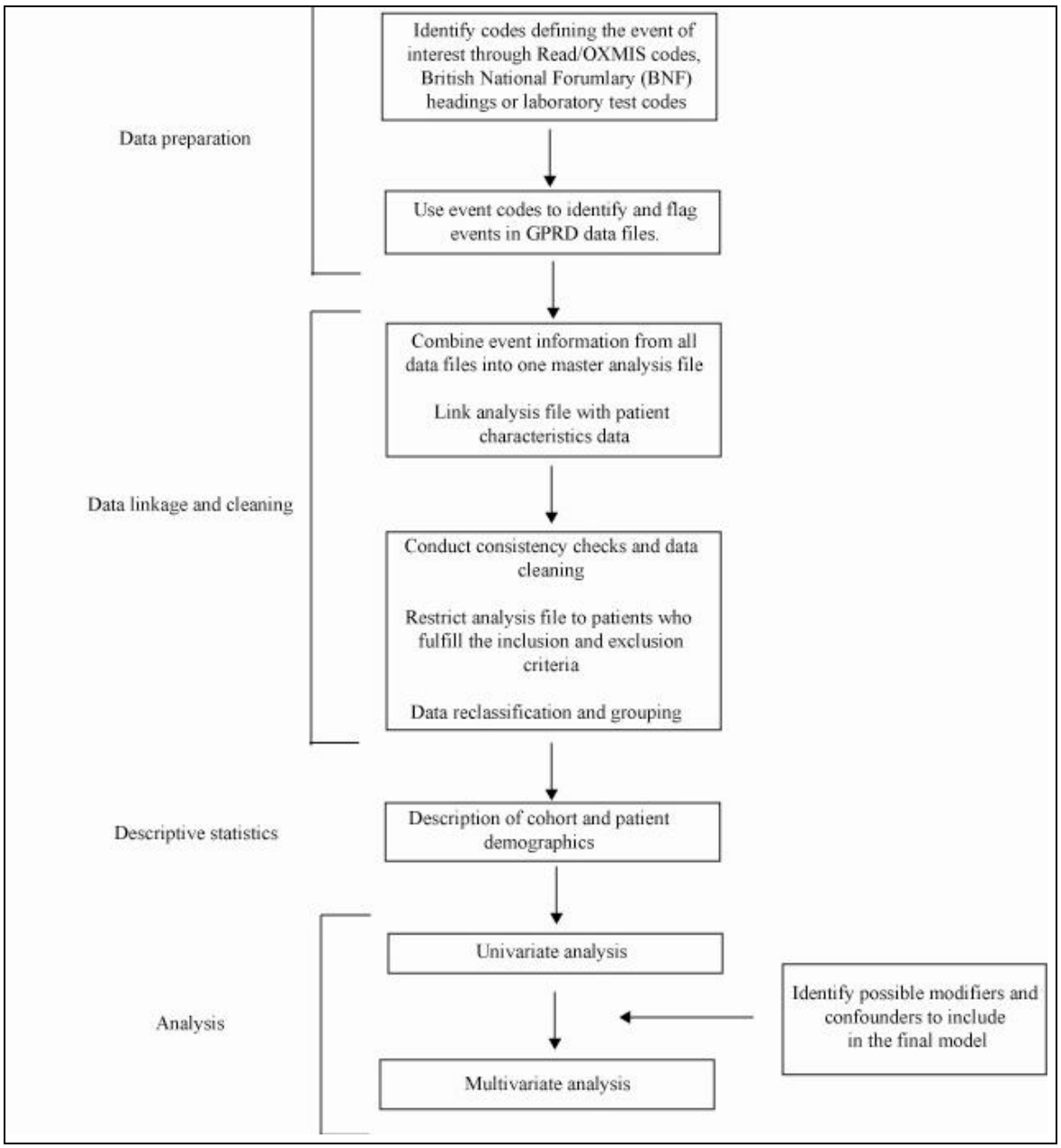
| Approach to missing data | Incidence rate ratio* |
|---|---|
| Complete case analysis | 1.25, 95% CI 1.06-1.49 |
| Multiple imputation | 1.27, 95% CI 1.07-1.51 |
| Use of a missing category | 1.25, 95% CI 1.05-1.48 |

* The control population were used as the baseline

In the above example, all of the results were largely similar, therefore it seems acceptable to use the simplest approach, the complete case analysis, where the missing data is limited to smoking or BMI. Because the proportion of missing data is generally low, and the numbers

available in the GPRD cohort are fairly large, there is no substantial loss in power by losing data in a complete case analysis.

**Figure 2.6: Flow chart of steps in GPRD analysis**



## 2.5 Development of a comorbidity score

### 2.5.1 Introduction

Individual disease status is an important predictor of mortality and health care usage. In some cases individuals may have more than one co-existing illness at the same time. It was important for many of the outcomes in this thesis to conduct risk adjustment for the additional health effects of these co-morbid diseases amongst the cancer survivors cohort.

Previous research has led to the development of summary comorbidity measures which classify patients according to their disease burden (35-38). The most widely used and validated index of comorbidity was developed by Charlson and colleagues in the late 1980s (39;40). The Charlson index includes 17 categories of comorbid disease weighted based on their association with 1 year all-cause mortality. Because the Charlson index is weighted and allows for additive scoring, it can take into account both the number and the severity of comorbidity to provide a summary of disease burden for individual patients (40). The index has been validated in several different populations, and has been widely used in studies involving cancer patients and survivors (41-45).

Recognizing the potential for its use in large database studies that require risk adjustment for individual patients, the Charlson index has previously been adapted for use with administrative data (46-49). However, these adaptations, which involve searching individual level hospital claims data for codes corresponding to the Charlson index, generally apply only to ICD-9 coded data. There is no current translation of the Charlson index for Read and OXMIS coded data as represented in the GPRD. I aimed to develop a comorbidity index based on the Charlson index for use with the cancer survivors cohort under study here. In

order to gauge the performance of the new measure, I tested the association between comorbidity and increased mortality within the cohort.

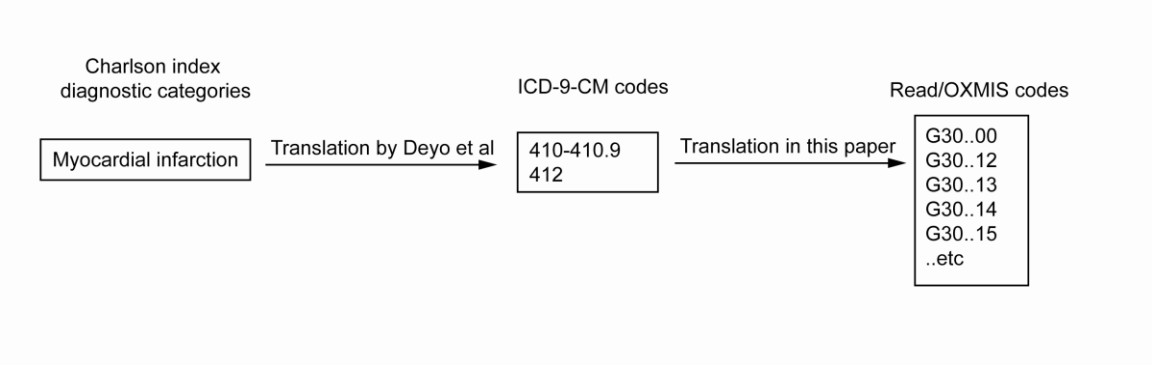
This set of analyses was written up as a paper and published in the BMC Family Practice (50). Please see Appendix 2 for a copy of the published paper.

## 2.5.2 Methods

**Development of Read/OXMIS codes lists**

The original Charlson index consists of 17 diagnostic categories which provide the basis for assigning weighted scores to each comorbid disease. Deyo et al (46) describe a validated translation of each diagnostic category of the Charlson index to ICD-9 codes. I used the ICD-9 codes suggested by Deyo et al to guide development of the Read/OXMIS code lists used in this comorbidity index. Figure 2.7 summarizes the process for translation of the index to Read/OXMIS codes using one of the Charlson diagnostic categories, myocardial infarction, as an example.

**Figure 2.7: Translation of Charlson index to Read/OXMIS codes**




Using definitions provided by Deyo et al for each Charlson diagnostic category, I searched the General Practice Research Database Medical Dictionary for potentially relevant

Read/OXMIS codes. I conducted these Read/OXMIS searches for 16 of the diagnostic categories used in the Charlson index. Cancer codes were treated separately; I included all Read codes starting with 'B', but excluded all codes for benign cancer (B7), cancer in situ (B8) and neoplasms of uncertain behaviour (B9).

Two clinicians experienced in the use of Read codes (Drs Peter Rose and Stephen Harper) independently reviewed the list of all Read/OXMIS codes identified through searches of the GPRD medical dictionary. The clinicians selected relevant Read/OXMIS codes and rejected codes not corresponding to ICD-9-CM codes used in the Deyo adaptation of the Charlson index. A third clinician, Dr. Lucy Jenkins, resolved any disagreement on coding. I calculated the degree of inter-rater agreement between the two clinicians reviewing Read/OXMIS code lists using the kappa score, which provides an estimate of the level of agreement between the two raters above that occurring due to chance.

**Validation dataset**

I used the entire GPRD cohort of cancer survivors and controls to test the adapted Charlson index, including those patients who either died or left the GPRD practice before the start of the analysis period on 1 September 2003. Following translation of the Charlson index to Read/OXMIS codes, I tested whether an increasing comorbidity score was associated with increased patient mortality by applying the adapted weighted Charlson index to the patient cohort. This adapted comorbidity score used the original Charlson score which does not include age. Charlson and colleagues have also since developed a combined age-comorbidity index (51).

Cox proportional hazards models were fit using mortality from July 1 2001 to 31 August 2006 as the dependent variable. Charlson score was coded as a continuous ordinal indicator variable, and was included along with age as explanatory variables. Survival was measured in days and associations are reported using hazard ratios with Charlson score of 0 as the referent group.

**Discriminatory power of the model**

The area under a receiver operating characteristic (ROC) curve, or c-statistic, can be used to quantify how well a predictor based on a number of variables discriminates a dichotomous outcome (52). I used a logistic model to estimate the relationship between death and the Charlson index after adjusting for age, quintiles of the Index of Multiple Deprivation (IMD) and sex before producing the ROC curve. Model discrimination was assessed by the area under the ROC curve.

**Adjusting variables**

I included age in 2001, sex and IMD score in the models for adjustment. Age was categorized in 5 groups (30-49, 50-59, 60-69, 70-79, 80+ years).

## 2.5.3 Results

**Coding exercise**

The inter-rater agreement between the two clinicians for including Read/OXMIS codes in the Charlson index was 84.6%, with a kappa of 0.45, indicating a moderate level of agreement (53). Including the cancer codes, this adaptation of the Charlson index includes a total of 3156 Read/OXMIS codes.

**Characteristics of the cohort**

60585 patients in this cohort did not have a comorbid disease (41% of the total cohort). Table 2.8 shows the frequency and percentages of patients with each of the diagnoses included in the comorbidity index.

**Table 2.8: Frequency of comorbid disease in validation cohort**

| Charlson diagnostic category | Weighted score in Charlson index (40) | Number of patients in the dataset |
|---|---|---|
| AIDS | 6 | 8 (0%) |
| Cerebrovascular disease | 1 | 9,028 (4.4%) |
| Chronic pulmonary disease | 1 | 27,698 (13.5%) |
| Congestive heart disease | 1 | 9,217 (4.5%) |
| Dementia | 1 | 3,624 (1.8%) |
| Diabetes | 1 | 14,418 (7.0%) |
| Diabetes with complications | 2 | 2,544 (1.2%) |
| Hemiplegia and paraplegia | 2 | 505 (0.25%) |
| Mild liver disease | 1 | 416 (0.2%) |
| Moderate or severe liver disease | 3 | 96 (0.05%) |
| Myocardial infarction | 1 | 6,512 (3.2%) |
| Peptic ulcer disease | 1 | 6,943 (3.4%) |
| Peripheral vascular disease | 1 | 6,731 (3.3%) |
| Renal disease | 2 | 12,624 (6.1%) |
| Rheumatological disease | 1 | 8,140 (3.9%) |
| Cancer | 2 | 34,750 (16.9%) |
| Metastatic tumour | 6 | 2,116 (1.0%) |
| No comorbid disease | - | 60,585 (29.4%) |
| Total | | 205,955 |

* Patients can be counted more than twice if they have more than one comorbid disease, therefore the total will not equal 146 442 (the total number of patients in the cohort)

The original Charlson index weights each disease category on the strength of its association with mortality. Using the original Charlson weights for each disease category, the breakdown by index score in the dataset is shown in Figure 2.8.

There were few patients (5.2%) with a very high Charlson score above 5. There was a strong positive association between increasing Charlson score and increasing age ($p<0.0001$).

**Patient mortality**

In total, 12217 patients died during the five-year period from July 1 2001 to August 31 2006. Figure 2.9 shows the survival curves for the population stratified according to Charlson score.

**Figure 2.8: Breakdown of Charlson score in patient dataset**

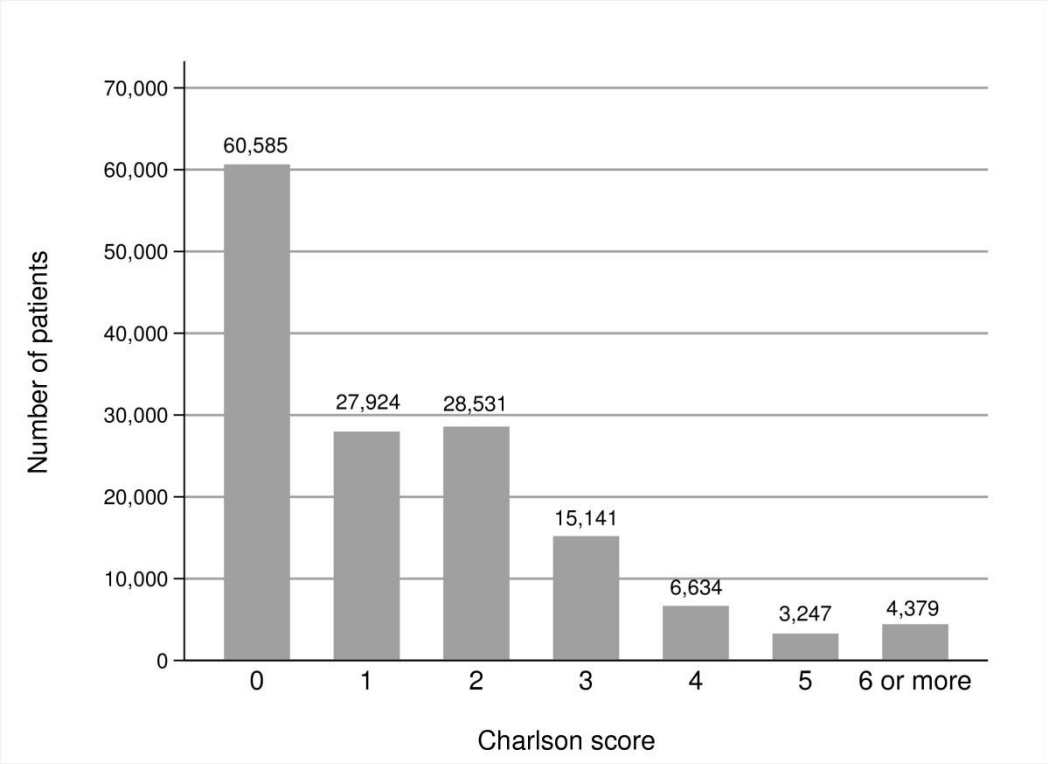
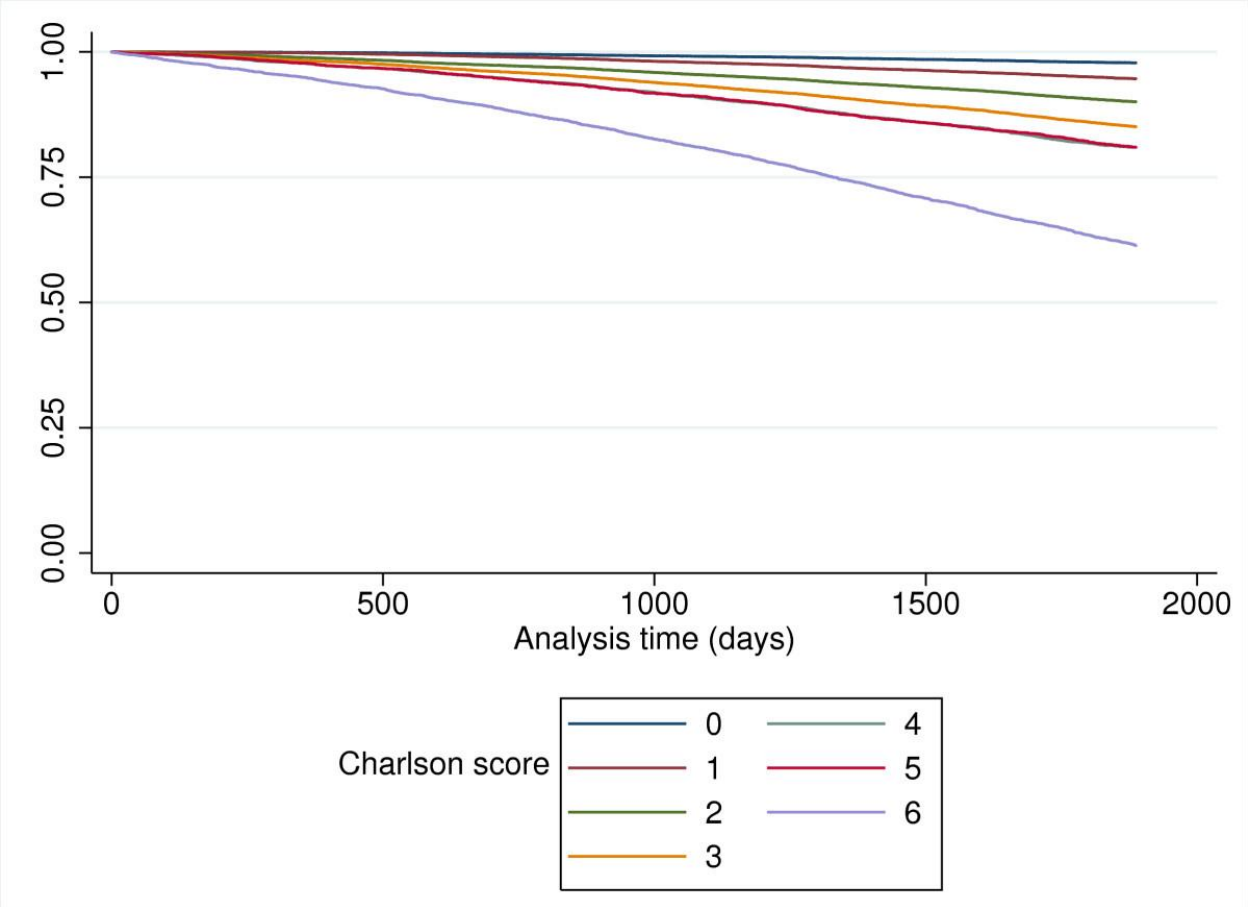


**Figure 2.9: 5 year mortality stratified by Charlson score**




Mortality was significantly associated with a Charlson score of 1 or more, with a positive increasing association as Charlson score increases to an HR of 14.2 (95% CI 13.2-15.3) (Table 2.9). There was an increased risk of death amongst older patients and amongst males.

**Table 2.9: Adjusted risk of death and 95% CI for 5 year mortality**

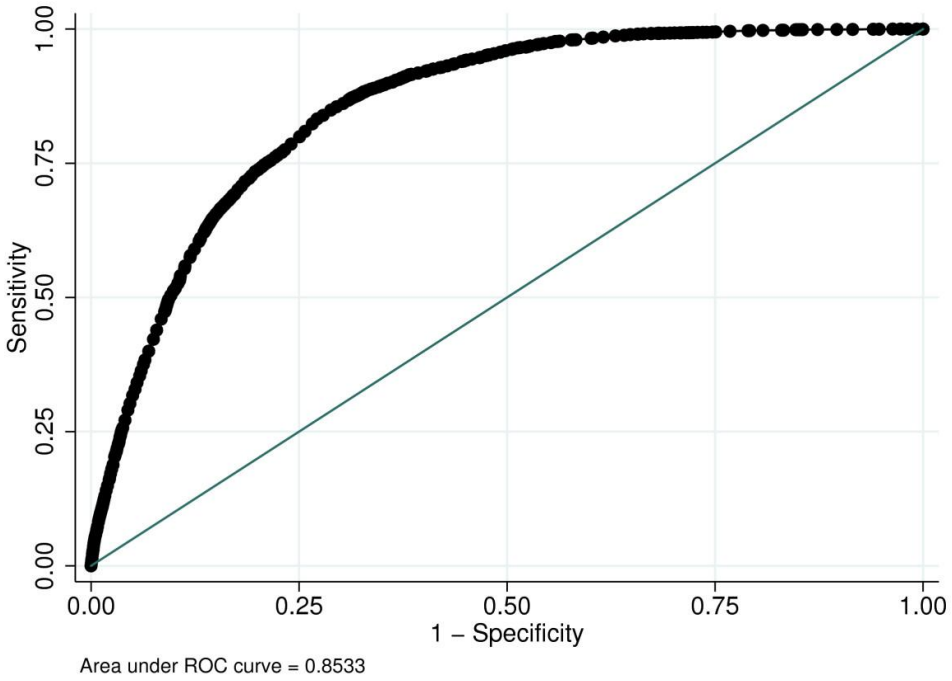
| | Adjusted hazard ratio* | 95% Confidence interval |
|---|---|---|
| Charlson score | | |
| 0 | 1 | |
| 1 | 1.87† | 1.74 - 2.02 |
| 2 | 3.68† | 3.45 - 3.93 |
| 3 | 4.71† | 4.40 - 5.05 |
| 4 | 5.47† | 5.06 - 5.91 |
| 5 | 5.25† | 4.77 – 5.78 |
| 6 or more | 14.2† | 13.2 – 15.3 |
| | | |
| Age | | |
| 30-49 | 1 | |
| 50-59 | 1.07 | 0.89 – 1.29 |
| 60-69 | 1.39† | 1.16 – 1.66 |
| 70-79 | 2.98† | 2.51 – 3.53 |
| 80+ | 10.5† | 8.89 – 12.4 |
| | | |
| IMD quintile‡ | | |
| 0‡ | 1 | |
| 1 | 1.00 | 0.94 - 1.06 |
| 2 | 1.04 | 0.98 - 1.09 |
| 3 | 1.05 | 1.00 - 1.12 |
| 4 | 0.97 | 0.91 - 1.03 |
| | | |
| Sex | | |
| Female | 1 | |
| Male | 1.16† | 1.12 - 1.21 |

* Adjusted for age, sex, and quintile of IMD
† Significant at the p<0.0001 level
‡ Lower IMD score indicates a higher level of deprivation; practices in the top quintile (IMD score=4) are the most affluent

**Discrimination of the model**

The discrimination of the logistic regression model was good, with an area under the ROC curve of 0.85 (Figure 2.10). This indicates that the adaptation of the Charlson index is a good predictor of mortality in the validation dataset.

**Figure 2.10: ROC curve for logistic regression model**




## 2.5.4 Discussion

In this cohort of cancer survivors and matched controls, a higher comorbidity score in this adaption of the Charlson index was associated with an increased risk of mortality after adjusting for age, deprivation scores and sex. Additionally, the translated comorbidity index showed a good discrimination the study population.

The primary outcome used in the development of the original Charlson score was mortality. The results of the validation exercise for this work confirmed that patients with a greater burden of disease were at a higher risk of death. One unexpected result was a large jump in the risk of mortality in patients with a Charlson score of 6 or above. This is likely due to the number of patients in the cohort with metastatic cancer, which generally has a very poor prognosis in the small but high risk group of patients with a score of 6 or more (54).

**Limitations**

This comorbidity index performed well in the validation exercise, however, there are several areas where the model may be inadequate. Firstly, it is possible that some codes were not included when developing the Read/OXMIS code lists for assessment. By using broad search terms, hierarchical searches of Read codes, and two reviewers to independently assess records, fewer potentially relevant Read/OXMIS codes were excluded from the final adaptation of the Charlson Index. Secondly, I used the original disease weights developed by the authors of the original Charlson index almost twenty years ago. One recent criticism of the Charlson index is that certain diseases have an improved prognosis since the original score was developed. For instance, according to the original Charlson weighting, a positive AIDS disease status carries an equivalent mortality risk to a diagnosis of metastatic cancer. Only eight patients in the GPRD dataset used for this thesis were diagnosed with AIDS, therefore, this issue is unlikely to affect the validation results.

## 2.6 Conclusions

This chapter has focussed on the methods involved with use of the General Practice Research Database (GPRD) to achieve objectives 2 and 3 of this thesis. Along with a description of the cohort selection, data quality and specific data preparation methods were discussed. Additionally, this chapter describes the development of a Charlson comorbidity index for use in Read/OXMIS databases, which can provide a summary of comorbidity for use in large studies such as this cohort study. The following two chapters describe the results of the analysis of the use of primary care services and risks involved with surviving cancer amongst a GPRD cohort of cancer survivors.

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# Chapter 3: Use and quality of primary care services in long-term survivors of breast, colorectal and prostate cancer

## 3.1 Introduction

Cancer survivors are at increased risk of ill health due to a number of factors, including second cancers, late effects related to treatment and other comorbidities, all of which can lead to an increase in primary care service use (1-3). Research from the UK has indicated that cancer survivors discharged from hospital follow-up have a median increase of one consultation per year, but there is no current evidence on broader aspects of their consultation patterns (4). There are a number of reasons why long term cancer survivors might have increased service use, including follow-up for cancer recurrence, symptoms related to cancer and its treatment, and provision of hormonal treatments for breast and prostate cancer. Depression is a commonly recognized disorder in the acute phase of cancer following diagnosis and treatment, with rates of depressive disorder up to four times higher in cancer patients compared to the general population (5;6). Part of an increase in primary care service use may be due to ongoing psychological morbidity, but patterns of use of primary care based psychological services have not been explored in long-term cancer survivors (7).

Cancer survivors have previously been shown to report poorer health than the general population (8). The risk of adverse health can be reduced through use of preventive services which can play an important part in the long-term care of populations at risk (9). Previous research looking at use of preventive care provided to cancer survivors in the United States has produced mixed results. Although the use of preventive services was better in some

cancer survivors, breast cancer survivors had poorer uptake of measures like cholesterol screening and influenza vaccination compared to non-cancer controls (10-13). In contrast, other studies found that while breast cancer survivors received adequate care, the uptake of preventive health in long-term colorectal cancer survivors was worse than in those without cancer (14;15).

Cancer is primarily a disease affecting an older population; currently, one in eight people aged 65 years and over are living beyond a diagnosis of cancer in the United Kingdom (16). Chronic disease management is an important issue for older, long-term survivors, many of whom will have one or more comorbid diseases (17). However, previous research from the United States has highlighted the under use of chronic disease monitoring in individuals with cancer (12;14;15;18-20). Furthermore, cancer survivors with a comorbid condition have a substantially higher likelihood of poor health and disability than those without a history of cancer (21;22). These disparities in health care may result partly from a focus on cancer follow-up at the expense of routine preventive or monitoring care for other diseases. Now that more than half of all people with a cancer diagnosis will live more than five years post-diagnosis, chronic illnesses will contribute to a significant proportion of the long-term morbidity and mortality in this population (23). Despite their long-term risks, there has been very little research on the cancer screening, preventive health or disease monitoring behaviours of cancer survivors in developed health economies other than the United States (24).

Cancer survivors experiencing long-term psychological morbidity may be more likely to receive anti-depressants or drugs to combat anxiety (anxiolytics) (5;6;25). Many cancer survivors also report pain as a result of surgery or late effects of radiotherapy, and may continue to use pain relief in the long-term (26-28). However, chronic pain amongst cancer survivors is a poorly studied area, with little data on prevalence and use of opiods (29). The majority of individuals in the UK, including long-term cancer survivors, will consult with their GP to access these commonly used therapies. Recording of pharmacological interventions in the GPRD can provide a useful proxy for investigating symptoms which have a specific therapeutic resolution, or for investigating symptoms or syndromes which may be less reliably recorded in the GPRD (30).

Prostate and colorectal cancer survivors are also significantly more likely to report sexual difficulties and erectile dysfunction, which may be due to a number of physical and psychological factors associated with cancer and its treatment (31). Although there are a number of treatment options for sexual difficulties, oral treatments such as sildenafil citrate (Viagra) are commonly used to sustain an erection in men with erectile dysfunction. Higher use of these therapies for erectile dysfunction may represent an increased prevalence of sexual difficulties amongst long-term cancer survivors.

### 3.1.2 Aims

In order to explore how cancer survivors use primary care services in the United Kingdom, the first objective of this thesis is to compare the use and quality of primary health care services in long-term survivors of breast, colorectal and prostate. Specifically, this chapter will report

analyses from the General Practice Research Database (GPRD) focussing on the following outcomes for each cancer site:

a) Primary health care consultation rates, patterns and behaviours
b) Uptake of preventive health services, including cancer screening
c) Management and monitoring of chronic diseases
d) Prescribing patterns for relevant drugs, including analgesics, anti-depressants, anxiolytics and drugs for erectile dysfunction.

## 3.2 Methods

These analyses were undertaken using the GPRD cohort of cancer survivors and controls over the main follow-up period, which is defined as the period from 1 September 2003 to 31 August 2006 (see Table 2.3, Chapter 2 for details of the participants in these analyses), except for where indicated. Follow-up was censored upon patient death or transfer out of the GPRD primary care practice as described in Chapter 2 (Section 2.4.3). Details of each specific analysis are presented below.

### 3.2.1 Primary care consultations

Using descriptive statistics, I calculated consultation rates within the GPRD relative to length of survival for the cancer survivors along with rates for the matched controls. I also compared the total number of consultations between cancer survivors and matched controls over the three year period. This was achieved using fixed-effects negative binomial regression, which accounts for the matched groups by firstly making comparisons within each set of matched cancer survivors and controls, and then averaging estimates across all the matched sets (32).

Differences in the number of consultations are expressed as incidence rate ratios (IRRs). The consultation rate was expressed in relation to the number of years each patient contributed data to the follow-up. Only face-to-face consultations in the practice with a member of the primary care team (GPs and nurses) were counted. Administrative events such as patient correspondence, claim payments that can appear as clinical events in the GPRD patient electronic medical record were excluded. In order to account for the fact that patients moved through survival periods during the three year period, I applied the -stsplit- command in Stata to the cohort, which splits the follow-up on each subject for separate, and annual time bands (33). This means that a person diagnosed with cancer in 1998 was counted as a five year survivor in 2003 and a six year survivor in 2004.

This analysis also compared consultation behaviour for depression and anxiety between cancer survivors and their matched controls over the follow-up period. I compared the percentage of cancer survivors and controls consulting for depression or anxiety, and then used conditional logistic regression to determine whether or not cancer survivors were more likely than their matched controls to have a consultation for depression or anxiety during the same follow-up period. This regression method accounts for the matching by effectively comparing cases to the controls for whom they were selected (34).

### 3.2.2 Screening and preventive care

In order to determine use of preventive services amongst cancer survivors, I examined adherence to three national cancer screening guidelines as outlined by the National Health Service (NHS) cancer screening programme and use of services for routine screening of

disease and disease prevention (Table 3.1). There are no national guidelines on frequency of blood pressure testing, bone mineral density scanning or cholesterol tests, therefore, I used a standard of receipt of one test every three years.

**Table 3.1: Summary of UK guidance for cancer screening and preventive health services**

| | National guidance | Age range | Frequency of test |
|---|---|---|---|
| Screening test | | | |
| Mammogram | NHS Breast Cancer Screening Programme (35) | 50-69 | Once every 3 years |
| Cervical smear | NHS Cervical Cancer Screening Programme (36) | 25-49 | Once every 3 years |
| | | 50-64 | Once every 5 years |
| Prostate specific antigen (PSA) test | Prostate Cancer Risk Management Programme (PCRMP) (37) | 50+ | Patient request |
| Preventive health | | | |
| Influenza vaccination | National Institute for Health and Clinical Excellence (NICE) (38) | 65 + | Annually |
| Blood pressure test | None | - | - |
| Bone density scan | None | - | - |
| Cholesterol test (HDL, LDL, serum cholesterol) | None | - | - |

**Inclusion and exclusion criteria for use of screening and preventive services**

This set of analyses did not include the entire GPRD cohort; I only included cancer survivors and controls who were within the age range and eligible for cancer screening. Those with history of prior disease which would indicate the need for monitoring and not prevention were excluded. I excluded women with a history of hysterectomy in the analysis of cervical smear, women with history of bilateral mastectomy in analysis of mammography and prostate cancer

survivors from the PSA test analysis. Breast cancer survivors less than 10 years post-diagnosis who would be receiving routine mammography as part of hospital follow-up were also excluded. For preventive services, I excluded patients with hypertension from blood pressure monitoring; patients with a clinical history of diabetes, cerebrovascular disease or stroke, hypertension and myocardial infarction from cholesterol testing, and patients with a clinical history of osteoporosis from bone density scanning. These patients are not part of a healthy screening population, and will receive regular disease monitoring as directed by the Quality and Outcomes Framework (QOF), an incentive programme for payments to primary care practices from the English government (39).

I compared the use of screening and preventive services between cancer survivors and their matched controls over main follow-up period. The analysis window was extended to five years starting from 1 September 2001 for the analysis of cervical smear screening in women aged 50-64 to capture events corresponding to the national cervical cancer screening programme guidelines (see Table 3.1 for screening recommendations).

**Statistical methods**

The comparison of use of services was achieved by examining the percentage of cancer survivors and controls receiving cancer screening and preventive services. I used conditional logistic regression to calculate odds ratios and 95% confidence intervals to determine the association between cancer survivor status and use of preventive services compared to matched controls.

### 3.2.3 Monitoring of chronic diseases

This analysis aimed to examine how well patients with a chronic disease were monitored in primary care. The participants were chosen from the main GPRD cohort, however, this analysis included only those patients with a chronic disease requiring monitoring. I therefore included only cancer survivors with diabetes, hypertension, history of stroke or transient ischaemic attack (TIA), myocardial infarction (MI) or coronary artery disease (CAD) diagnosed before the start of the main follow-up period. Cancer survivors and controls were not originally matched on chronic disease. Therefore, for the purposes of this analysis, I restricted cases to those cancer survivors with a chronic disease, then randomly sampled within all available controls on the basis of age, sex, primary care practice and chronic disease on a 1:1 ratio to make comparisons between cases and controls with the same condition.

I used levels for monitoring as indicated in the Quality and Outcomes Framework (QOF) in 2007 to define adequate control of disease for the indicators (39). Adequate control of blood pressure was defined as a measurement equal to or under 150/90 mm/Hg for hypertensive patients or 145/85 mm/Hg for diabetics. Adequate control of cholesterol was defined as a total cholesterol under 5 mmol/l for patients with a history of coronary artery disease, diabetes and cerebrovascular disease (stroke and TIA) and adequate control of diabetes was defined as a glycosylated haemoglobin (HbA1c) reading under 7.5%. Cancer survivors with more than one chronic condition requiring monitoring were included separately in each of the relevant analyses. For instance, a cancer survivor with hypertension and diabetes was included both in the analyses examining blood pressure and those examining HbA1c monitoring.

To examine disease control as defined by QOF, I produced a mean systolic and diastolic blood pressure, total cholesterol and HbA1c for each patient receiving monitoring based on readings in three month periods (quarterly) during the follow-up period to examine disease control. When a monitoring test was not conducted or not recorded, I assumed no change and used the same value as the previous time period.

**Statistical methods**

I compared receipt of monitoring in cancer survivors and controls during the three year main follow-up period using $X^2$ tests and binomial exact 95% confidence intervals. I also compared the proportion of patients receiving monitoring after excluding all matched pairs where either the case or control died during the study period. I used conditional logistic regression to report receipt of monitoring over the three year analysis window. For the analyses on disease control I compared the number of quarterly periods with a test reading in the control range using *t* tests. Univariate associations ($p<0.05$) were explored in multivariate models using conditional fixed-effects regression to account for the matched groups.

## 3.2.4 Prescribing analyses and defined daily doses

In order to analyse prescribing behaviour it is insufficient to simply count the number of prescriptions issued as GPs can prescribe a varying number of pills per prescription, with a different frequency of prescribing. Additionally, many of the drugs available for prescription in primary care are provided in different tablet strengths. For instance, citalopram, which is a selective serotonin reuptake inhibitor (SSRI) antidepressant drug, is available for prescription in 5mg, 10mg, 20mg and 40mg tablets. The number of prescriptions and the dosage for drugs

available at different strengths needs to be standardized in order to facilitate comparisons between patients prescribed the same compound.

The World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology assigns a standardized unit, the defined daily dose, for each drug to provide a standard protocol for drug prescribing measurement. The formal definition of the defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults (40). The DDD is useful for pharmacoepidemiological analyses because it provides a fixed unit of measurement independent of tablet strength. It is possible to add together the DDDs of all the drugs in the same drug category, for instance pain medication, since the DDD of one drug is assumed to be functionally equivalent to the DDD of any other drug used for a similar purpose.

The WHO Collaborating Centre for Drug Statistics Methodology website includes a searchable index of different pharmaceutical substances with the WHO assigned DDD (41). For each set of analyses using DDDs, I used this index to assign each of the drugs under investigation a DDD.

**Drug definitions**

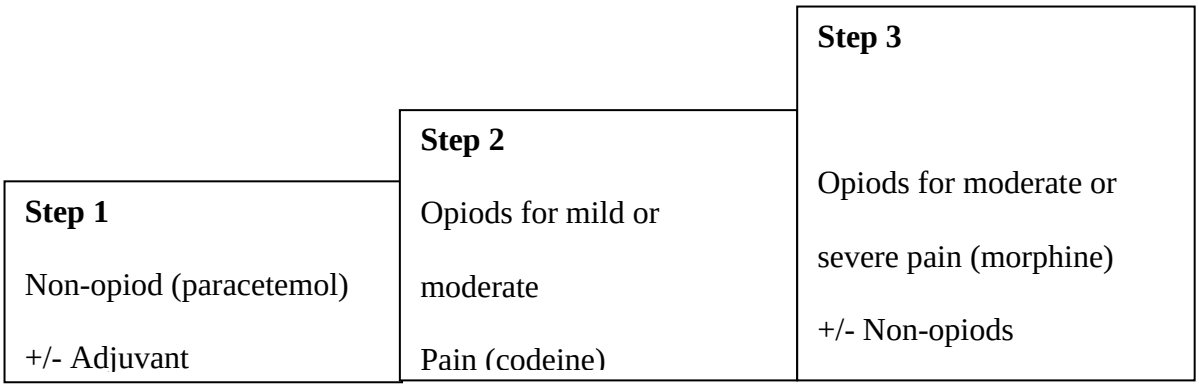
The British National Formulary (BNF) was used to identify all relevant prescriptions (42). Antidepressant drugs were defined as tricyclics, selective serotonin re-uptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs), and anxiolytics as benzodiazepines and busipirone, respectively listed in sections 4.3 and 4.1.2 of the BNF. The majority of

analgesics are listed under BNF header 4.7, and this analysis included non-steroidal anti-inflammatory drugs (NSAIDs) with the exception of Aspirin, which is also prescribed in primary care for primary prevention of cardiovascular events and myocardial infarction. Prescriptions for erectile dysfunction therapies listed in sections 7.4.5 of the BNF, including sildenafil (Viagra), apomorphone hydrochloride, vardenafil (Levitra), alprostadil (an injectable treatment) and tadalafil (Cialis) were included in the analyses of sexual dysfunction.

**Categorisation and defining pain medication (analgesics)**

The World Health Organization (WHO) has developed a three step pain ladder which provides a schematic for providing levels of pain relief to cancer patients (Figure 3.1). The guidance recommends administering pain relief in the following order: firstly non-opiods, secondly to add increasingly strong pain relief such as mild opiods, thirdly strong opiods until the patient is free of pain (43). I used the WHO pain ladder as a template for categorizing the numerous different analgesic drugs prescribed in primary care to the cancer survivors cohort. To help classify the mild and moderate opiod drugs, I met with a local expert in pain prescribing for cancer patients (Professor Henry McQuay, Nuffield Professor of Clinical Anaesthetics, University of Oxford). This classification system was used to assess the level of pain relief used by cancer survivors and controls by looking at the proportion of patients using analgesics at step 3 of the WHO pain ladder.

**Figure 3.1: WHO pain ladder**




**Statistical methods**

I compared prescribing between cancer survivors and their matched controls over the main follow-up period. I firstly compared the percentage of cancer survivors and controls receiving the prescription of interest. Secondly, I used conditional logistic regression to determine whether or not cancer survivors were more likely than their matched controls to receive at least one prescription during the same analysis period. Thirdly, I compared the volume of prescribing for the drugs of interest using World Health Organization defined daily doses to assign each of the prescribed drugs in the GPRD a defined daily dose (DDD) (13). I used conditional fixed-effects negative binomial regression, offset by follow up time for each individual, to compare the number of defined daily doses between cancer survivors and matched controls using incidence rate ratios (IRR). For prescribing of pain relief according to the WHO pain ladder I used conditional logistic models to consider the likelihood of receipt of a step 3 analgesic between cancer survivors and matched controls during the follow-up period.

### 3.2.5 Explanatory variables used in the regression analyses

For each outcome studied, there are other contributing factors which need to be considered. The analyses were adjusted for these factors as summarized in Table 3.2. Identification of these adjusting variables is discussed in Chapter 2, section 2.3.7, 'Data analysis'.

**Table 3.2: Factors adjusted for in specific analyses**

| Analysis | Adjusted for | Type of measure |
|---|---|---|
| Primary care consultation patterns | Charlson comorbidity index †<br>Death* | 5 categories<br>Binary |
| Depression | History of depression<br>History of anxiety<br>Death* | All binary |
| Screening and preventive care | Charlson comorbidity index | 5 categories |
| | Number of patient consultations | 5 categories |
| | Death* | Binary |
| | Body mass index (BMI) was included in multivariate models looking at blood pressure, cholesterol testing and bone density scanning | 4 categories, underweight, normal weight, overweight and obese |
| | History of mastectomy in women without a specific code for bilateral mastectomy | Binary |
| | History of hormone therapy in the | Binary |

| | | |
|---|---|---|
| | analysis for bone density scanning. | |
| Monitoring of chronic diseases | Charlson comorbidity index | 5 categories |
| | Number of patient consultations | 5 categories |
| | BMI | As above |
| | Death* | Binary |
| Prescribing | Number of patient consultations<br>Charlson comorbidity index<br>Death*<br>BMI was included in multivariate models looking at erectile dysfunction | All as above |

† See Chapter 2, Section 2.4 for details on how the Charlson comorbidity index was adapted for use in the GPRD (44)

*Formal tests for interactions with death as patients nearing the end of their life may be treated differently in primary care (45)

## 3.3 Results

### 3.3.1 Consultation rates

Descriptive results show that breast and colorectal cancer survivors have a significantly increased consultation rate up to 10 years post-diagnosis, with one extra consultation per year up to 5 years for breast cancer and 9 years for colorectal cancer (Figures 3.2 and 3.3). In comparison, prostate cancer survivors consulted up to three more times annually compared to controls, and this trend persisted even fifteen years post-diagnosis (Figure 3.4). The adjusted, matched analysis showed a slight increase in the overall number of consultations between breast cancer survivors (IRR 1.11, 99% CI 1.09 to 1.12) and colorectal survivors (IRR 1.12, 99% CI 1.08 to 1.14) versus controls. Compared to matched controls, prostate cancer

survivors had 39% more consultations over the follow-up period (IRR 1.39, 99% CI 1.35 to 1.43).

Prostate cancer survivors access primary care services for prostate specific antigen (PSA) testing to monitor cancer recurrence, which may partially explain the increased consultation rates amongst this population. PSA test events are recorded in GPRD clinical and test files; however, there were only 346 PSA test events coded amongst the prostate cancer survivors over the three year analysis period. I conducted a sensitivity analysis excluding these events from the consultation rate analysis in order to determine the impact of PSA testing. These events did not affect the overall consultation rate, suggesting that PSA testing alone is not driving the increase in consultation rates amongst prostate cancer survivors. I also tested the effect of excluding hormonal treatments such as injections and implants on the consultation rates amongst prostate cancer survivors. These included goserelin or Zolodex implants and Prostap injections which involve a face to face contact with a member of the primary care team, but I excluded prescription hormonal tablets such as bicalutamide or Casodex and cyproterone acetate. Of the total prostate cancer cohort, 1749 men had at least one hormonal injection or implant over the 2003 to 2006 analysis period. This corresponded to an average annual rate of 3.8 per year (standard deviation, SD 2.4) amongst the 1749 men receiving at least one injection/implant, and a rate of 1.37 (SD 2.3) amongst all prostate cancer survivors in the analysis. GP and nurse appointments to administer these injections and implants may therefore account for about half of the increased consultation patterns amongst long-term prostate cancer survivors.

I conducted a sensitivity analyses and repeated the matched analyses after excluding all patients who died from the analyses. However, there was still an increase in consultations amongst breast (adjusted IRR 1.07, 95% CI 1.06-1.09), colorectal (adjusted IRR 1.08, 95% CI 1.05-1.11) and prostate (adjusted IRR 1.33, 95% CI 1.29-1.37) cancer survivors compared to controls.

This set of work was written up as a paper and published in the British Journal of General Practice (46). Please see Appendix 3 for a copy of the published paper.

**Figure 3.2: Breast cancer survivors and controls consultation rates**

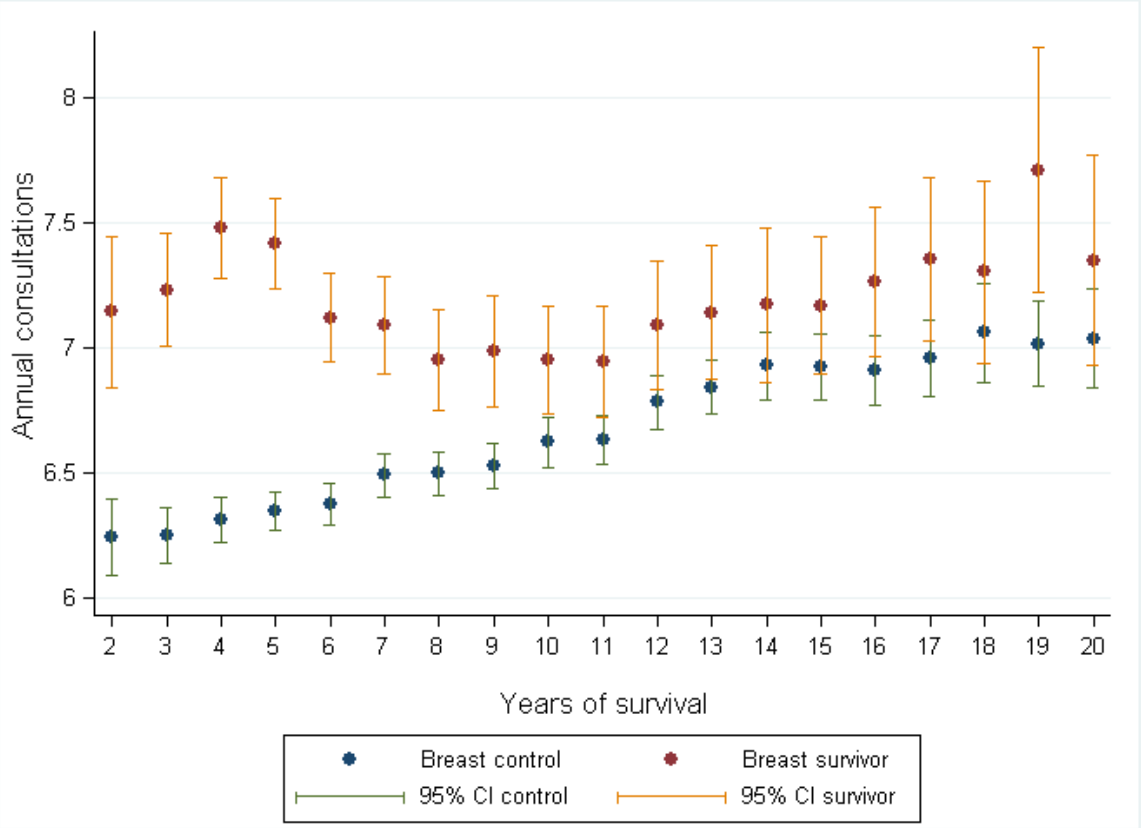


**Figure 3.3: Colorectal cancer survivors and controls consultation rates**

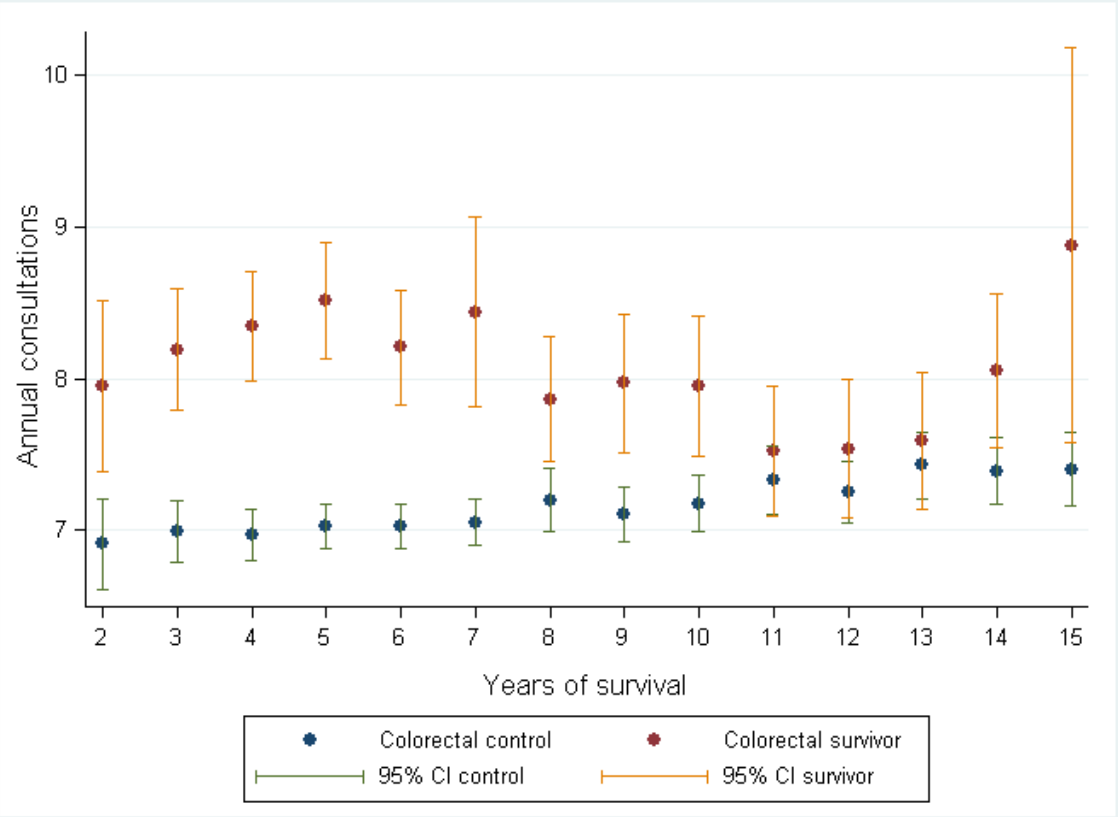
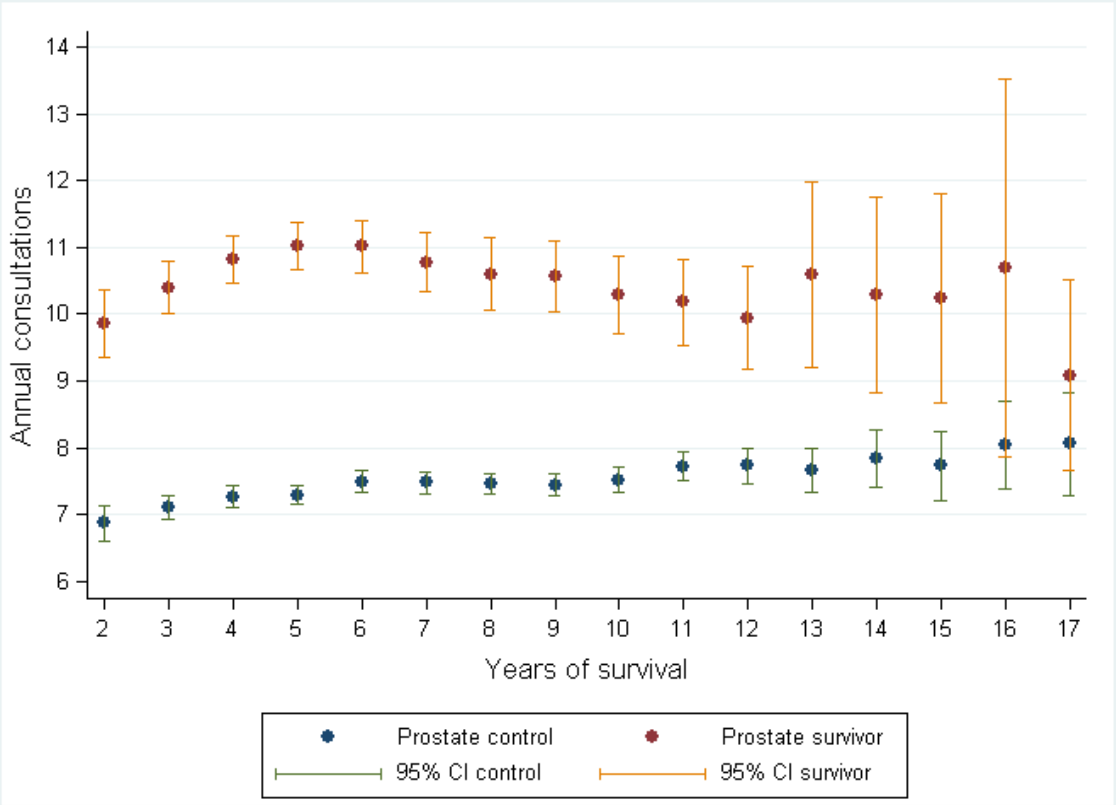


**Figure 3.4: Prostate cancer survivors and controls consultation rates**




*Clinical consultations for depression*

The majority of patients in this cohort (over 90% of all patients) did not consult for depression during the three year period (Table 3.3). After adjusting for comorbidity score, history of depression and death, there were no significant differences between any cancer survivors and matched controls in the likelihood of consulting for depression over the analysis period (Table 3.4). Previous history of depression and increasing Charlson comorbidity score were the strongest predictors of consultations for depression in all patients.

**Table 3.3: Depression and anxiety consultation behaviour, 2003-2006**

| | At least one consultation for depression during 2003-2006 | | At least one consultation for anxiety during 2003-2006 | |
|---|---|---|---|---|
| | Yes | No | Yes | No |
| Breast | | | | |
| Survivor | 1617 (9.6%) | 15,321(90.5%) | 908 (5.4%) | 16030 (94.6%) |
| Control | 5985 (8.9%) | 61664 (91.2%) | 3383 (5.0%) | 64266 (95.0%) |
| Colorectal | | | | |
| Survivor | 416 (8.2%) | 4652 (91.8%) | 178 (3.5%) | 4890 (96.5%) |
| Control | 1596 (7.9%) | 18,532 (92.1%) | 718 (3.6%) | 19410 (96.4%) |
| Prostate | | | | |
| Survivor | 393 (9.3%) | 3814 (90.7%) | 133 (3.2%) | 4074 (96.8%) |
| Control | 1356 (8.1%) | 15353 (91.9%) | 399 (2.4%) | 16310 (97.6%) |
| | 11363 | 119336 | 5719 | 124980 |

*Clinical consultations for anxiety*

Only a small proportion of cancer survivors and controls saw their GP for anxiety-related reasons during the follow-up period (Table 3.3). The univariate, matched analysis suggested an increase in the likelihood of having at least one primary care visit for anxiety amongst breast and prostate cancer survivors compared to controls. However, this association did not persist in multivariate models (Table 3.5). The strongest predictor for a consultation for anxiety during the analysis period was a previous history of anxiety.

**Table 3.4: Adjusted odds ratios (OR) for consulting for depression (with 95% confidence intervals)**

| | Breast cancer | | Colorectal cancer | | Prostate cancer | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| **Cancer status** | | | | | | |
| Control | 1.00 | | 1.00 | | | |
| Survivor | 1.06 | 1.00-1.14 | 1.07 | 0.94-1.22 | 1.12 | 0.98-1.34 |
| **Charlson score** | | | | | | |
| 0 | 1.00 | | 1.00 | | | |
| 1 | 1.78 | 1.66-1.91 | 2.23 | 1.93-2.57 | 2.47 | 2.09-2.92 |
| 2 | 2.34 | 2.12-2.58 | 2.98 | 2.51-3.54 | 3.47 | 2.88-4.18 |
| 3 | 3.21 | 2.83-3.63 | 3.69 | 3.02-4.52 | 4.65 | 3.75-5.76 |
| 4 | 3.79 | 3.17-4.54 | 3.91 | 2.95-5.20 | 5.27 | 4.04-6.87 |
| 5 or more | 2.82 | 2.39-3.33 | 4.75 | 3.63-6.21 | 6.77 | 5.20-8.83 |
| **Died during follow-up?** | | | | | | |
| No | 1.00 | | 1.00 | | | |
| Yes | 0.62 | 0.53-0.73 | 0.40 | 0.29-0.54 | 0.44 | 0.34-0.58 |
| **Pre-2003 depression?** | | | | | | |
| No | 1.00 | | 1.00 | | | |
| Yes | 4.39 | 4.13-4.67 | 3.77 | 3.30-4.30 | 3.39 | 2.89-3.98 |

**Table 3.5: Adjusted odds ratios for consulting for anxiety (with 95% confidence intervals)**

| | Breast cancer | | Colorectal cancer | | Prostate cancer | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| **Cancer status** | | | | | | |
| Control | 1.00 | | 1.00 | | | |
| Survivor | 1.06 | 0.97-1.16 | 0.90 | 0.74-1.10 | 1.25 | 0.98-1.59 |
| **Charlson score** | | | | | | |
| 0 | 1.00 | | 1.00 | | 1.00 | |
| 1 | 1.17 | 1.07-1.29 | 1.23 | 1.00-1.51 | 1.28 | 0.98-1.67 |
| 2 | 1.36 | 1.20-1.55 | 1.53 | 1.19-1.98 | 1.33 | 0.96-1.84 |
| 3 | 1.08 | 0.90-1.30 | 1.03 | 0.72-1.46 | 1.40 | 0.95-2.06 |
| 4 | 1.12 | 0.86-1.47 | 1.18 | 0.74-1.87 | 1.31 | 0.81-2.14 |
| 5 or more | 0.97 | 0.77-1.22 | 1.63 | 1.07-2.49 | 1.56 | 0.95-2.56 |
| **Died during follow-up?** | | | | | | |
| No | 1.00 | | 1.00 | | 1.00 | |
| Yes | 0.95 | 0.78-1.17 | 1.25 | 0.85-1.85 | 1.00 | 0.66-1.51 |
| **Pre-2003 anxiety?** | | | | | | |
| No | 1.00 | | 1.00 | | 1.00 | |
| Yes | 5.44 | 5.01-5.92 | 6.37 | 5.25-7.72 | 6.79 | 5.20-8.86 |

## 3.3.2 Uptake of preventive screening

*Patient characteristics and univariate analysis*

This analysis used patients eligible for screening from the cancer survivors and control cohort. Table 3.6 shows the number of patients eligible for each analysis and screening and preventive service use amongst cancer survivors and controls. Rates of cervical smear were similar in all

breast and colorectal cancer survivors and controls, and a similar proportion of colorectal cancer survivors and controls had mammography according to the national guidelines. A lower proportion of breast cancer survivors had a mammogram compared with controls.

**Table 3.6: Univariate analysis, with numbers eligible for analysis**

| | **Breast** | | **Colorectal** | | **Prostate** | |
|---|---|---|---|---|---|---|
| | Survivor | Control | Survivor | Control | Survivor | Control |
| Screening exam | | | | | | |
| Mammogram | 54.4% | 59.5% | 60.5% | 58.5% | | |
| *Number in analysis* | *2317* | *9974* | *513* | *2055* | - | - |
| Cervical smear | | | | | | |
| Aged 25-49 | 43.6% | 40.1% | 13.9% | 15.2% | - | - |
| *Number in analysis* | *755* | *3085* | *65* | *263* | | |
| Aged 50-64 | 45.7% | 44.4% | 41.6% | 41.9% | - | - |
| *Number in analysis* | *3419* | *14061* | *178* | *855* | | |
| PSA test | - | - | 22.1% | 19.0% | - | - |
| *Number in analysis* | | | 2489 | 9859 | | |
| Preventive health | | | | | | |
| Influenza vaccination | 75.8% | 74.4% | 74.9% | 73.2% | 74.6% | 70.2% |
| *Number in analysis* | *9488* | *37803* | *4118* | *16325* | *3854* | *15275* |
| Blood pressure | 68.0% | 69.2% | 70.1% | 70.4% | 70.7% | 68.7% |
| *Number in analysis* | *9771* | *38815* | *2531* | *10668* | *2105* | *9252* |
| Bone density scan | 14.1% | 10.3% | 13.2% | 10.5% | 17.1% | 9.3% |
| *Number in analysis* | *14574* | *59471* | *4455* | *17954* | *3928* | *16026* |
| Cholesterol test | 31.9% | 33.1% | 37.8% | 36.2% | 39.9% | 36.7% |
| *Number in analysis* | *9072* | *35311* | *2306* | *9235* | *1720* | *7563* |

Generally, cancer survivors were more likely to receive bone density scans, flu vaccination and cholesterol testing than the control population. However, breast cancer survivors were less likely to receive a blood pressure or cholesterol test compared with controls.

*Cancer screening*

After adjusting for history of mastectomy (*n*=885), comorbid disease and death, breast cancer survivors were 22% less likely to receive a mammogram as indicated by the national screening programme compared to their matched controls (Table 3.7). There was no difference in the receipt of mammography between female colorectal cancer survivors and matched controls. Breast cancer survivors in each age group were more likely than controls to have a cervical smear according to screening guidelines. There was no evidence for a difference in the utilization of cervical smear amongst female colorectal cancer survivors compared to controls. Because some women receiving mammography or cervical smear may have received screening just before or after the period of analysis, I conducted a sensitivity analysis allowing for a 3 month interval before and after the period of interest. The results were similar, and therefore are not presented.

Colorectal cancer survivors were 19% more likely to have had a PSA test compared with controls. There was no evidence for a difference in screening behaviours amongst cancer survivors who died during the analysis period.

*Preventive care*

Each group of cancer survivors was more likely to receive bone density scanning than their matched controls (Table 3.7). Additionally, cancer survivors over 65 were more likely to receive an influenza vaccination. In contrast, there were small differences in cholesterol testing between cancer survivors and their matched controls. Although colorectal cancer survivors were almost as likely to receive a blood pressure test as their matched controls, both breast and prostate cancer survivors were less likely to receive a blood pressure test. Increasing number of primary care visits was the strongest predictor of preventive care delivery.

**Table 3.7: Adjusted odds ratios for receipt of screening and preventive care**

| | Breast cancer | | Colorectal cancer | | Prostate cancer | |
|---|---|---|---|---|---|---|
| **Screening** | | | | | | |
| | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| Mammogram | 0.78 | 0.66-0.92 | 1.11 | 0.77-1.61 | - | |
| Cervical smear | | | | | - | |
| Aged 25-49 | 1.37 | 1.11-1.68 | 0.66 | 0.21-2.15 | - | |
| Aged 50-64 | 1.14 | 1.03-1.25 | 1.13 | 0.72-1.75 | - | |
| PSA testing | - | - | 1.19 | 1.06-1.34 | - | |
| **Preventive care** | | | | | | |
| Influenza vaccination | 1.15 | 1.07-1.23 | 1.15 | 1.03-1.28 | 1.39 | 1.22 - 1.59 |
| Blood pressure test | 0.81 | 0.74-0.87 | 0.97 | 0.81-1.17 | 0.70 | 0.57-0.87 |
| Bone density scan | 1.26 | 1.10-1.44 | 1.23 | 1.05-1.43 | 1.59 | 1.23-2.06 |
| Cholesterol testing | 0.93 | 0.87-1.00 | 1.01 | 0.85-1.18 | 0.83 | 0.69 - 1.01 |

This set of work was written up as a paper and published in the British Journal of Cancer (47). Please see Appendix 4 for a copy of the published paper.

### 3.3.3 Management and monitoring of chronic diseases

This analysis was conducted on 15800 hypertensive patients, 1346 diabetic patients, 1066 patients with a history of cerebrovascular disease (stroke or TIA), and 3154 patients with a

history of coronary artery disease (Table 3.8). The cancer survivors and corresponding controls were balanced on the basis of age, but a significantly higher proportion of all cancer survivors died during the main follow-up period. The majority of patients in this study had only one of the chronic diseases indicating monitoring (*n*=17254, 89.7%), however, a small proportion of patients (*n*= 1974, 10.3%) had more than one of the chronic conditions under investigation.

**Table 3.8: Patient characteristics for monitoring and disease management analyses**

| | Breast | | Colorectal | | Prostate | |
|---|---|---|---|---|---|---|
| | Survivors | Controls | Survivors | Controls | Survivors | Controls |
| History of hypertension | | | | | | |
| Number of patients | 4624 | 4624 | 1732 | 1732 | 1544 | 1544 |
| % patients who died | 14.7% | 2.6% | 18.2% | 3.2% | 25% | 5.1% |
| Age in 2003 | 73.7 | 73.7 | 77.1 | 77.1 | 77.0 | 77.0 |
| Years from diagnosis | 11.4 | - | 10.8 | - | 5.9 | - |
| History of diabetes | | | | | | |
| Number of patients | 334 | 334 | 167 | 167 | 172 | 172 |
| % patients who died | 20.1% | 3.6% | 23.4% | 5.9% | 27.9% | 6.9% |
| Age in 2003 | 73.3 | 73.3 | 75.7 | 75.7 | 76.3 | 76.3 |
| Years from diagnosis | 10.4 | - | 10.5 | - | 5.6 | - |
| History of coronary artery disease/MI | | | | | | |
| Number of patients | 499 | 499 | 478 | 478 | 600 | 600 |
| % patients who died | 25.2% | 7.4% | 24.5% | 8.8% | 27.3% | 6.2% |
| Age in 2003 | 78.9 | 78.9 | 79.0 | 79.0 | 78.1 | 78.0 |
| Years from diagnosis | 12.4 | - | 10.6 | - | 6.4 | - |
| History of cerebrovascular disease (e.g. stroke or TIA) | | | | | | |
| Number of patients | 229 | 229 | 156 | 156 | 148 | 148 |
| % patients who died | 34.5% | 10.5% | 33.3% | 11.5% | 39.2% | 15.5% |
| Age in 2003 | 81.5 | 81.5 | 81.6 | 81.5 | 80.8 | 80.8 |
| Years from diagnosis | 12.9 | | 11.1 | | 6.2 | |

*Proportion of patients receiving monitoring*

Firstly, I examined the proportion of individuals who received at least one monitoring test over the three year period (Table 3.9). Almost all cancer survivors were significantly less likely to receive any monitoring tests. However, compared to the control population, a

considerably higher proportion of cancer survivors died during the study period. Because patients at the end of life may receive different levels of disease monitoring, I also considered the receipt of monitoring amongst matched pairs when neither the case nor the control died during the analysis window (Table 3.10). After excluding individuals who died, all cancer survivors and controls received at least the same level of disease monitoring.

**Table 3.9: Proportion of all patients receiving a monitoring test**

| | Blood pressure | | Total cholesterol | | | HbA1c |
|---|---|---|---|---|---|---|
| | History of hypertension | History of diabetes | History of CAD/MI | History of diabetes | History of cerebrovascular disease | History of diabetes |
| Breast | | | | | | |
| Survivors | 91.6%* | 90.7%* | 78.6%* | 84.4%* | 62.4%* | 86.2% |
| 95% CI | 90.8-92.4% | 87.1-93.6% | 74.7-82.0% | 80.0-88.1% | 55.8-68.7% | 82.1-89.7% |
| Controls | 95.2% | 95.2% | 86.9% | 91.0% | 81.7% | 88.9% |
| 95% CI | 94.5-95.8% | 92.3-97.2% | 83.7-89.8% | 87.4-93.9% | 76.0-86.4% | 85.1-92.1% |
| Colorectal | | | | | | |
| Survivors | 91.8%* | 89.8% | 79.1%* | 79.6%* | 66.0%* | 83.2% |
| 95% CI | 90.4-93.1% | 84.2-93.9% | 75.2-82.6% | 72.7-85.4% | 58.0-73.4% | 76.7-88.6% |
| Controls | 95.4% | 92.2% | 87.5% | 89.8% | 80.7% | 87.4% |
| 95% CI | 94.3-96.4% | 87.0-95.8% | 84.1-90.2% | 84.2-93.9% | 73.7-86.6% | 81.4-92.0% |
| Prostate | | | | | | |
| Survivors | 88.9%* | 86.6%* | 79.2%* | 79.7%* | 64.2%* | 80.2%* |
| 95% CI | 87.2-90.4% | 80.6-91.3% | 75.7-82.3% | 72.9-85.4% | 55.4-71.5% | 73.5-85.9% |
| Controls | 93.4% | 94.2% | 88.7% | 89.5% | 78.4% | 90.1% |
| 95% CI | 92.0-94.6% | 89.6-97.2% | 85.8-91.1% | 83.9-93.7% | 70.9-84.7% | 84.6-94.1% |

*$p<0.05$ for univariate $X^2$ comparison between cancer survivors and controls

I explored all associations further in conditional multivariate models accounting for the matched groups. After adjusting for the matching, number of consultations, Charlson comorbidity score, BMI and death, there were no significant differences between any cancer survivors and controls in the odds of receiving chronic disease monitoring. There was no formal evidence for an interaction between death and delivery of care, however, the numbers of patients who died and had a chronic disease was small in each separate analysis.

**Table 3.10: Proportion of all patients receiving a monitoring test, excluding patients who died**

| | Blood pressure | | Total cholesterol | | | HbA1c |
|---|---|---|---|---|---|---|
| | History of hypertension | History of diabetes | History of CAD/MI | History of diabetes | History of cerebrovascular disease | History of diabetes |
| Breast | | | | | | |
| Survivors | 93.3% | 94.7% | 89.0% | 90.5% | 76.0% | 91.3% |
| 95% CI | 92.5-94.1% | 91.2-97.7% | 85.3-91.9% | 86.3-93.8% | 68.3-82.7% | 87.2-94.4% |
| Controls | 94.8% | 95.8% | 89.5% | 92.1% | 84.2% | 88.6% |
| 95% CI | 94.1-95.5% | 92.7-97.9% | 85.9-92.4% | 88.1-95.0% | 77.3-89.7% | 84.1-92.2% |
| Colorectal | | | | | | |
| Survivors | 93.9% | 93.5% | 86.2% | 84.7% | 74.7% | 86.3% |
| 95% CI | 92.5-95.1% | 87.7-97.2% | 82.2-89.6% | 77.1-90.5% | 65.2-82.8% | 78.9-91.8% |
| Controls | 95.3% | 91.9% | 90.1% | 89.5% | 85.4% | 88.7% |
| 95% CI | 94.1-96.4% | 85.7-96.1% | 86.6-93.0% | 82.7-94.3% | 77.1-91.6% | 81.8-93.7% |
| Prostate | | | | | | |
| Survivors | 92.5% | 90.2% | 88.7% | 86.9% | 77.0% | 83.7% |
| 95% CI | 90.8-93.9% | 83.6-94.9% | 85.3-91.5% | 79.7-92.4% | 66.8-85.4% | 76.0-89.8% |
| Controls | 92.1% | 93.5% | 89.6% | 86.9% | 79.3% | 86.9% |
| 95% CI | 90.3-93.6% | 87.6-97.2% | 86.3-92.3% | 79.7-92.4% | 69.3-87.3% | 79.7-92.4% |

*Control of disease*

To investigate disease control, I compared the proportion of quarterly periods when cancer survivors and controls had test readings in the adequate control range. The univariate analysis shows that most cancer survivors had similar adherence to the QOF clinical indicators for blood pressure, cholesterol and glycosylated haemoglobin levels compared to controls (Table 3.11). However, there were two exceptions; diabetic colorectal cancer survivors had significantly fewer quarterly periods with HbA1c levels within the control range, and diabetic prostate cancer survivors had significantly fewer periods with a total cholesterol reading under 5 mmol/L. These associations persisted after adjusting for the matching and covariates; diabetic prostate cancer survivors had a 17% (95% CI 7-26%) reduction in the proportion of cholesterol readings in the control range compared to matched controls. Colorectal cancer survivors also had a lower proportion of controlled HbA1c readings (12% reduction, 95% CI 2-23%). There was no evidence for effect modification for differential control of disease amongst patients who died within the study period.

**Table 3.11: Proportion of calendar quarters with adequate control of disease**

| | Blood pressure | | Total cholesterol | | | HbA1c |
|---|---|---|---|---|---|---|
| | History of hypertension | History of diabetes | History of CAD/MI | History of diabetes | History of Cerebrovas-cular disease | History of diabetes |
| Breast | | | | | | |
| Survivor | 69.0% | 62.8% | 58.3% | 64.2% | 50.2% | 69.6% |
| 95% CI | 68.1-70.1% | 58.9-66.6% | 54.1-62.6% | 59.7-68.8% | 43.0-57.4% | 59.6-68.7% |
| Control | 68.1% | 57.9%% | 56.5% | 70.4% | 49.5% | 64.1% |
| 95% CI | 67.2-69.1% | 54.1-61.8% | 52.6-60.6% | 66.1-74.6% | 43.2-55.8% | 59.6-68.7% |
| Colorectal | | | | | | |
| Survivor | 69.6% | 63.7% | 74.4% | 75.3% | 65.4% | 63.7%* |
| 95% CI | 67.9-71.3% | 57.7-69.7% | 70.6-78.2% | 69.1-81.6% | 57.4-73.5% | 57.2-70.4% |
| Control | 68.3% | 63.6% | 73.1% | 78.6% | 69.4% | 73.3% |
| 95% CI | 66.7-69.9% | 57.9-62.3% | 69.3-76.8% | 73.0-84.1% | 62.3-76.4 | 67.7-78.9% |
| Prostate | | | | | | |
| Survivor | 74.4% | 67.9% | 78.0% | 74.6%* | 66.7% | 72.5% |
| 95% CI | 72.7-76.1% | 61.7-74.0% | 74.7-81.3% | 68.2-80.9% | 58.1-75.4% | 66.0-79.1% |
| Control | 72.8% | 65.1% | 81.5% | 83.7% | 76.9% | 68.5% |
| 95% CI | 71.1-74.5% | 59.7-70.5% | 78.7-84.2% | 78.6-88.7% | 70.4-83.3% | 62.1-74.9% |

*$p<0.05$ for univariate $X^2$ comparison between cancer survivors and controls

This set of work was written up as a paper and published in the Annals of Family Medicine (48). Please see Appendix 5 for a copy of the published paper.

## 3.3.4 Prescribing for antidepressants and anxiolytics

*Prescribing for antidepressants*

The proportion of cancer survivors and controls receiving at least one prescription for an antidepressant during the main follow-up period is shown in Table 3.12.

**Table 3.12: Prescribing for antidepressants and anxiolytic drugs, 2003-2006**

| | **Prescribed an antidepressant at least once between 2003-06** | | **Prescribed an anxiolytic at least once between 2003-06** | |
|---|---|---|---|---|
| | Yes | No | Yes | No |
| Breast | | | | |
| Survivor | 4007 (23.7%) | 12931 (76.3%) | 1531 (9.0%) | 15407 (91.0%) |
| Control | 13681 (20.2%) | 53968 (79.8%) | 5194 (7.7%) | 62455 (92.3%) |
| Colorectal | | | | |
| Survivor | 874 (17.3%) | 4194 (82.8%) | 333 (6.6%) | 4735 (93.4%) |
| Control | 3166 (15.7%) | 16962 (84.3%) | 1122 (5.6%) | 19066 (94.4%) |
| Prostate | | | | |
| Survivor | 757 (18.0%) | 3450 (82.0%) | 235 (5.6%) | 3972 (94.4%) |
| Control | 1823 (10.9%) | 14866 (89.1%) | 713 (4.3%) | 15996 (95.7%) |

After adjusting for Charlson score, death, number of consultations and stratifying on matched groups, both breast cancer survivors (adjusted OR 1.16, 95% CI 1.11-1.22) and prostate cancer survivors (adjusted OR 1.31, 95% CI 1.17-1.47) were more likely to receive at least one prescription for an antidepressant compared to matched controls. There was no evidence for a statistical difference in the likelihood of being prescribed an antidepressant amongst

colorectal cancer survivors. There was a positive trend between increasing number of consultations and the odds of receiving an antidepressant (Table 3.13).

**Table 3.13: Adjusted odds ratios and 95% CI for odds for being prescribed an antidepressant**

| | Breast | | Colorectal | | Prostate | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| Cancer status | | | | | | |
| Control | 1 | | | | | |
| Cancer survivor | 1.16 | 1.11-1.22 | 1.07 | 0.96-1.18 | 1.31 | 1.17-1.47 |
| Charlson category | | | | | | |
| 0 | 1 | | | | | |
| 1 | 1.10 | 1.04-1.16 | 1.13 | 1.01-1.26 | 1.16 | 1.01-1.34 |
| 2 | 1.13 | 1.04-1.22 | 1.17 | 1.02-1.35 | 1.48 | 1.26-1.75 |
| 3 | 1.10 | 0.99-1.22 | 1.13 | 0.95-1.34 | 1.28 | 1.04-1.56 |
| 4 | 1.12 | 0.96-1.29 | 1.37 | 1.08-1.72 | 1.40 | 1.09-1.81 |
| 5 or more | 1.17 | 1.03-1.34 | 1.03 | 0.82-1.29 | 1.28 | 1.00-1.64 |
| Number of consultations | | | | | | |
| 0-6 | 1 | | | | | |
| 7-14 | 2.74 | 2.50-3.00 | 2.53 | 2.07-3.09 | 2.28 | 1.81-2.87 |
| 15-25 | 5.43 | 4.94-5.96 | 4.42 | 3.59-5.44 | 3.40 | 2.67-4.32 |
| 26-35 | 8.83 | 7.97-9.79 | 7.13 | 5.71-8.90 | 6.39 | 4.94-8.25 |
| 36 and over | 15.98 | 14.39-17.74 | 12.44 | 9.96-15.55 | 9.06 | 6.99-11.74 |
| BMI | | | | | | |
| Underweight | 1 | | | | | |
| Normal | 0.86 | 0.77-0.97 | 1.21 | 0.96-1.53 | 0.73 | 0.52-1.01 |
| Overweight | 0.86 | 0.76-0.96 | 1.13 | 0.89-1.43 | 0.67 | 0.48-0.94 |
| Obese | 0.88 | 0.78-0.99 | 1.19 | 0.93-1.52 | 0.74 | 0.52-1.06 |
| Died during follow-up | | | | | | |
| No | 1 | | | | | |
| Yes | 1.40 | 1.22-1.60 | 1.63 | 1.30-2.04 | 1.60 | 1.30-1.98 |

There was evidence for an interaction between increased defined daily doses of anti-depressants and death; cancer survivors who died had substantially more doses than cancer survivors who did not die. I conducted a subgroup analysis which showed that both breast cancer survivors who survived (IRR 1.15, 95% CI 1.10-1.19), and breast cancer survivors who died (IRR 2.00, 95% CI 1.61 - 2.48) received significantly more doses of antidepressants (as defined by DDDs) than their respectively matched controls. Similarly, prostate cancer survivors who remained alive throughout the analysis period (IRR 1.29, 95% CI 1.16-1.43) and prostate cancer survivors who died (IRR 2.80, 95% CI 2.07-3.78) received more antidepressants than matched controls.

Differences in defined daily doses amongst cancer survivors may be due to increased dosage. I considered prescribing for fluoxetine and tested whether cancer survivors received more pills compared to controls as a proxy for differences in dosage. There were significant differences between the number of pills prescribed to breast cancer survivors compared to controls (31 pills vs. 28, $p<0.0001$) and between prostate survivors and controls (28 pills vs. 25, $p< 0.0001$) within patients who received a monthly prescription.

*Prescribing for anxiolytics*

The majority of cancer survivors and controls did not receive an anxiolytic during the follow-up period (Table 3.11). After adjusting for matching and covariates, there was no evidence for a difference in anxiolytic prescribing between colorectal or prostate cancer survivors and their matched controls. In contrast, breast cancer survivors were slightly more likely to receive a prescription for an anxiolytic (adjusted OR 1.09, 95% CI 1.02-1.18) than matched

controls (Table 3.14). There was no evidence for interactions between receipt of anxiolytics and death. The strongest predictor of receipt of anxiolytics was an increasing number of consultations.

**Table 3.14: Adjusted odds ratios and 95% CI for odds for being prescribed an anxiolytic**

| | Breast | | Colorectal | | Prostate | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| Cancer status | | | | | | |
| Control | 1 | | | | | |
| Cancer survivor | 1.09 | 1.02-1.18 | 0.96 | 0.81-1.12 | 0.87 | 0.72-1.06 |
| Charlson category | | | | | | |
| 0 | 1 | | | | | |
| 1 | 1.04 | 0.96-1.13 | 1.04 | 0.87-1.25 | 0.92 | 0.74-1.15 |
| 2 | 0.99 | 0.88-1.10 | 1.31 | 1.05-1.63 | 1.00 | 0.77-1.29 |
| 3 | 0.82 | 0.70-0.96 | 0.85 | 0.64-1.14 | 0.76 | 0.55-1.04 |
| 4 | 0.86 | 0.69-1.07 | 0.99 | 0.67-1.45 | 0.87 | 0.58-1.20 |
| 5 or more | 1.01 | 0.83-1.21 | 1.03 | 0.82-1.45 | 0.83 | 0.57-1.21 |
| Number of consultations | | | | | | |
| 0-6 | 1 | | | | | |
| 7-14 | 2.42 | 2.10-2.80 | 2.75 | 1.93-3.93 | 2.67 | 1.82-3.94 |
| 15-25 | 4.64 | 4.01-5.37 | 4.86 | 3.41-6.96 | 4.21 | 2.82-6.28 |
| 26-35 | 7.07 | 6.05-8.26 | 8.52 | 5.85-12.42 | 9.05 | 5.92-13.84 |
| 36 and over | 13.49 | 11.53-15.78 | 14.11 | 9.72-20.49 | 11.49 | 7.52-17.56 |
| BMI | | | | | | |
| Underweight | 1 | | | | | |
| Normal | 0.69 | 0.59-0.81 | 1.04 | 0.74-1.48 | 1.24 | 0.75-2.04 |
| Overweight | 0.65 | 0.56-0.77 | 0.93 | 0.65-1.33 | 1.00 | 0.61-1.66 |
| Obese | 0.56 | 0.47-0.66 | 0.84 | 0.58-1.22 | 0.88 | 0.51-1.52 |
| Died during follow-up | | | | | | |
| No | 1 | | | | | |
| Yes | 1.83 | 1.52-2.20 | 2.03 | 1.45-2.86 | 1.99 | 1.46-2.72 |

There was a small but significant difference between the number of defined daily doses for anxiolytics between breast cancer survivors and their matched controls (IRR 1.09, 95% CI 1.02-1.16) and strong evidence for an interaction by death. While breast cancer survivors who survived past the end of the follow-up period had the same anxiolytic prescribing behaviours as matched controls (IRR 1.04, 95% CI 0.97-1.12), breast cancer survivors who died had an 84% increase in prescribed defined daily doses (IRR 1.84, 95% 1.36-2.49).

Along with the analysis on consultation patterns for depression and anxiety (section 3.3.1), this set of work was written up as a paper and published in the European Journal of Cancer (49). Please see Appendix 6 for a copy of the published paper.

### 3.3.5 Prescribing for pain relief

All groups of cancer survivors were slightly more likely to have received a prescription for any analgesic between 2003-2006 (Table 3.15).

**Table 3.15: Proportion of breast, colorectal and prostate cancer survivors and controls receiving at least one prescription for an analgesic, 2003-06**

| | Breast | | Colorectal | | Prostate | |
|---|---|---|---|---|---|---|
| | Survivor | Control | Survivor | Control | Survivor | Control |
| Didn't receive a prescription from 2003-06 | 14964 | 60521 | 4437 | 17864 | 3695 | 15083 |
| % | 88.4% | 89.5% | 87.6% | 88.8% | 87.8% | 90.3% |
| Received a prescription from 2003-06 | 1974 | 7128 | 631 | 2263 | 512 | 1626 |
| % | 11.6% | 10.5% | 12.5% | 11.2% | 12.2% | 9.7% |
| Total | 16938 | 67649 | 5068 | 20127 | 4207 | 16709 |

Univariate, conditional logistic regression models showed that breast (OR 1.12, 95% CI 1.06-1.18), colorectal (OR 1.12, 95% CI 1.02-1.24) and prostate (OR 1.28, 95% CI 1.15-1.42) cancer survivors were also statistically more likely to have received a prescription for an analgesic between 2003-2006 compared to their matched controls.

I explored these associations further in multivariate models. Only colorectal cancer survivors demonstrated an increase in the odds of prescription for an analgesic. The strongest predictor for receipt of an analgesic across all groups was increasing number of consultations (Table 3.16).

**Table 3.16: Adjusted odds ratios and 95% CI for odds for being prescribed an analgesic**

| | Breast | | Colorectal | | Prostate | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| Cancer status | | | | | | |
| Control | 1 | | | | | |
| Cancer survivor | 1.13 | 0.98-1.32 | 1.35 | 1.04-1.75 | 1.22 | 0.90-1.66 |
| Charlson category | | | | | | |
| 0 | 1 | | | | | |
| 1 | 1.27 | 1.08-1.49 | 0.81 | 0.61-1.08 | 1.28 | 0.93-1.76 |
| 2 | 1.27 | 1.00-1.61 | 1.14 | 0.78-1.67 | 1.41 | 0.93-2.13 |
| 3 | 1.31 | 0.93-1.83 | 1.32 | 0.83-2.09 | 0.97 | 0.60-1.57 |
| 4 | 1.27 | 0.76-2.13 | 1.54 | 0.77-3.08 | 1.56 | 0.84-2.91 |
| 5 or more | 1.47 | 0.94-2.28 | 1.01 | 0.55-1.88 | 2.00 | 0.95-4.18 |
| Number of consultations | | | | | | |
| 0-6 | 1 | | | | | |
| 7-14 | 2.91 | 2.30-3.68 | 2.07 | 1.39-3.06 | 4.02 | 2.43-6.65 |
| 15-25 | 5.80 | 4.52-7.44 | 3.20 | 2.13-4.81 | 7.52 | 4.42-12.78 |
| 26-35 | 10.16 | 7.64-13.52 | 6.94 | 4.35-11.06 | 16.37 | 8.77-30.56 |
| 36 and over | 23.59 | 17.31-32.13 | 13.48 | 8.03-22.63 | 29.17 | 15.21-55.97 |
| Died during follow-up? | | | | | | |
| No | 1 | | | | | |
| Yes | 3.05 | 1.84-5.07 | 1.73 | 0.89-3.37 | 1.25 | 0.65-2.41 |

Because cancer survivors at the end of life may be more likely to receive a prescription for pain medication, I included an interaction term to investigate whether those cancer survivors who died during follow-up had higher odds of receipt of analgesics. There was no evidence for an interaction by death amongst any of the groups of cancer survivors.

*Volume of prescribing for analgesia*

Next, I considered the number of prescriptions issued during the follow-up period, as described by WHO defined daily doses (DDDs). The univariate analysis showed an increase in the number of analgesia prescriptions issued to all groups of cancer survivors; breast cancer survivors received 33% more DDDs (IRR 1.33, 95% CI 1.24-1.43), colorectal cancer survivors received 40% more DDDs (IRR 1.40, 1.24-1.59) and prostate cancer survivors received 80% more DDDs (IRR 1.80, 95% 1.56-2.09) than the age and practice matched control group.

I explored associations further in multivariate models taking comorbidity, number of consultations into account, as well as an indicator for whether or not the patients died during the analysis period (Table 3.17). All cancer survivors received a significantly higher number of prescriptions, defined as DDDs, for analgesics compared to the matched control population. The strongest predictor for number of pain medication prescriptions was increasing number of consultations over the three year period. There was no evidence for effect modification by death.

**Table 3.17: Adjusted incidence rate ratios and 95% CI for number of analgesics prescribed between 2003 and 2006**

| | Breast | | Colorectal | | Prostate | |
|---|---|---|---|---|---|---|
| | IRR | 95% CI | IRR | 95% CI | IRR | 95% CI |
| Cancer status | | | | | | |
| Control | 1 | | | | | |
| Cancer survivor | 1.15 | 1.06-1.25 | 1.31 | 1.13-1.52 | 1.29 | 1.09-1.54 |
| Charlson category | | | | | | |
| 0 | 1 | | | | | |
| 1 | 1.28 | 1.18-1.40 | 0.99 | 0.84-1.16 | 1.24 | 1.02-1.50 |
| 2 | 1.33 | 1.18-1.49 | 1.30 | 1.07-1.59 | 1.24 | 0.99-1.56 |
| 3 | 1.26 | 1.08-1.47 | 1.36 | 1.06-1.73 | 1.03 | 0.78-1.36 |
| 4 | 1.35 | 1.08-1.70 | 1.31 | 0.94-1.84 | 1.36 | 0.97-1.90 |
| 5 or more | 1.45 | 1.19-1.77 | 1.32 | 0.97-1.80 | 1.43 | 1.02-2.02 |
| Number of consultations | | | | | | |
| 0-6 | 1 | | | | | |
| 7-14 | 2.07 | 1.77-2.42 | 1.75 | 1.35-2.25 | 2.78 | 1.99-3.88 |
| 15-25 | 3.17 | 2.72-3.70 | 1.95 | 1.52-2.50 | 3.34 | 2.38-4.67 |
| 26-35 | 4.27 | 3.62-5.03 | 3.23 | 2.46-4.23 | 5.12 | 3.57-7.34 |
| 36 and over | 6.47 | 5.50-7.62 | 4.40 | 3.36-5.75 | 5.94 | 4.14-8.53 |
| Died during follow-up? | | | | | | |
| No | 1 | | | | | |
| Yes | 2.63 | 2.18-3.15 | 1.94 | 1.45-2.59 | 1.70 | 1.27-2.28 |

*Level of pain relief*

In order to assess whether or not cancer survivors in this cohort were more likely to receive stronger pain relief than controls, I compared the proportion of individuals receiving analgesia at step 1, 2 and 3 of the WHO pain ladder (Table 3.18). All differences reached significance but absolute numbers using step 3 drugs were small. The most pronounced difference was amongst the prostate cancer survivors compared to controls and also compared to breast and colorectal survivors.

**Table 3.18: Highest step of pain relief used, 2003 to 2006**

| | Breast | | Colorectal | | Prostate | |
|---|---|---|---|---|---|---|
| | Survivor | Control | Survivor | Control | Survivor | Control |
| Step 1 | 314 | 1266 | 138 | 494 | 97 | 432 |
| | 1.9% | 1.9% | 2.7% | 2.5% | 2.3% | 2.6% |
| Step 2 | 1421 | 5515 | 422 | 1667 | 317 | 1122 |
| | 8.4% | 8.2% | 8.3% | 8.3% | 7.5% | 6.7% |
| Step 3 | 239 | 347 | 71 | 103 | 98 | 72 |
| | 1.4% | 0.5% | 1.4% | 0.5% | 2.3% | 0.4% |
| No pain relief | 14964 | 60521 | 4437 | 17864 | 3695 | 15083 |
| prescribed | 88.4% | 89.5% | 87.6% | 88.8% | 87.8% | 90.3% |
| **Total** | **16938** | **67649** | **5068** | **20128** | **4207** | **16709** |

I considered the odds of receiving a step 3 analgesic in matched, conditional logistic models. Breast (OR 2.76, 95% CI 2.35-3.27), colorectal (OR 2.78, 95% CI 2.04-3.77) and prostate (5.42, 95% CI 4.00-7.37) cancer survivors were all significantly more likely to have received at least one prescription for a step 3 analgesic during the follow-up period. However, the

absolute number of patients receiving step 3 pain relief was small, therefore, it is difficult to make any broad conclusions about strength of analgesic prescribing in this cohort.

### 3.3.6 Prescribing for erectile dysfunction therapies

*Receipt of erectile dysfunction therapies*

The vast majority of men in the GPRD did not receive a prescription for an erectile dysfunction (ED) treatment during the follow-up period, however, both prostate and colorectal cancer survivors were significantly more likely to have received at least one prescription for an erectile dysfunction drug compared to controls (Table 3.19). Sildenafil was the most commonly prescribed treatment, comprising 68.8% of all ED therapies in this cohort.

**Table 3.19: Proportion of patients receiving at least one prescription for an erectile dysfunction therapy, 2003-2006**

| | Colorectal | | Prostate | |
|---|---|---|---|---|
| | Survivor | Control | Survivor | Control |
| Received at least one ED prescription | 186 | 507 | 296 | 720 |
| % | 7.2% | 5.0% | 7.0% | 4.3% |
| Did not receive an ED prescription | 2,383 | 9,671 | 3,912 | 15,989 |
| % | 92.8% | 95.0% | 93.0% | 95.7% |
| Total | 2,569 | 10,178 | 4,208 | 16,709 |

This difference persisted in the univariate conditional regression analyses which accounted for the matched groups. Colorectal cancer survivors were 53% more likely (OR 1.53, 95% CI 1.28-1.83) and prostate cancer survivors were 73% more likely (OR 1.73, 95% CI 1.50-2.00) to have received a prescription for an erectile dysfunction treatment.

In order to take into account other factors such as comorbidity, weight, and consultations in primary care, I conducted a multivariate analysis adjusting for these variables. Colorectal and prostate cancer survivors were still significantly more likely to have received at least one prescription for an ED drug from 2003-2006 even after adjustment for other covariates (Table 3.20). Colorectal cancer survivors were 38% (adjusted OR 1.38, 95% CI 1.13-1.68) and prostate cancer survivors 56% (adjusted OR 1.56, 95% CI 1.33-1.82) more likely to have received a prescription for an erectile dysfunction therapy than their matched controls. Increasing number of consultations was the strongest predictor of prescribing, while there was a trend of lower odds for receipt of ED drugs with an increasing number of comorbidities.

*Number of prescriptions for erectile dysfunction therapies*

I considered prescribing for erectile dysfunction therapies using a matched analysis to compare the rate of DDDs prescribed. The univariate, matched results show that cancer survivors had a higher volume of prescriptions for erectile dysfunction therapies compared to the control population, with colorectal cancer survivors accessing 62% more doses (IRR 1.62, 95% CI 1.36-1.91) and prostate cancer survivors using 86% (IRR 1.86, 95% CI 1.65-2.13) more erectile dysfunction therapies than the matched control group.

**Table 3.20: Adjusted odds ratios and 95% CI for receipt of at least one prescription for an erectile dysfunction therapy amongst colorectal and prostate cancer survivors**

| | Colorectal | | Prostate | |
|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI |
| Cancer status | | | | |
| Control | 1.00 | | 1.00 | |
| Cancer survivor | 1.38 | 1.13-1.68 | 1.56 | 1.33-1.82 |
| Charlson index | | | | |
| 0 | 1.00 | | 1.00 | |
| 1 | 0.89 | 0.70-1.13 | 1.07 | 0.89-1.30 |
| 2 | 1.01 | 0.74-1.39 | 1.03 | 0.81-1.33 |
| 3 | 0.96 | 0.63-1.44 | 1.00 | 0.72-1.38 |
| 4 | 0.86 | 0.49-1.51 | 0.60 | 0.37-0.98 |
| 5 or more | 0.74 | 0.42-1.28 | 0.71 | 0.45-1.12 |
| BMI groups | | | | |
| Underweight | 1.00 | | 1.00 | |
| Normal weight | 3.41 | 1.01-11.48 | 2.88 | 1.22-6.80 |
| Overweight | 3.51 | 1.05-11.77 | 3.70 | 1.57-8.73 |
| Obese | 3.68 | 1.08-12.50 | 3.14 | 1.32-7.50 |
| Consultations | | | | |
| 0 to 6 | 1.00 | | 1.00 | |
| 7 to 14 | 2.19 | 1.52-3.16 | 1.78 | 1.34-2.36 |
| 15 to 25 | 2.92 | 2.01-4.25 | 2.93 | 2.16-3.98 |
| 26 to 35 | 4.57 | 3.02-6.93 | 3.21 | 2.27-4.55 |
| 36 and over | 4.55 | 2.96-6.98 | 2.85 | 1.99-4.08 |

*Multivariate analysis*

I explored the differences in volume for prescribing for erectile dysfunction further in multivariate models taking comorbidity, weight, and the number of consultations in primary care into account (Table 3.21). Prostate and colorectal cancer survivors received a significantly higher volume of prescriptions, as demonstrated by number of defined daily doses, for erectile dysfunction therapies even after adjustment for covariates.

**Table 3.21: Adjusted incidence rate ratios and 95% CIs for the number of defined daily doses of an erectile dysfunction therapy amongst colorectal and prostate cancer survivors**

| | Colorectal | | Prostate | |
|---|---|---|---|---|
| | IRR | 95% CI | IRR | 95% CI |
| Cancer status | | | | |
| Control | 1.00 | | 1.00 | |
| Cancer survivor | 1.46 | 1.21-1.76 | 1.66 | 1.43-1.93 |
| Charlson index | | | | |
| 0 | 1.00 | | 1.00 | |
| 1 | 0.90 | 0.72-1.13 | 1.10 | 0.92-1.31 |
| 2 | 0.99 | 0.74-1.33 | 1.06 | 0.84-1.34 |
| 3 | 0.92 | 0.63-1.34 | 0.98 | 0.72-1.32 |
| 4 | 0.81 | 0.48-1.37 | 0.66 | 0.42-1.05 |
| 5 or more | 0.75 | 0.45-1.27 | 0.78 | 0.51-1.19 |
| BMI groups | | | | |
| Underweight | 1.00 | | 1.00 | |
| Normal weight | 3.00 | 0.92-9.82 | 2.96 | 1.28-6.85 |
| Overweight | 3.18 | 0.98-10.38 | 3.73 | 1.61-8.63 |
| Obese | 3.35 | 1.02-11.01 | 3.38 | 1.45-7.89 |
| Consultations | | | | |
| 0 to 6 | 1.00 | | 1.00 | |
| 7 to 14 | 1.93 | 1.36-2.74 | 1.45 | 1.11-1.90 |
| 15 to 25 | 2.61 | 1.83-3.72 | 2.22 | 1.68-2.94 |
| 26 to 35 | 3.66 | 2.48-5.40 | 2.33 | 1.69-3.20 |
| 36 and over | 3.71 | 2.48-5.53 | 2.02 | 1.45-2.80 |

*Only one prescription for an erectile dysfunction therapy*

I considered whether colorectal or prostate cancer survivors prescribed treatment for erectile dysfunction drugs were more likely to have just one prescription (Table 3.22). Previous research has shown dropout rates of over 50% amongst any modality of erectile dysfunction therapy amongst prostate cancer survivors (50). Our hypothesis in conducting this further test is that cancer survivors may try an erectile dysfunction drug to improve their sexual function, however, the treatment may not work if the cancer survivor has nerve or organ damage due to radiotherapy or surgery. The proportion of patients receiving at least one prescription for erectile dysfunction treatments was similar across the colorectal and prostate cancer survivors when compared to the control population (Table 3.22).

**Table 3.22: Proportion of cancer survivors and controls receiving only one prescription for erectile dysfunction therapy**

| | **Colorectal** | | **Prostate** | |
|---|---|---|---|---|
| | Survivor | Control | Survivor | Control |
| More than 1 prescription for an ED drug | 133 | 329 | 215 | 499 |
| % | 71.5% | 64.9% | 72.6% | 69.3% |
| Only one prescription for an ED drug | 53 | 178 | 81 | 221 |
| % | 28.5% | 35.1% | 27.4% | 30.7% |
| Total | 186 | 507 | 296 | 720 |

* I only included patients who had at least one prescription

Univariate logistic regression also failed to show an association, with colorectal cancer survivors (OR 0.91, 95% CI 0.41-2.07) and prostate cancer survivors (OR 0.93, 95% CI 0.47-

1.82) no more likely to have had only one prescription for an ED drug. These results suggest that cancer survivors are no more likely than controls to only try a prescription for an erectile dysfunction drug once. However, the numbers in this analysis are fairly small, and it is underpowered to find an effect unless there was a large difference between the two groups.

## 3.4 Discussion

### 3.4.1 Main findings

This chapter has described the use of primary care services by long-term survivors through an analysis of the General Practice Research Database. The main aims were to understand the use of primary health care services and any gaps in that care, and to explore whether there were differences in the provision of care between cancer survivors and a representative group of patients without a diagnosis of cancer. The main findings are presented in Box 3.1.

**Box 3.1: Summary of main findings**

- Breast and colorectal cancer survivors have a higher rate of primary care consultations compared to controls until 10 years post-diagnosis, while prostate cancer survivors consult at a higher rate for a more prolonged period
- Long-term cancer survivors do not consult more often for depression or anxiety, but do access more anti-depressants and anxiolytics compared to controls.
- Most cancer survivors receive similar preventive care, screening for other cancers, and management of comorbidities compared to controls, with the exception of mammography for long-term breast cancer survivors.

- Cancer survivors received a higher volume of prescriptions for analgesics and erectile dysfunction than controls, which may be a proxy for continuing pain and sexual dysfunction.

This analysis of consultation rates amongst cancer survivors in the GPRD has shown a significant difference in the number of consultations between survivors and matched controls, with the greatest difference for prostate cancer survivors. While breast and colorectal cancer survivors have higher consultation rates than a control population during the first ten years post-diagnosis, the increase in consultation rates for prostate cancer survivors persists for many years post-diagnosis. There are a variety of reasons why cancer survivors may be consulting at a greater rate compared to controls; however, it is difficult to explore all of the different reasons why patients may consult with their GP without a pre-defined hypothesis. It has been suggested that cancer survivors experience depression and anxiety at a higher rate than the general population. These results suggest that long-term survivors of cancer were no more likely to consult for depression or anxiety related reasons compared to a control population. Psychological services alone are likely not a major contributing factor towards the increased consultation patterns amongst this population. The main predictors for primary care consultations for depression or anxiety were other comorbid diseases (in depression) and history of depression or anxiety, rather than a history of cancer.

In general, most cancer survivors in the UK receive similar primary care based cancer screening and preventive services compared to individuals who have not had cancer. All cancer survivors were more likely to receive influenza vaccination and bone density scans.

However, long-term breast cancer survivors were less likely to receive mammography, and breast and prostate cancer survivors were less likely to receive a blood pressure test.

The analyses on the care of chronic diseases presented in Section 3.3.3 suggests that chronic diseases are well managed in UK primary care; most cancer survivors who are not at the end of life receive the same level of care as non-cancer patients. History of cancer is not associated with poorer management of hypertension, diabetes, cerebrovascular disease or coronary artery disease. Of those who did receive monitoring, disease was generally controlled at the same level in both populations. There seem to be some differences in the receipt of monitoring amongst patients at the end of life, however, there were not enough patients to conduct a formal subgroup analysis in the multivariate models. Changes in disease maintenance strategies are likely to be appropriate in palliative patients.

While the results from section 3.3.1 suggest that most longer-term cancer survivors do not access a GP for depression or anxiety related services at a higher rate than a control population, long-term breast and prostate cancer survivors were more likely to receive at least one prescription for an antidepressant during the analysis period. This was an unexpected finding, and I explored several hypotheses to explain the results. Firstly, it is possible that cancer survivors are more likely to receive long-term and persistent treatment for depression. However, there were no clear differences in rates of repeat prescribing for antidepressants between any of the cancer survivors and control groups. Secondly, it is possible cancer survivors were receiving certain tricyclic drugs for neuropathic pain relief. I conducted a sensitivity analysis to determine whether removing tricyclic drugs from the analyses would

affect these findings, however, the results were similar whether or not tricyclic prescriptions were included or excluded. The third hypothesis was that long-term cancer survivors receive higher dosages of pharmacological interventions for depression and anxiety due to increased severity of depression. When I considered prescribing for fluoxetine, which is administered at a single strength, cancer survivors received a greater number of doses compared to controls, which supports this final hypothesis but is not definitive.

All groups of cancer survivors received a higher volume of pain medication than the matched control population, ranging from 15% more defined daily doses amongst breast cancer survivors to 31% in the colorectal cancer survivors. This set of analyses was conducted as a proxy to assess the burden of long-term pain amongst cancer survivors, as Read coding of pain as a symptom is incomplete within the GPRD.

Previous research has shown that sexual problems after surgery for colorectal cancer are common, inadequately discussed, and untreated (51). This analysis has shown that amongst a large, primary care based cohort, prostate and colorectal cancer survivors are significantly more likely to access pharmaceutical interventions for erectile dysfunction compared to a control population. Additionally, the overall volume of use of erectile dysfunction therapies was up to 66% higher amongst the cancer survivors population.

### 3.4.2 Comparison with other research

There has been little research looking at the primary care consultation patters of cancer survivors. A recent study identified women diagnosed with early stage breast cancer and

found that in the active treatment phase women had twice as many face-to-face contacts with GPs compared to women who had not had breast cancer (median consultation 6.0 per year compared to 3.0 per year, respectively) (52). This study of early breast cancer only considered the phase immediately post-diagnosis, whereas the results from this thesis show consultation rates from two years and more post-diagnosis.

The findings relating to preventive care and monitoring for chronic diseases differ from previous research from the United States which has shown deficiencies in care for long-term cancer survivors (12;15;53). This divergence in quality of care is likely a result of differences in health care delivery in the United States and the United Kingdom. In the US, patients who only saw their oncologist in the long-term received poorer preventive care for other diseases, but those engaged with both primary and secondary care physicians received the best care (12;14;15;20). Earle and colleagues suggested that a lack of clarity of the roles of secondary and primary care in the United States may lead to fragmentation of care, with cancer survivors unclear about where to turn for different aspects of their health care. Long-term cancer survivors in the UK are unlikely to maintain contact with oncologists, and will rely on their GP to provide care for their cancer and other comorbidities following discharge from hospital follow-up. Compared to the United States, the role of primary care in the general health care of cancer survivors in the UK is well defined, and this difference may explain why cancer survivors in this cohort received preventive care and chronic disease management at similar levels to a non-cancer population. Additionally, the introduction of incentives for chronic disease monitoring, universal health care and a clear role for primary care in the UK may play a role in ensuring appropriate provision of chronic disease management in cancer survivors.

The quality of management of chronic diseases in British primary care has been improving steadily since the late 1990s due to the introduction of national initiatives and guidelines for the provision of improved health services (54;55). The launch of the Quality and Outcomes Framework (QOF) in England in 2004 helped to accelerate and standardize clinical performance for many of the indicators included in the incentive programme (56-58). Under QOF, primary care practices can claim financial rewards upon meeting clinical indicators relating to monitoring of ten chronic conditions, including coronary artery disease, stroke, hypertension and diabetes (58). These incentives are likely to play a part in ensuring adequate chronic disease care for cancer survivors.

A recent systematic review found that the majority of long-term cancer survivors experience few psychological problems more than five years post-diagnosis, a finding that is supported by the analyses on consultation patterns for depression and anxiety reported in section 3.3.1 (59). However, certain groups of patients will remain at risk of long-term psychological morbidity. The results on prescribing suggest that cancer survivors at the end of life comprise one of those groups at increased risk of depression and anxiety. Depression is a widely recognized problem in palliative care (60). Depression and anxiety at the end of life are treatable, and primary care is well placed to offer pharmacological interventions to this population. Breast and prostate cancer survivors in these analyses nearing the end of life consistently accessed more prescriptions than other cancer survivors to manage depression and anxiety. Previous research has shown that breast cancer patients at the end of life were more likely to receive prescribed antidepressants than other palliative patients, which corresponds to these results (61;62).

Breast cancer survivors may experience chronic pain as a result of mastectomy (63), lymphoedema or arm swelling (64) and prevalence of chronic pain amongst breast cancer survivors was estimated at 50% amongst women undergoing surgery (65). Prostate cancer survivors are at risk of pain related to late effects of brachytherapy and radiotherapy (66), and colorectal cancer survivors can continue to experience long-term pain related to surgery or pelvic radiotherapy even three years and more post-diagnosis (67). Previous research has shown that repeated surgery, nerve trauma, radiation therapy and chemotherapy predict post-operative pain, however, treatment predictors of pain could not be explored in this analysis (29). However, the results do show that all groups of cancer survivors accessed higher volumes of pain relief, supporting previous research showing the extent of chronic pain even five years or more post-cancer diagnosis.

The majority of long-term sexual difficulties amongst colorectal and prostate cancer survivors are treatment based. However, erectile dysfunction may only appear as late effects years after treatment. For instance, pelvic radiotherapy can cause long-term penile microvessel damage and can lead to a continued decline of sexual function up to five years after initial treatment (68;69). The results presented in section 3.3.6 support the suggestion that even long-term survivors of cancer experience ongoing sexual difficulties relating to their cancer or its treatment.

This chapter looks at the use, and quality of primary care services in a cohort of cancer survivors. Quality of service is a complex construct which can be described in terms of

patient experience of health care delivery from a health care professional, comparisons with quality standards such as the Quality and Outcomes Framework, or patient satisfaction with care which may be distinct from the recommended standard of health care. This chapter has focussed primarily on a database analysis comparing two standards: chronic disease care recommended by the Quality and Outcomes Framework (QOF) and cancer screening recommended by the national cancer screening programmes, with the actual health care delivered to the to the cohort of cancer survivors and controls. However, this measurement of quality of care using the GPRD is unidimensional and may miss important aspects of what is happening on an individual level. There is an important distinction between care that is offered by primary care and care that is taken up or requested by patients. A GP may offer a patient care that is rejected, for instance an influenza vaccination that is not taken up. Conversely, a patient may actively request a blood pressure test. These GP and patient behaviours and preferences will affect the patient's experience of the quality of primary health care service provided or accessed by the cancer survivors considered in this chapter, however, it is not possible to examine these preferences or behaviours using a large anonymised database like the GPRD.

### 3.4.3 Implications for primary care

Half of cancer survivors have healthcare needs relating to ongoing health conditions, which include secondary effects from the disease and its treatment and risk of second cancers (70;71). The early peak in consultation rates in primary care amongst all groups of survivors may reflect the need to address aspects of ongoing physical morbidity related to the cancer. These trends in increased consultation behaviours are impacting on the workload in British

primary care, and this impact will increase as the population of cancer survivors continues to grow. As many as one in six adults over the age of 65 seen by a GP is likely to be a cancer survivor, and a significant proportion of these will be breast, colorectal and prostate survivors (72). A GP with a list size of 2000 patients would provide 60-180 extra consultations per year for all cancer patients, assuming a cancer prevalence of 3% in UK and the extra consultation rate for all cancers mirrors the one to three extra consultations per year of the three cancers in this study.

Second cancers can be detected at an earlier stage when appropriate screening guidelines are being met (73). It is concerning that long-term breast cancer survivors are significantly less likely to receive breast cancer screening than women without a history of breast cancer. Breast cancer survivors are at risk of recurrence and primary cancer in the contralateral breast, therefore, even women who have a unilateral mastectomy should receive regular mammography (74). This is the not the first report of underuse of breast cancer screening; previous research has shown under use of mammography in breast cancer survivors and childhood cancer survivors despite an increased risk of mortality (75-79). Although lack of access to mammographic services contributes to underuse of breast screening in the United States, this is unlikely to explain cancer screening practices in the UK as all eligible women are invited for free breast cancer screening through a national programme.

Prescriptions for pain relief are effective in relieving cancer-related pain, however, previous research has shown that use of analgesics in outpatient cancer services is inadequate (80). Barriers to use of pain medication include patient reluctance to talk to their physicians about

ongoing pain, and physician reluctance to prescribe opiods, or drugs at step 3 of the WHO pain ladder. Pain management is an important issue for the subgroup of cancer survivors who may experience diminished quality of life due to ongoing pain (28). Discussion of these symptoms should be considered as part of any post-treatment survivorship consultations or survivorship care planning within primary care.

It is important that sexual difficulties, especially erectile dysfunction which can be treated effectively, are discussed with survivors of cancer who may be experiencing these issues in the long-term. GPs should ensure that these therapies are offered to long-term survivors, who may not be aware that therapies such as sildenafil can be beneficial. Previous research has shown that it is important to encourage men who fail a first line treatment to try methods such as injectable treatments or penile prostheses; in a study of prostate cancer survivors those who had tried a greater number of treatments achieved higher scores on erectile function measures (50). Padma-Nathan published an example of a step-wise treatment algorithm beginning with first-line therapy including oral medications, vacuum device therapy and psychosexual therapy either alone or in combination, moving to second-line therapy involving penile injection and intraurethral therapy and finally a third-line approach of penile prosthesis (81). The main goal of the step-wise algorithm is to encourage people who do not find sildenafil effective to try alternative approaches to improve their sexual function.

### 3.4.4 Strengths and limitations

The strengths of this study include the large number of cancer survivors and controls, and the representative nature of the population. Some of the limitations of this research are common

to other studies using large administrative databases. Firstly, because patient records were not primarily collected for research purposes, it is possible that some tests and diagnoses were not accurately or fully recorded. Additionally, some procedures may have occurred outside of primary care and may not be recorded on the patient primary care record. For instance, it is possible that some of the mammograms conducted amongst the cancer survivors cohort were conducted in secondary care follow up clinics and were not recorded on the primary care record. One proxy of the completeness of recording in the GPRD is a comparison of rates of screening and preventive care with national data. Rates of mammography through the national screening programme are currently 73%, and hence may be slightly underestimated in this GPRD cohort (82). Cervical screening, which does occur in UK primary care, was not well captured in this GPRD cohort. National coverage of cervical screening is 78%; suggesting that rates of cervical smear are drastically underestimated in this study (36). This underestimate is a recognised problem in the GPRD because of under recording of cervical smear results in computerised patient medical records before the widespread use of electronic transfer of cervical smear results from laboratories. Despite these limitations, the majority of cancer survivors in the UK are discharged to the care of their primary care physician by five years post-diagnosis. Therefore, the majority of their care will occur in primary care and is likely to be captured in this cohort of long-term survivors in the GPRD. Additionally, because these analyses were conducted as comparisons between cases and controls, completeness of recording should not affect our results; it is unlikely that most of the services considered in this chapter would be coded preferentially in either population.

It has been suggested research using administrative data may underestimate rates of bilateral mastectomy which may have affected the analyses on breast cancer survivors use of mammography services as women with a bilateral mastectomy are not called for breast cancer screening (83). However, this analysis was conducted using surgery data from both cancer registries and primary care. Some of the clinical codes used to identify mastectomy in the GPRD were not precise enough to determine whether the procedure was a bilateral or unilateral. This may be a limitation as patients receiving a bilateral mastectomy will not be eligible for breast screening. However, to account for this, I excluded all women with a specific primary care code for bilateral mastectomy, or two mastectomy codes more than a year apart. This definition of bilateral mastectomy resulted in an overall rate of 4.2% in the cohort of breast cancer survivors, which corresponds to rates in the Surveillance, Epidemiology and End Results (SEER) database (84). I also conducted a sensitivity analysis excluding all women with any clinical code for mastectomy. The results were similar and therefore not presented.

When considering prescribing patterns for analgesics, it was surprising to find no evidence for an interaction with death, as cancer survivors at the end of life are likely to access higher levels of pain medication (85). However, it is possible that patients at the end of life are using acute palliative care specialized services such as hospice-based care, or are receiving inpatient hospital care, which may have resulted in an underestimate of use of analgesics at step 3 of the WHO pain ladder. Step 1 and 2 analgesics can also be accessed directly from pharmacies or as over-the-counter medications without a prescription, so it is possible that usage of these therapies was underestimated in these analyses.

There are two specific methodological limitations to the analyses considering adherence to monitoring for chronic diseases. Although some of the individuals had a history of more than one of the chronic diseases under investigation, they were treated separately in each analysis. A higher proportion of all cancer survivors had more than one chronic disease, and it is possible that this may have introduced a bias as patients with multimorbidities may receive better care (86;87). However, it is appropriate to analyze the patients with two or more chronic diseases similarly to those with only one chronic disease, as the QOF guidelines which were used as the benchmark of care are specific to each condition regardless of multimorbidity. Secondly, although these analyses involve numerous statistical tests for the proportion of individuals receiving monitoring and quarterly control of disease, I have not adjusted for multiple comparisons. Previous work has shown, however, that it is not always necessary to make adjustments for multiple comparisons, especially as these results are based on observed, and not random data (88).

### 3.4.5 Conclusions

This analysis of the General Practice Research Database has shown an increase in the primary care consultation of long-term cancer survivors and higher usage of prescriptions such as anti-depressants, anxiolytics, analgesics and erectile dysfunction therapies. While previous research from the United States has shown deficiencies in the preventive care and chronic disease care of some long-term cancer survivors, this analysis has shown that most cancer survivors receive similar preventive care, screening for other cancers and management of comorbidities compared to a non-cancer control population. However, breast cancer survivors

in this study were less likely to receive screening mammographies. This chapter has provided some indication of the patterns of primary care usage by cancer survivors in the United Kingdom, which is a previously under-researched area.

## 3.5 References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# Chapter 4: Risks of morbidity and mortality amongst long-term survivors of breast, colorectal and prostate cancer

## 4.1 Introduction

Long-term cancer survivors may continue to be at risk of increased morbidity and mortality either due to common risk factors between the cancer and other diseases, or late relapse of the primary cancer. Additionally, while improvements in cancer treatment have led to both an increase in the chance of surviving cancer and the length of survival, these treatments can result in debilitating side effects. The most commonly used forms of primary and adjuvant treatment are chemotherapy, radiotherapy, hormonal treatment and surgery, each of which can have long-term side effects and late toxicities, or late effects, which may manifest months to years after the completion of primary cancer treatment (1). Late effects related to treatment are widely variable, and are linked to characteristics of the cancer, the modality and intensity of treatment and the underlying health status of the individual experiencing cancer. A brief summary of late effects and long-term effects of treatments for breast, colorectal and prostate cancer is presented in Table 4.1.

Some late effects have been studied in detail, for instance, radiotherapy for breast cancer can lead to an increased incidence of hypothyroidism and heart failure in breast cancer patients (2-4). The effects of hormonal treatments are also well described in the literature; changes in bone physiology and increases in osteoporosis due to the effects of oestrogen and testosterone therapy are increasingly found in patients treated with hormone deprivation (5-9). The

population based prevalence of other late effects is still uncertain, but it is likely that with sophisticated and intense treatments, these will become more common (10). Cancer survivors also remain at risk of cancer recurrence and second primary malignancies; for instance, breast cancer has a significant late-relapse rate which persists even 20 years post-diagnosis (11-13).

Not only are cancer survivors at risk of late effects of treatment and second cancers, they may also be at a greater risk of premature death. Elevated all-cause mortality has been demonstrated in several studies of long-term survivors of childhood and adolescent cancers even 15 years after cancer (14-17). Part of the increased risk of death in this population is due to cancer recurrence, however, there is also a substantial increase in risk of dying from other causes. Data on long-term mortality in adult cancer survivors has focussed mainly on long-term follow up of people in clinical trials of cancer therapies. However, studies of patients in trials represent a highly selected population (18;19). Published population-based studies are limited to Korean, Australian and American cohorts, with results suggesting elevated all-cause and non-cancer mortality amongst these population (20-22). There is a lack of large scale, European studies in this area, and most research in adults has only considered mortality in breast cancer survivors.

It is important to determine the burden of late effects, second malignancies and risk of mortality in cancer survivors in order to provide guidance on monitoring, case finding for disease, and health promotion in this population. To date, few studies have used population level data including individuals with comorbid diseases precluding entrance to a clinical trial.

### 4.1.1 Aims

To achieve a better understanding of the long-term morbidity within cancer survivors, the aims of the analyses reported in this chapter are to assess the long-term risks associated with being a long-term survivor of breast, colorectal or prostate cancer. Specifically, the following outcomes will be considered for each cancer site:

a) Incidence of new diagnoses and late effects related to cancer treatment
b) Risk of second primary cancers
c) All-cause and cause-specific mortality

These outcomes amongst cancer survivors will be compared against a matched control population.

**Table 4.1 Potential long-term and late effects of treatment amongst breast, colorectal and prostate cancer survivors***

| | Surgery | Radiotherapy | Chemotherapy | | Hormone therapy | |
|---|---|---|---|---|---|---|
| **Breast** | Mastectomy<br>Reconstruction<br>Lymphoedema | Shoulder stiffening<br>Lymphoedema<br>Skin telangiectasia<br>Cardiac damage<br>Second malignancy<br>Thyroid damage | Anthracyclines | Heart failure<br>Left ventricular (LV) dysfunction | Tamoxifen | Endometrial cancer<br>Osteopenia<br>Thromboembolism |
| | | | Cyclophosphamide | Heart failure<br>Pericarditis<br>Premature menopause | Aromatase inhibitors | Bone loss (23)<br>Increased risk of artherosclerosis (24) |
| | | | Trastuzumab | Heart failure<br>LV dysfunction | | |
| | | | Bevacizumab | Hypertension<br>Thromoembolic events<br>Heart failure (25) | | |
| | | | General effects | Weight gain<br>Cognitive dysfunction (26) | | |
| **Prostate** | Urinary incontinence<br>Sexual dysfunction | Pelvic fibrosis<br>Bowel fibrosis<br>Bladder/bowel telangiectasia<br>Second malignancy | Rarely used | | LHRH† analogs | Coronary artery disease<br>Myocardial infarction (27)<br>Osteoporosis (7;27)<br>Mild obesity<br>Sexual dysfunction |
| | | | | | Bicalutamide | Breast enlargement |
| **Colorectal** | Stoma<br>Bowel and urinary incontinence<br>Sexual dysfunction | Pelvic necrosis<br>Hip osteoporosis<br>Second malignancy | Bevacizumab | Hypertension<br>Thromoembolic events<br>Heart failure | | |
| | | | 5- Fluorouracil | Cardiac ischemia | | |
| | | | Oxaliplatin | Peripheral neuropathy (1) | | |
| | | | General effects | Cognitive dysfunction (28) | | |

*Developed with input from Dr. Elaine Sugden, consultant oncologist at the Churchill Hospital † Luteinizing-hormone releasing hormone

## 4.2 Methods

### 4.2.1 Incidence of late effects in cancer survivors

The aim of this analysis was to quantify the risk of developing incident disease related to late effects of cancer as suggested by previous studies. Specifically, these included radiotherapy effects in breast cancer (hypothyroidism, heart failure, lymphoedema, coronary artery disease) (2;3;10;29;30), chemotherapy effects in colorectal cancer (dementia) (28), and hormonal effects in breast (osteoporosis) and prostate (osteoporosis and coronary artery disease) (6;8;9;27). Diabetes mellitus was also pre-specified as an outcome because of its reported association with colorectal cancer (31;32). Incident events were identified through Read or OXMIS codes for the clinical diagnosis, with the exception of osteoporosis for which patients prescribed a bisphosphonate were included even if they did not have a clinical code for osteoporosis or osteoporotic fracture.

The analyses were undertaken using the GPRD cohort of cancer survivors and controls over the main follow-up period from 1 September 2003 to 31 August 2006 (see Table 2.3, Chapter 2 for details). Because these analyses considered incidence of new diagnoses, I excluded any patients with a previous diagnosis of the condition of interest within the GPRD medical record prior to 1 September 2003.

### 4.2.2 Second cancers

The aim of this set of analyses was to identify the risk of developing a second primary cancer and also examine site-specific tumour patterns amongst the cancer survivors in the GRPD. In

order to achieve this aim, I accessed the NCIN-GPRD linkage to identify clinically coded cancers. Because the original cancer survivors cohort was also identified using cancer codes from the GPRD electronic medical record, it was important to ensure that only second diagnoses were considered, excluding the original cancer which determined the patient's eligibility as a cancer survivor. Therefore, I excluded any codes for cancer up to one year post-diagnosis recorded in the NCIN in the cancer survivors cohort, and only counted cancer events 1 year or more post-diagnosis as new or second cancers. The terminology 'second cancers' is misleading amongst the controls as all cancer diagnoses within the control population over the three year analysis period were considered in this analysis.

Primary cancers are recorded in the linked NCIN data, however, cancer registries do not code cancer recurrence as these are considered 'existing cases' of cancer. The last recorded cancer diagnosis available in the NCIN data was on 31 December 2006.

The cancer diagnoses were coded using ICD-10 in the registry data. I removed cancers of uncertain behavior (ICD-10 codes D37-48), in situ neoplasms (ICD-10 codes D00-09) and benign neoplasms (ICD-10 codes D10-36) as these were not the focus of this analysis. It was not possible to distinguish between primary cancers and recurrences in the GPRD or NCIN databases. I removed any cancers in the survivors' cohort that potentially could have represented a recurrence, for instance, second breast cancer diagnoses in the breast survivors or colon cancers in the colorectal cancer survivors. However, this means that rates of second primary breast cancer will be underestimated amongst the breast cancer survivors cohort. I also removed any cancers of ill-defined or secondary sites from the survivors cohort as these

were likely to represent recurrences.

Because the NCIN data includes information on cancer site, it was possible to explore sites of second cancers amongst the survivors and controls. These results are reported descriptively.

### 4.2.3 Mortality

This analysis uses data from the main GPRD cohort of cancer survivors but only included those patients with data linked to death registration information from the Office for National Statistics (ONS). ONS data was accessed primarily for information on underlying cause of death, as coded by ONS and defined as 'the disease or injury which initiated the train of morbid events leading directly to death'. Underlying cause of death was coded by ONS using software developed by the National Centre for Health Statistics (NCHS), which automatically codes death certificates using ICD-10 (International classification of diseases, $10^{th}$ revision) (33;34). The primary analysis was a comparison of cause of death using mortality rates and rate ratios between cancer survivors and the control population. Mortality rates were calculated for all cause mortality and twelve chapters of ICD-10 listed in Table 4.2.

**Table 4.2: Chapters of the ICD-10 considered in the mortality analysis**

| **Chapter**<br>*ICD-10 code* | **Examples of diseases included** |
|---|---|
| Infections<br>*A00-B99* | Intestinal infectious diseases, bacterial and viral diseases, HIV |
| Neoplasms<br>*C00-D48* | All cancers |
| Blood diseases<br>*D50-D89* | Anaemia, coagulation defects |
| Endocrine and metabolic diseases<br>*E00-E90* | Disorders of the thyroid, diabetes, obesity/metabolic disorders |
| Mental and behavioural diseases<br>*F00-F99* | Dementia, Alzheimer's disease, schizophrenia, mental retardation |
| Nervous system diseases<br>*G00-G99* | Cerebral palsy, encephalitis, myelitis, |
| Circulatory system diseases<br>*I00-I99* | Ischaemic heart diseases, cerebrovascular diseases, hypertensive diseases |
| Respiratory system diseases<br>*J00-J99* | Acute upper respiratory infections, influenza and pneumonia, chronic lower respiratory diseases, lung diseases |
| Digestive system diseases<br>*K00-K93* | Oesophageal obstructions, ulcers, ulcerative colitis, diverticulitis, intestinal abscesses, liver disease |
| Muskoskeletal system diseases<br>*M00-M99* | Osteoporotic diseases, arthritis, joint disorders |
| Genitourinary system diseases<br>*N00-N99* | Renal failure |
| External causes<br>*V01-Y98* | Accidents, self harm |

The mortality analysis used a different analysis period than the main GPRD analysis due to a longer follow-up period available from the ONS data. Follow-up started on 1 September 2001, and continued for each individual until the date of death, transfer from the GPRD primary care practice, or 1 November 2009, which was the last date for which ONS data was complete. I conducted exploratory subgroup analyses of the risk of death attributed to all causes, cancers other than the index cancer, and non-cancer causes by years since cancer diagnosis at death and age of cancer diagnosis.

### 4.2.4 Statistical methods

The primary analysis for assessing the risk of new diagnoses related to cancer, risk of second cancers and mortality was to compare incidence rates and hazard ratios between cancer survivors and the control population. I firstly calculated the incidence rate for each outcome based on the number of events and cumulative person years for each group of cancer survivors and controls within the analysis period. Person years for each group of cancer survivors and controls were used as the denominator to calculate the rates for each outcome (per 1000 person years) along with 95% confidence intervals. I used multivariate Cox proportional hazard models, stratifying for the matched groups, to compute hazard ratios (HRs) and 95% confidence intervals (95% CIs). In order to formally test the proportional hazards model assumption that the hazard ratio is proportional over time, I conducted post estimation tests of the correlation between Schoenfeld residuals from each multivariate model and time (35). Stratified rate ratios were not calculated for any groups with less than 10 deaths (36).

### 4.2.5 Explanatory variables used in the regression analyses

There are other contributing factors influencing each outcome, and the analyses were adjusted for these factors as summarized in Table 4.3.

**Table 4.3: Adjustors used in specific analyses**

| **Analysis** | | **Adjusted for** |
|---|---|---|
| Incidence of late effects | Heart failure | Smoking, BMI |
| | Coronary artery disease | |
| | Osteoporosis (37) | |
| | Dementia | |
| | Diabetes | |
| | Hypothyroidism | BMI, history of hormone therapy |
| Second cancers | | Smoking, BMI |
| Mortality | | Calendar year of death, smoking, comorbidity score† |

† See Chapter 2, Section 2.4 for details on how the Charlson comorbidity index was adapted for use in the GPRD (38)

## 4.3 Results

### 4.3.1 Incidence of late effects

**Breast cancer survivors**

Incidence rates and risk of new diagnoses related to late effects of treatment amongst breast cancer survivors and controls are shown in Table 4.4. Long-term survivors of breast cancer

had an incident rate for heart failure of 5.73 per 1000 person years compared to 4.40 in controls. This excess persisted in matched, multivariate models (adjusted HR 1.95, 95% CI 1.27-3.01). Additionally, breast cancer survivors had a significantly elevated incidence of osteoporosis compared to controls (adjusted HR 1.26, 95% CI 1.13-1.40). 260 breast cancer survivors were clinically coded with lymphoedema, which corresponded to an incidence rate of 6.73 per 1000 person years (95% CI 5.95-7.59) and a substantially elevated rate of disease compared to controls (HR 18.12, 95% CI 13.6-24.1).

While coronary artery disease and hypothyroidism crude incidence rates were similar in breast cancer survivors and controls, after accounting for matched groups and additional covariates, there was evidence for increased rates of coronary artery disease (adjusted HR 1.27, 1.11-1.44) and of hypothyroidism (adjusted HR 1.26, 95% CI 1.02-1.56) in breast cancer survivors.

**Table 4.4 Incidence of new diagnoses related to treatment amongst breast cancer survivors**

| | Incidence | | | Hazard ratio† | | | |
|---|---|---|---|---|---|---|---|
| | n | Incidence rate per 1000 person-years | 95% CI | Unadjusted | 95% CI | Adjusted | 95% CI |
| **Heart failure** | | | | | | | |
| Cancer survivors | 228 | 5.73 | 5.0-6.5 | 1.80 | 1.51-2.13 | 1.95 | 1.27-3.01 |
| Controls without cancer | 760 | 4.40 | 4.1-4.7 | | | - | |
| **Coronary artery disease** | | | | | | | |
| Cancer survivors | 410 | 10.86 | 9.9-12.0 | 1.29 | 1.14-1.45 | 1.27 | 1.11-1.44 |
| Controls without cancer | 1726 | 10.60 | 10.1-11.1 | | | - | |
| **Hypothyroidism** | | | | | | | |
| Cancer survivors | 437 | 11.76 | 10.7-12.9 | 1.18 | 1.05-1.32 | 1.26 | 1.02-1.56 |
| Controls without cancer | 1772 | 10.95 | 10.5-11.5 | | | - | |
| **Osteoporosis** | | | | | | | |
| Cancer survivors | 656 | 18.07 | 16.7-19.5 | 1.40 | 1.28-1.54 | 1.26 | 1.13-1.40 |
| Controls without cancer | 2305 | 14.57 | 13.9-15.2 | | | - | |
| **Lymphoedema** | | | | | | | |
| Cancer survivors | 260 | 6.73 | 5.95-7.59 | 18.12 | 13.6-24.1 | - | - |
| Controls without cancer | 77 | 0.34 | 0.34-0.54 | | | | |

† The hazard ratio in each case is based on individual comparison with controls matched for age, sex and primary care practice. The adjusted hazard ratio takes account of the potential confounding effect of smoking and BMI, except for hypothyroidism which is adjusted for BMI and history of hormone therapy only.

**Colorectal cancer survivors**

There was evidence for an increase in the incidence of dementia compared to controls (adjusted HR 1.68, 95% CI 1.20-2.35) after adjusting for BMI and Charlson score (Table 4.5). Additionally, there was an increase of incident diabetes amongst colorectal cancer survivors, and this risk remained after adjusting for BMI and smoking (adjusted HR 1.39, 95% 1.12-1.72). Colorectal cancer survivors also had a significantly higher incidence of osteoporosis (adjusted HR 1.41, 95% CI 1.15-1.73).

**Prostate cancer survivors**

Prostate cancer survivors had a large increase in the rate of osteoporosis compared to matched controls (adjusted HR 2.49, 95% CI 1.93-3.22) but no differences in the incidence rate of heart failure or coronary artery disease (Table 4.5).

**Table 4.5: Incidence of new diagnoses related to treatment amongst colorectal and prostate cancer survivors**

| | Incidence | | | Hazard ratio† | | | |
|---|---|---|---|---|---|---|---|
| | n | Incidence rate per 1000 person-years | 95% CI | Unadjusted | 95% CI | Adjusted | 95% CI |
| **Colorectal cancer survivors** | | | | | | | |
| *Dementia* | | | | | | | |
| Cancer survivors | 116 | 10.08 | 8.4-12.1 | 2.10 | 1.65-2.68 | 1.68 | 1.20-2.35 |
| Controls without cancer | 356 | 7.02 | 6.3-7.8 | | | | - |
| *Osteoporosis* | | | | | | | |
| Cancer survivors | 190 | 18.02 | 15.6-20.8 | 1.60 | 1.35-1.91 | 1.41 | 1.15-1.73 |
| Controls without cancer | 597 | 12.86 | 11.9-13.9 | | | | - |
| *Diabetes* | | | | | | | |
| Cancer survivors | 176 | 17.01 | 14.7-19.7 | 1.40 | 1.15-1.70 | 1.39 | 1.12-1.72 |
| Controls without cancer | 616 | 13.21 | 12.2-14.3 | | - | | |
| **Prostate cancer survivors** | | | | | | | |
| *Heart failure* | | | | | | | |
| Cancer survivors | 129 | 17.1 | 14.4-20.3 | 1.66 | 1.32-2.10 | 1.23 | 0.91-1.66 |
| Controls without cancer | 486 | 13.8 | 12.6-15.1 | | | | |
| *Coronary artery disease* | | | | | | | |
| Cancer survivors | 173 | 27.95 | 24.1-32.4 | 1.27 | 1.05-1.56 | 1.17 | 0.94-1.46 |
| Controls without cancer | 863 | 29.15 | 27.3-31.2 | | | | |
| *Osteoporosis* | | | | | | | |
| Cancer survivors | 120 | 15.38 | 12.9-18.4 | 2.39 | 1.89-3.00 | 2.49 | 1.93-3.22 |
| Controls without cancer | 292 | 7.98 | 7.1-8.9 | | | | |

### 4.3.2 Second cancers

This analysis utilized the NCIN-GPRD linkage, and therefore the cohort was limited to the patients and practices contributing data to the linkage scheme (see table 2.5, Chapter 2 for details).

All cancer survivors were at a substantially increased risk of second cancers compared to the control population (Table 4.6). The incidence rate for prostate cancer survivors and controls was higher due to the older age distribution of these patients. These events may include recurrence of the index cancer or second primary cancers, however, the GPRD coding did not distinguish between these.

**Table 4.6: Incidence rates for second cancers and 95% confidence intervals**

| | | | **Incidence** | |
|---|---|---|---|---|
| | n | Person years | Incidence rate per 1000 person-years | 95% CI |
| **Breast** | | | | |
| Survivor | 914 | 261900 | 3.49 | 3.27-3.72 |
| Control | 1081 | 1064000 | 1.02 | 0.96-1.08 |
| **Colorectal** | | | | |
| Survivor | 436 | 81439 | 5.35 | 4.87-5.88 |
| Control | 546 | 329600 | 1.66 | 1.52-1.80 |
| **Prostate** | | | | |
| Survivor | 359 | 47488 | 7.56 | 6.82-8.38 |
| Control | 682 | 193000 | 3.53 | 3.28-3.80 |

The unadjusted hazard ratios showed that breast cancer survivors (HR 3.69, 95% CI 3.38-

4.05), colorectal cancer survivors (HR 3.67, 95% CI 3.21-4.18) and prostate cancer survivors (HR 2.35, 95% CI 2.06-2.67) were all significantly more likely to have a second cancer diagnosed compared to their matched controls. These associations were explored in adjusted models (see Table 4.7).

**Table 4.7: Adjusted proportional hazard models and 95% CI for risk of developing a second cancer**

| | **Breast** | | **Colorectal** | | **Prostate** | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| Cancer status | | | | | | |
| Control | Reference | | | | | |
| Survivor | 3.67 | 3.3-4.1 | 3.76 | 3.2-4.4 | 2.36 | 2.0-2.7 |
| BMI groups | | | | | | |
| Underweight | Reference | | | | | |
| Normal weight | 0.8 | 0.7-1.1 | 1.1 | 0.7-1.6 | 0.8 | 0.5-1.2 |
| Overweight | 0.8 | 0.6-1.1 | 1.1 | 0.7-1.7 | 0.7 | 0.5-1.1 |
| Obese | 0.8 | 0.6-1.1 | 1.2 | 0.7-1.8 | 0.7 | 0.4-1.1 |
| Ever smoked? | | | | | | |
| No | Reference | | | | | |
| Yes | 1.1 | 0.9-1.3 | 0.9 | 0.7-1.1 | 0.9 | 0.8-1.1 |

All cancer survivor groups were significantly more likely to experience a second cancer following adjustment for weight and smoking status. The distribution of second cancers is shown in Table 4.8.

**Table 4.8: Distribution of second cancers diagnosed amongst cancer survivors and controls**

| Cancer site | Breast | | Colorectal | | Prostate | |
|---|---|---|---|---|---|---|
| | Survivor n=10798 | Control n=43084 | Survivor n=3323 | Control n=13161 | Survivor n=2894 | Control n=11460 |
| Anus | 2 | 1 | 2 | 2 | 0 | 3 |
| Biliary tract | 1 | 0 | 0 | 2 | 1 | 3 |
| Bone | 1 | 0 | 2 | 0 | 0 | 1 |
| Breast | 0† | 81 | 59 | 13 | 0 | 1 |
| Bronchus or lung | 65 | 65 | 35 | 48 | 24 | 76 |
| Cervix | 9 | 15 | 3 | 0 | 0 | 0 |
| Colon | 75 | 43 | 0† | 17 | 38 | 27 |
| Eye, brain or CNS | 6 | 14 | 2 | 0 | 2 | 3 |
| Gallbladder | 3 | 2 | 1 | 0 | 0 | 0 |
| Heart | 2 | 1 | 0 | 1 | 1 | 0 |
| Hodgkin's disease | 31 | 55 | 15 | 15 | 6 | 27 |
| Ill-defined, or secondary sites | 0† | 29 | 0† | 20 | 0† | 26 |
| Larynx | 1 | 7 | 5 | 5 | 7 | 9 |
| Leukemia | 22 | 29 | 3 | 13 | 11 | 20 |
| Lip, oral cavity, pharynx | 7 | 11 | 2 | 4 | 4 | 8 |
| Liver | 5 | 6 | 1 | 4 | 1 | 5 |
| Male genital organs | 0 | 0 | 0 | 1 | 2 | 2 |
| Mesothelioma | 3 | 5 | 2 | 2 | 5 | 3 |
| Multiple myeloma | 9 | 14 | 4 | 8 | 8 | 8 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Nasal cavity and sinus | 2 | 0 | 1 | 1 | | |
| Oesophagus | 24 | 15 | 8 | 9 | 11 | 14 |
| Other digestive organs | 5 | 2 | 2 | 2 | 1 | 0 |
| Other female genital | 2 | 1 | 0 | 0 | 0 | 0 |
| Ovary | 46 | 52 | 7 | 8 | 0 | 0 |
| Pancreas | 21 | 19 | 10 | 10 | 4 | 14 |
| Peritoneum | 6 | 7 | 0 | 2 | 3 | 7 |
| Prostate | 0 | 0 | 58 | 26 | 0† | 45 |
| Rectosigmoid junction | 8 | 4 | 9 | 0 | 4 | 4 |
| Rectum | 41 | 14 | 0† | 9 | 24 | 9 |
| Skin | 392 | 476 | 180 | 284 | 186 | 308 |
| Small intestine | 3 | 1 | 1 | 1 | 0 | 4 |
| Stomach | 19 | 17 | 19 | 12 | 10 | 22 |
| Thyroid or other endocrine sites | 3 | 8 | 1 | 5 | 0 | 0 |
| Urinary tract | 44 | 47 | 42 | 33 | 37 | 64 |
| Uterus | 138 | 66 | 9 | 5 | 0 | 0 |
| Vaginal | 7 | 9 | 4 | 3 | 0 | 0 |
| Total new cancers* | 1003 | 1116 | 487 | 565 | 390 | 713 |

*These don’t match the totals in the survival analysis as some people had more than one cancer diagnosis †Cancers at these sites were excluded and assumed to represent recurrence amongst the cancer survivors

### 4.3.3 Mortality in long-term survivors of cancer

This analysis includes data on the patients and practices involved in the linkage scheme (see Table 2.5, Chapter 2 for a summary of linked patients and practices). When compared with their matched controls, all cancer survivors had a significantly elevated risk of death over the 8 year period from 2001 to 2009. Additionally, all cancer survivors had a significantly elevated risk of death due to malignant neoplasms and diseases of the circulatory and respiratory systems (Tables 4.9-4.11).

**Death rates in breast cancer survivors**

*Numbers of deaths*

In total, 3002 breast cancer survivors and 5494 breast cancer controls died during the 2001-2009 follow up period (Table 4.9). The leading cause of death amongst breast cancer survivors was breast cancer (1087 deaths, or 36.2% of all deaths), corresponding to an additional 8.8 deaths due to breast cancer per 1000 person years compared to the control population. Breast cancer survivors diagnosed pre-1995 may not have received adjuvant chemotherapy or radiotherapy and therefore may have been at a higher risk of late relapse. However, this is unlikely as 562 (51.7%) of the 1087 breast cancer survivors diagnosed before 1995 died with breast cancer as the underlying cause of death compared to 525 (48.3%) of women diagnosed post-1995.

I considered other cancer-related deaths amongst breast cancer survivors and controls. There was a slight increase in the number of deaths due to cancers of the female genital organs (ICD codes C51-C58), which includes endometrial, ovarian, cervical and uterine cancers. A higher

proportion of breast cancer survivors also died from neoplasms of ill-defined or secondary sites (ICD codes C76-C80, 71 breast cancer survivor deaths compared to 112 breast controls, $p<0.001$) and malignant neoplasms of independent multiple sites (ICD code C97, 23 breast cancer deaths compared to 6 breast controls, $p<0.001$). These are likely to represent breast cancer deaths amongst the breast cancer survivors.

*Relative risk of death*

Overall, breast cancer survivors demonstrated a substantially increased risk of death from all causes compared to the control population (HR 2.47, 95% CI 2.36-2.58). The increased risk of death persisted even after excluding deaths attributed to breast cancer (HR 1.60, 95% CI 1.52-1.69). Of neoplastic causes, breast cancer survivors had a greatly increased risk of death from breast cancer and from all other malignant neoplasms compared to controls (HR 2.33, 95% CI 2.09-2.60). I considered the effect of excluding deaths attributed to ill-defined malignancies on the risk of dying from all other malignancies; the risk remained elevated at a rate of 2.09 (95% CI 1.85-2.35).

Mortality from other causes was elevated in this cohort of breast cancer survivors: there was evidence for increased mortality due to circulatory disease (HR 1.40, 95% CI 1.28-1.53), respiratory disease (HR 1.48, 95% CI 1.29-1.70), endocrine disease (HR 1.68, 95% CI 1.11-2.54), diseases of the digestive system (HR 1.35, 95% CI 1.07-1.72), diseases of the nervous system (HR 1.82, 95% CI 1.34-2.46), mental and behavioural causes (HR 1.37, 95% CI 1.08-1.75), infectious and parasitic causes (HR 2.66, 95% CI 1.75-4.03) and diseases of the genitourinary system (HR 1.62, 95% CI 1.20-2.18).

Analysis of risk of death by years since diagnosis at death showed a significant elevation in mortality due to malignant and non-malignant causes even 20 years post-diagnosis (Table 4.12). Although women diagnosed between 30-49 years of age had the highest relative risk of mortality, those diagnosed at a later age also demonstrated an elevation in all-cause, cancer and non-cancer mortality (Table 4.13).

**Death rates in colorectal cancer survivors**

*Numbers of deaths*

In total, 1283 colorectal cancer survivors died in this cohort, corresponding to an all-cause mortality rate of 36.5 deaths per 1000 person years, compared to 20.0 per 1000 person years amongst the control population (Table 4.10). 194 colorectal survivors who survived at least five years (15.1% of all colorectal cancer deaths) died from colorectal cancer listed as their underlying cause of death, of whom 59 died with metastatic cancer (C80). Death from cancers of the digestive organs (ICD codes C15-C26 but excluding C18-C21), including stomach, small intestine, liver and pancreatic were elevated amongst colorectal cancer survivors, with 75 deaths amongst colorectal survivors and 92 amongst the matched colorectal controls ($p<0.001$).

*Relative risk of death*

Overall all-cause mortality was significantly elevated in colorectal cancer survivors (HR 1.89, 95% CI 1.77-2.02). This excess persisted even after excluding deaths due to colorectal cancer (HR 1.63, 95% CI 1.52-1.75). Compared to controls, mortality rates for colorectal cancer

(HR 19.43, 95% CI 14.0-26.9), all malignant neoplasms after excluding colorectal cancer (HR 2.13, 95% CI 1.82-2.49), nervous system disease (HR 1.53, 95% CI 1.02-2.30), circulatory disease (HR 1.58, 95% CI 1.42-1.76), respiratory disease (HR 1.54, 95% CI 1.29-1.83), diseases of the digestive system (HR 1.67, 95% CI 1.23-2.27) and genitourinary disease (HR 2.14, 95% CI 1.47-3.10) were elevated among the colorectal cancer survivors. All cause mortality remained elevated amongst colorectal cancer survivors even 20 years post-diagnosis (Table 4.12). This risk of death comprised deaths due to malignant and non-malignant causes at each stage in the survivorship trajectory and amongst colorectal cancer survivors diagnosed later in life (Table 4.13).

**Death rates in prostate cancer survivors**

*Numbers of deaths*

There were 1458 deaths amongst prostate cancer survivors in this analysis (Table 4.11), corresponding to a mortality rate of 58.9 per 1000 person years. This compared to 27.2 per 1000 person years amongst the prostate controls. A significant proportion of all deaths in prostate cancer survivors were due to prostate cancer and all other malignancies: 631 (43.3%) died with prostate cancer listed as their underlying cause of death and 187 (12.8%) died with any other cancer listed as the underlying cause of death. There were no clear patterns amongst the mortality rates for specific cancer related deaths among prostate cancer survivors and controls. However, mortality rates for death due to circulatory disease were significantly elevated amongst prostate cancer survivors (Table 4.11).

*Relative risk of death*

All-cause mortality was significantly elevated amongst the long-term prostate cancer survivors population, with an over twofold increase in the risk of death (HR 2.30, 95% CI 2.17-2.46). The overall risk of dying from all causes after excluding prostate cancer was still elevated in survivors compared to controls (HR 1.34, 95% CI 1.24-1.45). Compared to matched controls, prostate cancer survivors were significantly more likely to die from prostate cancer (HR 72.8, 95% CI 53.1-99.9), all other malignant causes (HR 1.47, 95% CI 1.25-1.73), circulatory disease (HR 1.44, 95% CI 1.28-1.62) and respiratory disease (HR 1.27, 95% CI 1.06-1.52). While all-cause mortality remained elevated amongst prostate cancer survivors even 20 years post-diagnosis, risk of death due to non-cancer causes and other cancers were not significantly elevated after 10 years post-diagnosis compared to the control population (Table 4.12). Prostate cancer survivors aged 70 and above continued to experience increased risk of mortality due to all-causes, malignancies and all non-cancer causes (Table 4.13).

**Table 4.9: Rate ratios for mortality by ICD coded cause of death within breast cancer survivors and controls**

| | Number of deaths | | Mortality rate per 1000 person years, 95% CI | | Difference in mortality rate per 1000 person years | Hazard ratio[¥] | 95% CI |
|---|---|---|---|---|---|---|---|
| | Survivors | Controls | Survivors | Controls | | | |
| **All causes** | **3002** | **5494** | **24.6 (23.7-25.5)** | **10.3 (10.0-10.6)** | **14.3** | **2.47*** | **2.36-2.58** |
| **Malignant causes** | | | | | | | |
| Breast cancer | 1087 | 54 | 8.9 (8.3-9.4) | 0.1 (0.1-0.1) | 8.8 | 87.66* | 66.7-115.2 |
| Other malignant neoplasms | 498 | 970 | 4.1 (3.7-4.4) | 1.9 (1.8-2.0) | 2.2 | 2.33* | 2.09-2.60 |
| *Excluding ill-defined malignancies* | *474* | *852* | *3.9 (3.5-4.2)* | *1.6 (1.5-1.7)* | *2.3* | *2.09** | *1.85-2.35* |
| **All causes excluding breast cancer** | 1915 | 5440 | 15.7 (15.0-16.4) | 10.2 (9.9-10.4) | 5.5 | 1.60* | 1.52-1.69 |
| **All cause excluding malignancies** | 1417 | 4470 | 11.6 (11.0-12.2) | 8.4 (8.1-8.6) | 3.2 | 1.44* | 1.36-1.54 |
| **Non-cancer medical causes** | | | | | | | |
| Infectious and parasitic | 35 | 59 | 0.3 (0.2-0.4) | 0.1 (0.1-0.1) | 0.2 | 2.66* | 1.75-4.03 |
| Blood disease | 20 | 63 | 0.2 (0.1-0.2) | 0.1 (0.1-0.2) | 0.2 | 1.44 | 0.87-2.38 |
| Endocrine and metabolic | 31 | 81 | 0.3 (0.2-0.3) | 0.2 (0.1-0.2) | 0.1 | 1.68* | 1.11-2.54 |
| Mental and behavioural | 86 | 284 | 0.7 (0.6-0.9) | 0.5 (0.5-0.6) | 0.2 | 1.37* | 1.08-1.75 |
| Nervous system | 58 | 145 | 0.5 (0.4-0.6) | 0.3 (0.2-0.3) | 0.2 | 1.82* | 1.34-2.46 |
| Circulatory system | 647 | 2103 | 5.3 (4.9-5.7) | 3.9 (3.7-4.1) | 1.4 | 1.40* | 1.28-1.53 |
| Respiratory system | 277 | 845 | 2.3 (2.0-2.5) | 1.6 (1.5-1.7) | 0.7 | 1.48* | 1.29-1.70 |
| Digestive system | 89 | 297 | 0.7 (0.6-0.9) | 0.6 (0.5-0.6) | 0.1 | 1.35* | 1.07-1.72 |
| Musculo-skeletal system | 20 | 65 | 0.2 (0.1-0.2) | 0.1 (0.1-0.2) | 0.1 | 1.39 | 0.84-2.30 |
| Genitourinary system | 59 | 166 | 0.5 (0.4-0.6) | 0.3 (0.3-0.4) | 0.2 | 1.62* | 1.20-2.18 |
| Other medical causes | 75 | 310 | - | - | | - | - |
| **Non-medical causes** | | | | | | | |
| External causes | 20 | 52 | 0.2 (0.1-0.2) | 0.1 (0.1-0.1) | 0.2 | 1.75* | 1.04-2.92 |

The crude mortality rates were based on a total of 122041.3 person years for the breast cancer survivors and 533938.7 person years for controls

*Significant at $p<0.05$ [¥]These represent hazard ratios from proportional hazards regression models conditional on the matched groups (matched on age and primary care practice) †Diseases of the ear and mastoid process (H00-H59), Diseases of the skin and subcutaneous tissue (L00-L99), Pregnancy childbirth and the puerperium (O00-O99), Certain conditions originating in the perinatal period (P00-P96), Congenital malformations (Q00-Q99), Injury and poisoning (S00-T98)

**Table 4.10: Rate ratios for mortality by ICD coded cause of death comparing colorectal cancer survivors and controls**

| | Number of deaths | | Mortality rate per 1000 person years, and 95% CI | | Difference in mortality rate per 1000 person years | Hazard ratio[¥] | 95% CI |
|---|---|---|---|---|---|---|---|
| | Survivors | Controls | Survivors | Controls | | | |
| **All causes** | **1283** | **3110** | **36.5 (34.5-38.5)** | **20.0 (19.3-20.7)** | **16.5** | **1.89*** | **1.77-2.02** |
| **Malignant causes** | | | | | | | |
| Colorectal cancer | 194 | 44 | 5.5 (4.7-6.3) | 0.3 (0.2-0.4) | 5.2 | 19.43* | 14.0-26.9 |
| Other malignant neoplasms | 232 | 493 | 6.6 (5.8-7.5) | 3.2 (2.9-3.5) | 3.4 | 2.13* | 1.82-2.49 |
| *Excluding ill-defined malignancies* | *205* | *425* | *5.8 (5.0-6.6)* | *2.7 (2.5-3.0)* | *3.1* | *2.14** | *1.81-2.53* |
| **All causes excluding colorectal cancer** | 1089 | 3066 | 30.9 (29.1-32.8) | 19.7 (19.0-20.4) | 11.2 | 1.63* | 1.52-1.75 |
| **All cause excluding malignancies** | 857 | 2573 | 24.4 (22.8-26.1) | 16.5 (15.9-17.2) | 7.9 | 1.53* | 1.41-1.65 |
| **Non-cancer medical causes** | | | | | | | |
| Infectious and parasitic | 13 | 39 | 0.4 (0.2-0.6) | 0.3 (0.2-0.3) | 0.1 | 1.54 | 0.82-2.88 |
| Blood disease | 9 | 36 | 0.3 (0.1-0.4) | 0.2 (0.2-0.3) | 0.1 | 1.12 | 0.54-2.33 |
| Endocrine and metabolic | 9 | 64 | 0.3 (0.1-0.4) | 0.4 (0.3-0.5) | -0.1 | 0.65 | 0.32-1.31 |
| Mental and behavioural | 45 | 154 | 1.3 (0.9-1.7) | 1.0 (0.8-1.2) | 0.3 | 1.34 | 0.96-1.87 |
| Nervous system | 31 | 92 | 0.9 (0.6-1.2) | 0.6 (0.5-0.7) | 0.3 | 1.53* | 1.02-2.30 |
| Circulatory system | 427 | 1238 | 12.2 (11.0-13.3) | 8.0 (7.5-8.4) | 4.2 | 1.58* | 1.42-1.76 |
| Respiratory system | 173 | 514 | 4.9 (4.2-5.7) | 3.3 (3.0-3.6) | 1.6 | 1.54* | 1.29-1.83 |
| Digestive system | 56 | 154 | 1.6 (1.2-2.0) | 1.0 (0.8-1.2) | 0.6 | 1.67* | 1.23-2.27 |
| Musculo-skeletal system | 9 | 38 | 0.3 (0.1-0.4) | 0.2 (0.2-0.3) | 0.1 | 1.08 | 0.52-2.24 |
| Genitourinary system | 40 | 87 | 1.1 (0.8-1.5) | 0.6 (0.4-0.7) | 0.5 | 2.14* | 1.47-3.10 |
| Other medical causes | 37 | 133 | - | - | | - | - |
| **Non-medical causes** | | | | | | | |
| External causes | 8 | 24 | 0.2 (0.1-0.4) | 0.2 (0.1-0.2) | 0 | 1.5 | 0.67-3.35 |

The crude mortality rates were based on a total of 35145.8 person years for the colorectal cancer survivors and 155633.7 person years for controls. *Significant at $p<0.05$. [¥]These represent hazard ratios from proportional hazards regression models conditional on the matched groups (matched on the basis of age, sex and primary care practice) †Diseases of the ear and mastoid process (H00-H59), Diseases of the skin and subcutaneous tissue (L00-L99), Pregnancy childbirth and the puerperium (O00-O99), Certain conditions originating in the perinatal period (P00-P96), Congenital malformations (Q00-Q99), Injury and poisoning (S00-T98)

**Table 4.11: Rate ratios for mortality by ICD coded cause of death comparing prostate cancer survivors and controls**

| | Number of deaths | | Crude mortality rate per 1000 person years, and 95% CI | | Difference in mortality rate per 1000 person years | Hazard ratio[¥] | 95% CI |
|---|---|---|---|---|---|---|---|
| | Survivors | Controls | Survivors | Controls | | | |
| **All causes** | **1458** | **3162** | **58.9 (55.9-62.0)** | **27.2 (26.2-28.1)** | **31.7** | **2.30*** | **2.17-2.46** |
| **Malignant causes** | | | | | | | |
| Prostate cancer | 631 | 41 | 25.5 (23.5-27.5) | 0.4 (0.3-0.5) | 25.1 | 72.85* | 53.1-99.9 |
| Other malignant neoplasms | 187 | 641 | 7.6 (6.5-8.7) | 5.5 (5.1-5.9) | 2.1 | 1.47* | 1.25-1.73 |
| *Excluding ill-defined malignancies* | *151* | *560* | *6.1 (5.1-7.1)* | *4.8 (4.4-5.2)* | *1.3* | *1.46** | *1.20-1.66* |
| **All causes excluding prostate cancer** | 827 | 3121 | 33.5 (31.4-35.9) | 26.8 (25.9-27.8) | 6.7 | 1.34* | 1.24-1.45 |
| **All cause excluding malignancies** | 640 | 2480 | 26.0 (24.1-28.1) | 21.3 (20.5-22.2) | 4.7 | 1.31* | 1.20-1.43 |
| **Non-cancer medical causes** | | | | | | | |
| Infectious and parasitic | 9 | 37 | 0.4 (0.1-0.6) | 0.3 (0.2-0.4) | 0.1 | 1.21 | 0.58-2.53 |
| Blood disease | 7 | 28 | 0.3 (0.1-0.5) | 0.2 (0.2-0.3) | 0.1 | 1.24 | 0.54-2.85 |
| Endocrine and metabolic | 13 | 39 | 0.5 (0.2-0.8) | 0.3 (0.2-0.4) | 0.2 | 1.63 | 0.87-3.07 |
| Mental and behavioural | 20 | 87 | 0.8 (0.5-1.2) | 0.8 (0.6-0.9) | 0 | 1.24 | 0.77-2.02 |
| Nervous system | 22 | 111 | 0.9 (0.5-1.3) | 1.0 (0.8-1.1) | -0.1 | 1.00 | 0.63-1.59 |
| Circulatory system | 352 | 1236 | 14.2 (12.8-15.7) | 10.6 (10.0-11.2) | 3.6 | 1.44* | 1.28-1.62 |
| Respiratory system | 146 | 581 | 5.9 (4.9-6.9) | 5.0 (4.6-5.4) | 0.9 | 1.27* | 1.06-1.52 |
| Digestive system | 33 | 127 | 1.3 (0.9-1.8) | 1.1 (0.9-1.3) | 0.2 | 1.32 | 0.89-1.93 |
| Musculo-skeletal system | 6 | 20 | 0.2 (0.1-0.4) | 0.2 (0.1-0.3) | 0 | 1.58 | 0.63-3.94 |
| Genitourinary system | 14 | 91 | 0.6 (0.3-0.9) | 0.8 (0.6-0.9) | -0.2 | 0.89 | 0.49-1.47 |
| Other causes† | 10 | 87 | - | - | | - | - |
| **Non-medical causes** | | | | | | | |
| External causes | 8 | 36 | 0.3 (0.1-0.6) | 0.3 (0.2-0.4) | 0 | 1.12 | 0.52-2.43 |

The crude mortality rates were based on a total of 24723.9 person years for the prostate cancer survivors and 116308.4 person years for controls

*Significant at $p<0.05$ ¥These represent hazard ratios from proportional hazards regression models conditional on the matched groups (matched on the basis of age and primary care practice) † Diseases of the ear and mastoid process (H00-H59), Diseases of the skin and subcutaneous tissue (L00-L99), Certain conditions originating in the perinatal period (P00-P96), Congenital malformations (Q00-Q99), Injury and poisoning (S00-T98)

**Table 4.12: Risk of death by years since diagnosis**

| Years since diagnosis of index cancer at death | All cause mortality | | Malignancies | | | Deaths due to all non-cancer causes | |
|---|---|---|---|---|---|---|---|
| | | | Index cancer | Other cancers | | | |
| | n | HR* | N | n | HR* | n | HR* |
| **Breast cancer** | | | | | | | |
| 5-9 | 1042 | 4.0 (3.7-4.4) | 498 | 148 | 3.0 (2.5-3.8) | 396 | 1.9 (1.7-2.2) |
| 10-14 | 833 | 2.2 (2.0-2.4) | 320 | 151 | 2.1 (1.8-2.6) | 362 | 1.2 (1.1-1.4) |
| 15-19 | 524 | 2.2 (1.9-2.4) | 149 | 89 | 2.2 (1.7-2.8) | 286 | 1.5 (1.3-1.7) |
| 20 and above | 603 | 1.8 (1.6-1.9) | 120 | 110 | 2.1 (1.6-2.6) | 373 | 1.4 (1.2-1.5) |
| Total | 3002 | | 1087 | 498 | | 1417 | |
| **Colorectal cancer** | | | | | | | |
| 5-9 | 490 | 2.8 (2.5-3.2) | 143 | 102 | 3.3 (2.5-4.3) | 245 | 1.7 (1.5-2.0) |
| 10-14 | 334 | 1.7 (1.5-1.9) | 27 | 61 | 1.8 (1.3-2.4) | 246 | 1.5 (1.3-1.7) |
| 15-19 | 185 | 1.5 (1.3-1.8) | 13 | 32 | 1.7 (1.1-2.5) | 140 | 1.4 (1.1-1.6) |
| 20 and above | 274 | 1.5 (1.3-1.8) | 11 | 37 | 1.5 (1.0-2.2) | 226 | 1.5 (1.3-1.7) |
| Total | 1283 | | 194 | 232 | | 857 | |
| **Prostate cancer** | | | | | | | |
| 5-9 | 919 | 3.0 (2.8-3.3) | 398 | 130 | 2.2 (1.8-2.7) | 391 | 1.7 (1.5-1.9) |
| 10-14 | 425 | 1.7 (1.5-1.9) | 184 | 46 | 0.9 (0.6-1.2) | 195 | 1.0 (0.9-1.2) |
| 15-19 | 90 | 1.4 (1.1-1.8) | 39 | 8 | 0.7 (0.3-1.5) | 43 | 0.8 (0.6-1.2) |
| 20 and above | 24 | 1.7 (1.2-2.6) | 10 | 3 | 0.9 (0.3-2.9) | 11 | 1.3 (0.7-2.1) |
| Total | 1458 | | 631 | 187 | | 640 | |

*****These represent hazard ratios from proportional hazards regression models stratified on the matched groups (on the basis of age and primary care practice) and using the control population as baseline

**Table 4.13: Risk of death by age at diagnosis**

| Age at cancer diagnosis | All cause mortality | | Malignancies | | | Deaths due to all non-cancer causes | |
|---|---|---|---|---|---|---|---|
| | | | Index cancer | Other cancers | | | |
| | n | HR* | N | n | HR* | n | HR* |
| **Breast cancer** | | | | | | | |
| 30-49 | 528 | 5.1 (4.5-5.8) | 316 | 78 | 2.4 (1.8-3.2) | 134 | 2.0 (1.7-2.5) |
| 50-69 | 1382 | 2.9 (2.7-3.1) | 509 | 285 | 2.6 (2.2-3.0) | 588 | 1.6 (1.5-1.8) |
| 70 and above | 1092 | 1.7 (1.6-1.8) | 262 | 135 | 1.9 (1.5-2.3) | 695 | 1.2 (1.1-1.4) |
| Total | 3002 | | 1087 | 498 | | 1417 | |
| **Colorectal cancer** | | | | | | | |
| 30-49 | 66 | 2.9 (2.1-4.0) | 14 | 9 | 2.1 (0.9-4.6) | 43 | 2.5 (1.7-3.6) |
| 50-69 | 534 | 2.2 (1.9-2.5) | 84 | 118 | 2.4 (1.9-2.9) | 332 | 1.8 (1.6-2.0) |
| 70 and above | 683 | 1.6 (1.5-1.8) | 96 | 105 | 1.9 (1.5-2.4) | 482 | 1.4 (1.2-1.5) |
| Total | 1283 | | 194 | 232 | | 857 | |
| **Prostate cancer** | | | | | | | |
| 30-49 | 3 | 4.8 (0.9-23.9) | 2 | 1 | - | 0 | - |
| 50-59 | 425 | 3.3 (2.9-3.7) | 224 | 58 | 1.4 (1.1-1.9) | 143 | 1.7 (1.4-2.1) |
| 70 and above | 1030 | 2.0 (1.9-2.2) | 405 | 128 | 1.5 (1.2-1.8) | 497 | 1.2 (1.1-1.4) |
| Total | 1458 | | 631 | 187 | | 640 | |

*****These represent hazard ratios from proportional hazards regression models stratified on the matched groups (on the basis of age and primary care practice) and using the control population as baseline

## 4.4 Discussion

### 4.4.1 Summary of main findings

This chapter has considered the long-term risks that are associated with a diagnosis of cancer and its treatment. A summary of the main findings is presented in Box 4.1.

**Box 4.1: Summary of main findings**

- Breast cancer survivors are at increased risk of developing heart failure, coronary artery disease, hypothyroidism and lymphoedema
- There was evidence for an increase risk of dementia and diabetes amongst colorectal cancer survivors
- All three groups of cancer survivors were at a significantly higher risk of developing osteoporosis more than five years post-diagnosis
- All three groups of cancer survivors had substantially increased risks of second cancers
- Survivors of breast, colorectal and prostate cancer are at a significantly elevated risk of all-cause, non-cancer and cancer mortality 5 years and more after diagnosis and even when diagnosed with cancer later in life
- Cardiovascular and respiratory disease deaths were higher in all three groups of cancer survivors

Section 4.3.1 described the incidence of new diagnoses related to late-effects of treatment in long term survivors of breast, colorectal and prostate cancer. The analyses have confirmed previously reported associations between breast cancer and heart failure, coronary artery disease and hypothyroidism and the increased risk of osteoporosis in all three cancers.

Analysis of cause-specific mortality amongst the long-term adult survivors in the GPRD

shows a prolonged and increased risk of dying compared with age matched controls, with the relative risk varying from 2.47 for breast cancer and 2.30 for prostate cancer to 1.89 for colorectal cancer. These increased risks persist even 20 years post-diagnosis. A high proportion of breast and prostate cancer survivors still die from their index cancer despite surviving relapse-free for at least five years past their original diagnosis. The excess mortality amongst cancer survivors is not attributable solely to neoplastic causes; rates of circulatory and respiratory deaths are higher amongst all groups of survivors. Amongst colorectal cancer survivors and in contrast to breast and prostate survivors, excess deaths from non-cancer causes exceed those from colorectal cancer after 5 years. The risk of dying due to non-cancer causes remained elevated amongst breast and colorectal cancer survivors even 20 years post-diagnosis and is evident even when the cancer is diagnosed later in life.

### 4.4.2 Comparison with other research

The study of late effects of treatment confirms most of the reported associations between treatment and outcomes drawn from cross-sectional studies and specialist databases. The risk of heart failure, hypothyroidism and osteoporosis amongst breast cancer survivors in this cohort was similar to previously reported research (2;23;39). However, rates of osteoporosis amongst all prostate cancer survivors in this cohort were substantially higher compared to the results from a meta-analysis assessing the risk of androgen deprivation therapy related osteoporosis (27).

Second primary cancers and new incident diseases such as heart disease amongst cancer survivors may be due to shared risk factors with the first cancer, including lifestyle (smoking, poor diet or excessive alcohol intake), genetic, infectious (human papilloma virus, HPV) or

environmental factors (40). Additionally, radiotherapy and hormonal treatments are associated with an increased risk of second malignancies (41;42). Much of the previous research considering risk of second cancers comes from analysis of the Surveillance, Epidemiology and End Results (SEER) program, which is a regional cancer registration and information service covering 28% of the United States population (43). Analysis of the SEER database over the course of 27 years from 1973 to 2000 showed that cancer survivors have a 14% increased chance of developing a second primary cancer compared with the general population (44). While a proportion of new cancers may be attributable to radiotherapy, another SEER based study showed that only about 8% of second solid tumours amongst adult cancer survivors are related to radiotherapy; the majority are due to lifestyle or genetic factors (45). In breast cancer survivors, the excess risk of cancer could be due to tumours in the contralateral breast or the associated risk of ovarian cancer, and for colorectal cancer it could be due to metachronous tumours. Breast cancer has a significant late-relapse rate which persists even 20 years post-diagnosis; however, risk of recurrence is associated with tumour characteristics such as stage, grade and hormone receptor status, data which was unavailable in this study (11-13).

The excess risk of death in these people comprises two elements: excess deaths from cancer and excess deaths from other causes. In this study, both breast and prostate cancer patients had significant excess mortality from the original cancer. Previous research amongst breast cancer survivors has also shown that the leading cause of death is breast cancer, contributing to 76% of all deaths in a large population based cohort in the Netherlands and 74% of all deaths in a large Korean cohort of cancer survivors (22;46). In this analysis of cause-specific mortality in

the GPRD-ONS linked data, the index cancer was responsible for 36% of all deaths in breast cancer survivors, 15% in colorectal and 43% amongst prostate cancer survivors.

Late effects of treatment may be responsible for a proportion of the increased mortality in cancer survivors (1;21). Studies of childhood cancer survivors have suggested that excess cardiovascular mortality amongst childhood cancer survivors may be attributed to mediastinal irradiation or combination chemotherapy regimes including anthracyclines (14). Use of androgen deprivation therapy amongst prostate cancer survivors and radiotherapy amongst breast cancer survivors has been linked with increased cardiovascular morbidity (46;47). A recent population based study in Sweden indicated an increased relative risk of cardiovascular death amongst prostate cancer survivors treated with androgen deprivation therapy, corresponding to an extra 7 deaths per 1000 person years, compared to the additional 3.6 deaths per 1000 person years amongst the total population of prostate cancer survivors in this analysis (48).

Much of the previous research in this area showing an excess in all-cause and cause-specific mortality has come from long-term studies of survivors of childhood cancers (14-17). The results from this analysis have highlighted the continuing excess all-cause, cancer-specific and non-cancer mortality amongst cancer survivors diagnosed at age 70 and above.

### 4.4.3 Strengths and limitations

The main drawback of this observational research is that it is not possible to determine causal relationships between specific cancers, treatments and incidence of new diagnoses or risk of non-cancer mortality. Additionally, because individual level data is limited, it was only

possible to take a small proportion of potentially confounding patient characteristics into account. The results need to be interpreted with caution as the mechanisms underlying these new diagnoses have not been fully elucidated, disease definitions are not standardized in the GPRD and incident diseases may be due to shared risk factors with the initial cancer (49). The second limitation of this research is the lack of detailed treatment information from the GPRD and the NCIN linkages, which prevented analysis of treatment effects amongst the entire cohort. For instance, previous research considering late effects of chemotherapy and radiotherapy has used a dose-response approach, and reports associations between increased dose and increased severity of late effects.

Outcomes such as impotence and incontinence are not widely recorded in the GPRD. Therefore, in this analysis it was not possible to investigate the incidence or risk of these additional treatment complications which often have an immediate and debilitating impact on patient quality of life (50). Additionally, risk of heart disease and osteoporosis amongst the breast cancer survivors could be due to secondary amenorrhea caused by chemotherapy, however, information on menopausal status pre and post-diagnosis was poorly recorded within the GPRD. Risk factors which may be shared between the original cancer and any incident diagnoses, such as diet and exercise, are not reliably recorded in the GPRD and it has not been possible to adjust for these factors in these analyses.

A new malignancy in the contralateral breast is the most common second primary cancer amongst breast cancer survivors (51;52). In order to assess the risk of second cancers, I excluded any diagnoses which potentially could have represented cancer recurrence, including

second diagnoses of breast cancer amongst breast cancer survivors. Because neither the NCIN nor GPRD datasets collected complete data on laterality of breast cancer, it was not possible to distinguish between cancer recurrence and contralateral breast cancer, and therefore, I was unable to assess the risk of second primary breast cancers within breast cancer survivors and the analysis of second cancers will underestimate the true risk of all second cancers amongst the breast cancer survivor population.

An additional consideration relating to the analyses investigating risk of second cancers was my decision to exclude second cancer diagnoses of the same site within one year of the primary cancer diagnoses. The main reason for excluding these cancers was to ensure that the primary cancer diagnosis was not counted twice, however, this does mean that metachronous tumours occurring within the same year of the primary cancer in the breast or colorectal cancer survivors will not have been taken into account. This means that it is possible that the risk of second cancers is underestimated within the breast and colorectal cancer survivors cohort.

The long-term excess risk of death amongst colorectal cancer survivors has not been shown in national studies of mortality amongst cancer survivors in the UK (53). These statistics use relative survival against the national population, while in this study we have been able to compare risk of mortality amongst individual patients matched to controls on the basis of primary care practice. Death rates amongst male colorectal cancer survivors vary with deprivation category, and our methodology has adjusted for practice-level deprivation markers which may account for the findings amongst colorectal cancer survivors (54).

Primary care records in the GPRD rarely contain data on cause of death. This mortality analysis uses the linked GPRD and ONS datasets, which allowed an investigation of cause-specific deaths that is not currently possible by using the GPRD alone. I have only been able to look at the excess causes of death in broad categories due to small numbers of deaths for specific causes. Despite this limitation, these results do highlight an excess risk of non-cancer mortality amongst cancer survivors, and mechanisms for this increased risk should be explored in future studies. Studying mortality in broad categories also may mean that this analysis has avoided inaccuracies in death certification coding for specific diseases. Generally, the reliance on ONS-coded underlying cause of death may mean that some of the deaths were attributed to the wrong cause of death, however, misclassification of underlying cause of death compared to medical record review is low amongst cancer patients (55;56).

### 4.4.4 Implications for clinicians

The results of these analyses also show that long-term cancer survivors remain a population at risk of early mortality. Much of this risk is due to the original cancer, despite a perception amongst some cancer patients and the media that individuals surviving five years post-diagnosis are 'cancer-free' (57;58). Despite the increased and long-term risk of mortality due to the original tumour, the results presented in section 3.2.2 have shown that some breast cancer survivors may under-utilize screening mammography (59-62). Aside from mammography amongst breast cancer survivors, sections 3.3.2 and 3.3.3 (Chapter 3) show that British cancer survivors do not get worse care for screening and co-morbidity, therefore the increased non-cancer mortality may be due to the treatment these individuals receive. Additionally, while deaths due to late relapse are difficult to prevent, clinicians may be able to

help address common risk factors and late effects of treatment to reduce the increased risk of non-cancer mortality. Lifestyle modifications such as smoking cessation and exercise and dietary interventions to reduce the excess risk of circulatory disease should be encouraged in long-term cancer survivors (63). Additionally, patient education initiatives can play a key role in encouraging long-term survivors to continue surveillance for second cancers through the national screening programmes and to maintain preventive measures to reduce the risk of long-term effects. Knowledge of those at higher risk of specific outcomes due to their disease or treatment might allow clinicians to target interventions to those at higher risk.

Most cancer survivors will be cared for in primary care and general practitioners will need an awareness of the increased risks in individual patients. Guidelines developed by the National Institute for Health and Clinical Excellence (NICE) recommend baseline dual energy X-ray absorptiometry (DEXA) scans to women with breast cancer, however, no current guidelines exist for the management of bone loss amongst prostate cancer survivors (64). These findings certainly suggest a substantially increased risk of osteoporosis amongst prostate cancer survivors, and adequate surveillance systems are required to manage this risk. GPs will also need to pay special attention to the presence of risk factors in this population that may have led to the original cancer diagnosis as well as managing long term treatment effects.

### 4.4.5 Conclusions

This large, population based cohort study has demonstrated an excess risk of incident diseases which may be associated with cancer treatment, second cancers and mortality in long-term survivors of three common cancers in the United Kingdom. The incidence of new diseases amongst cancer survivors may be attributable to shared risk factors with the original cancer diagnosis or late effects of treatment. A substantial proportion of the long-term morbidity

mortality, even five or more years post-diagnosis, in survivors of breast, colorectal and prostate cancer may be attributable to non-cancer causes and treatment effects.

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# Chapter 5: A qualitative study of unmet needs of cancer survivors and their interactions with primary care

## 5.1 Introduction

As the population of cancer survivors grows and with increasing focus on earlier discharge from hospital follow-up to primary care for cancer patients, it is important to understand the use and quality of primary care services within this population. The overall aims of this thesis are to examine how survivors of breast, colorectal and prostate cancer use primary care services and to explore their unmet needs for health care in the United Kingdom.

The first and second objectives, to investigate the use and quality of primary care services and risks associated with cancer, were met through a cohort study of breast, colorectal and prostate cancer survivors registered in the General Practice Research Database (GPRD) and reported in Chapters 3 and 4. While analysis of the GPRD provided a quantitative overview of how cancer survivors use primary care services across the UK, it is difficult to explore the personal stories behind living past a cancer diagnosis within a database study. Quantitative data can provide information on how a large number of people use primary care services but is limited in the amount of detail on individual experiences and unmet needs. In order to meet the third objective, a qualitative interview study of long-term survivors of breast, colorectal and prostate cancer was conducted and is described in this chapter. The benefit of incorporating a qualitative component to this thesis means that it is possible to explore the individual views of long-term cancer survivors on the quality of the primary care services they received, and what further services, if any, were recommended.

As general practices take on an increasing role in the care of cancer survivors, it is important to understand the ways in which cancer survivors use GP services and identify areas where care could be improved. There is little previous qualitative research in the area of cancer care following discharge from hospital care. One of the few studies involved a series of focus groups of cancer patients and their carers, which investigated how primary care could best support cancer patients through each phase of the cancer journey (1). Participants in the focus groups established five key time points for primary care involvement in the cancer trajectory: diagnosis, treatment, discharge from hospital follow-up, recurrence and palliative care. Specifically, the time following discharge from hospital follow-up was described by the focus group participants as a 'black hole' when patients felt abandoned at a vulnerable time. This stage, when regular hospital-based appointments finish, is when primary care becomes the main source of supportive and follow-up care for cancer survivors.

Aside from the focus group study described above, there is currently a lack of evidence investigating the individual cancer survivor's experience of primary care services and patient unmet needs. In order to gain greater understanding of the patient experience in surviving cancer and use of primary care services, I conducted a secondary analysis of existing patient interview studies. The Health Experiences Research Group has previously conducted interviews with breast, colorectal and prostate cancer patients, from which thematic analyses illustrated with interview extracts are presented on the Healthtalkonline website (www.healthtalkonline.org). Most of the cancer patients in these interview collections were closer to the point of diagnosis, and therefore these discussions do not specifically deal with long-term primary care or survivorship issues. Secondary analysis

of relevant thematic topic summaries from the Healthtalkonline website suggests that some cancer patients felt that GP support after treatment for cancer was lacking, with several people stating that their GP was indifferent or unprepared to deal with cancer patients. However, those individuals who had good GP support after treatment for cancer felt that this greatly aided them in their recovery and helped them regain confidence in their health. These findings highlight the importance of good quality primary care services and its impact on cancer patients in the long-term.

### 5.1.2 Aims

The third objective of this thesis is to describe the experience of cancer survivors' use of GP services, their views on the care that they have received from the time of hospital discharge, and to identify good practice, unmet needs as identified and defined by each cancer survivor, and the current role of primary care using a qualitative interview study. Additionally, these interviews will:

a. Follow-up on the GPRD analysis, and investigate how the results from the quantitative analysis compares with individual patient experiences
b. Explore patient experiences that cannot be described in a quantitative database analysis

## 5.2 Methods

### 5.2.1 Sampling frame

The qualitative study was linked to a cancer survivors questionnaire study which was conducted by our research team at the Department of Primary Care from 2009 to 2010 (2). I was responsible for developing the questionnaire and conducting face to face interviews

to determine the face and content validity of the survey. The aims of the questionnaire survey were to describe current care, psychological health, hospital discharge procedures and unmet needs of long-term cancer survivors. The questionnaire included four standardised measures: the Cancer Survivors' Unmet Needs (CaSUN) (3), the European Quality of Life – 5 Dimensions (EQ-5D) (4), the State Trait Anxiety Inventory (STAI – Trait only) (5) and the Hospital Anxiety and Depression Scale (HADS) (6). It also included questions on patients' experience of discharge and their current use of primary care, diagnosis and treatment information, general health and basic demographic information.

The questionnaire was sent to cancer survivors identified using two regional cancer registries, the Oxford Cancer Intelligence Unit (OCIU) and the Northern and Yorkshire Cancer Registry and Information Service (NYCRIS). The OCIU covers four counties in the south east, including Berkshire, Buckinghamshire, Northamptonshire and Oxfordshire, while the NYCRIS regions include Yorkshire, Humber and the North East regions of England. Questionnaires were distributed through primary care practices in the regions covered by these two registries to 1133 randomly selected cancer survivors who were 5-7, 9-11 and 14-16 years post-diagnosis. As one of the aims of the questionnaire study was to explore experiences of discharge from hospital follow-up, a greater proportion of questionnaires were sent to survivors 5-7 years post-diagnosis to minimize recall bias. The questionnaire included the following question, 'Our research team will be conducting a number of interviews with patients to follow up some of the issues identified in this questionnaire. Would you be interested in participating in these interviews?' Respondents indicating their interest in participating in the qualitative interviews provided their name, address and phone number at the end of the questionnaire upon return. The total response

rate for the questionnaire study was 51.7% (587 out of 1133 sent the questionnaire), and 418 of these respondents (71.2%) indicated their interest in being interviewed.

I conducted a purposive and iterative sample from this subgroup of questionnaire respondents intending to recruit roughly 40 participants for interview. In the initial stages of sampling, I considered demographic characteristics such as cancer type (breast, colorectal or prostate), age, sex (colorectal cancer), geographical location (OCIU or NYCRIS regions) and time since diagnosis in order to identify a purposive sample (7). Additionally, I used responses to the survivors questionnaire, including results of the Cancer Survivors Unmet Needs measure (CaSUN) (3), State-Trait Anxiety Inventory (STAI) (5) and the Hospital Anxiety and Depression Scale (HADS) (8) to identify cancer survivors with low and high unmet cancer needs, anxiety and depression for interview. Using this sampling strategy I iteratively selected questionnaire respondents who had agreed to participate in the interview study and sent them a postal pack that included the following information:

1. A brief letter introducing the qualitative study
2. A patient information leaflet explaining the purpose of the qualitative study
3. A reply slip for respondents interested in taking part in the interview
4. A stamped, reply paid envelope

Potential respondents were sampled in batches of 8-10 patients in order to maintain an ongoing balance of cancer type, location and length of diagnosis in the overall sample. Towards the end of the sampling period, there were fewer prostate cancer survivors and fewer respondents based in the NYCRIS region than I had hoped to interview. Therefore,

the last batch of interview invitations was targeted at prostate cancer survivors residing in the northern sampling region. Respondents who wished to take part in the qualitative study returned the reply slip directly to me; I then telephoned the interviewee and scheduled a time for the qualitative interview. This purposeful sampling strategy allowed me to select cases strategically to ensure a wide range of cases to get variation on the dimensions of interest (9). Interview collection and analysis ran simultaneously in order to gain a greater understanding of the issues raised by cancer survivors, to reflect upon and revise the interview schedule, and to determine when all viewpoints and experiences had been covered by the interview sample. The interviews continued until a point of theoretical data saturation; or in other words, I felt that I was not gaining any additional information or insights from the cancer survivors towards the end of the study (10).

### 5.2.2 Health talk online

Healthtalkonline (HTO, www.healthtalkonline.org) is a website that allows people to share their experiences of health and illness and acts as a resource to support those living with a wide variety of health conditions. In order to make these interviews suitable for future use on the HTO website, interviewees were given the choice of having their interview recorded in either video or audio format or as text excerpts alone. Three respondents declined to contribute towards the HTO website altogether, and their interviews were used for research purposes only. All interviews were audio recorded in order to facilitate transcription even when the respondent did not wish to take part in the HTO website.

### 5.2.3 The interviews

All interviews were conducted face to face at the interviewee's home between October 2009 and August 2010. All interviewees were given an information sheet and signed a consent form before the interview started.

Based on my own knowledge of the field and discussions with my supervisors I developed an interview schedule to guide the content of the semi-structured component (see Appendix 7 for the interview schedule). The interview schedule was used flexibly according to the natural direction taken by the conversation. In order to allow the respondents to describe their experience in their own words focussing on the issues that were of most importance to them, the first part of the interview involved an open-ended question:

"I'm interested in how having cancer impacts on your life nowadays. For example, how has it changed your life, and has it had any physical or emotional long-lasting effects. I realize that in order to make me make sense of that you may need to tell me a bit about your diagnosis and treatment. Can you tell me about your experience of living beyond cancer with reference, where necessary, to aspects of your diagnosis and treatment?"

After my introduction and the initial question, the interviewee began describing their experience of living past cancer, and was allowed to continue this initial narrative without interruption. Following the response to the initial open-ended question, I prompted the interviewee on any aspects of their initial narrative which needed clarification.

The second part of the interview was semi-structured and directed to seek further detail where required on topics covered in the initial narrative and to explore any areas of relevance that had not been covered in the initial part of the interview.

An experienced senior qualitative researcher, Julie Evans (JE), watched videos of the first few interviews and provided feedback on interviewing technique. JE also read interview transcripts throughout the period of the interview study to check the quality of my interview technique as the study progressed. Early comments on my interview technique were to avoid interrupting the respondents' initial narrative and to ensure that sensitive topics such as sexual dysfunction were not missed. JE also provided advice for interviews where a partner or family member sat in the room during the interview; I have not included any quotations from other family members as part of my analysis.

### 5.2.4 Transcribing and checking

The digital audio recording of each interview was sent electronically to a professional transcriber, who transcribed all of the interviews verbatim. Upon return, I checked each transcript against the video recording, adding any missing words and correcting any typographical errors. The original transcripts included hesitations, 'ums' and 'ers' and repetitions as spoken verbatim by the interviewees, however, for the purposes of any quoted text, these have been removed in order to improve the readability and presentation of interview data (11).

### 5.2.5 Analysis

All interviews were read and re-read, then coded thematically using NVivo 7 qualitative software. This involved labelling sections of each transcript against categories (or themes) developed from the first few interviews and adding new categories when new concepts or ideas emerged from the later interviews (12). The thematic categories were labelled using descriptive terms, and the majority of themes were emergent and grounded in the narratives provided by the respondents. Other broad themes were driven by questions on the interview schedule.

The coding categories were developed using the constant comparison method to relate the commonalities and differences between each individual narrative (13). This method involved reading the transcripts and coding sections of each transcript to common coding categories, or themes, which linked ideas from the different narratives together. Each separate theme incorporated aspects of the different interviews, which assisted when trying to summarize the shared experiences of the cancer survivors.

In total, the interview data were coded against 13 major themes (see Box 5.1). Some of these encompassed several sub-themes, for instance, the major theme 'feelings about cancer in the long-term' was broken into smaller themes such as 'anger', 'feeling lucky' or 'moving on from cancer'.

**Box 5.1 – Major themes from interviews with long-term cancer survivors**

*Themes relating to health service use*

Cancer follow-up care

Discharge from hospital care

Interactions with primary care

Information needs

Treatment descriptions

*Long-term physical and practical effects of cancer*

Lifestyle changes as a result of cancer

Physical long-term effects of treatment

Practical issues

Recurrence of cancer

Unmet needs

*Long-term feelings and impact on relationships*

Feelings about cancer in the long-term

Impact on relationships

Support needs

Other issues not coded against the major themes listed above

Following initial coding of the interviews, major themes were examined using the 'One Sheet of Paper' (OSOP) method (14). This secondary and more detailed method of coding, which involves listing subthemes on a sheet of paper and noting the respondent ID number for each participant describing the theme, facilitated the recognition of patterns and commonalities between the respondents. The OSOP also allowed identification of the commonest subthemes within the major themes and importantly, also highlighted the deviant cases, or individuals who did not share the same experiences or views as the majority of the interviewees. OSOPs were developed for the 'interactions with primary

care' (see Appendix 8 for my OSOP as an example) and 'unmet needs' subthemes, which were used to describe unmet needs and use of primary care services amongst the cancer survivors in this project.

JE also independently produced OSOPs for the major themes classified as 'interactions with primary care' and 'unmet needs', which were used for comparative purposes against my own OSOPs. The two interpretations of the data were comparable, with the majority of subthemes being identified by both analysts. Where there were differences, I checked through the interview transcripts to see how these quotations would affect our overall findings. There were no instances where one of the analysts identified a subtheme that refuted or conflicted with ideas on the other analyst's OSOP.

A visual model was constructed to summarise/illustrate the different pathways of primary care use described by these long term cancer survivors (Figure 5.1).

### 5.2.6 Evaluation by interview participants

In order to ensure that the findings of this work reflected the experiences of the participants, I sent the entire chapter to three interview participants for an informal evaluation (LBC14, 18 and 34). The purpose of sending the chapter to participants was three fold, firstly to verify that I had reflected their perspectives, secondly to inform me of sections which could be problematic to the participants if the work was published, and thirdly to help develop any new ideas and interpretations which I may have missed (15). Specifically, I requested any general feedback or comments, and asked the respondents to comment on the overall results and conclusions. Each of these interviewees responded with written feedback on the chapter.

## 5.3 Results

In total, I interviewed 40 long-term survivors of breast, colorectal and prostate cancer. A summary of the respondents and their main characteristics is shown in Table 5.1. I sent out 82 invitations to participate in the qualitative interviews to the 418 questionnaire respondents who had expressed interest in being interviewed, which corresponds to a response rate of 48.7% for the interview study.

**Table 5.1: The interview sample**

| | Breast | Colorectal | Prostate | **Total** |
|---|---|---|---|---|
| Total number | **15** | **13** | **12** | **40** |
| Sex | | | | |
| Male | 0 | 6 | 12 | **18** |
| Female | 15 | 7 | 0 | **22** |
| Location | | | | |
| OCIU regions | 10 | 10 | 6 | **26** |
| NYCRIS regions | 5 | 3 | 6 | **14** |
| Age | | | | |
| 60 years or younger | 5 | 3 | 0 | **8** |
| 61-70 | 5 | 3 | 2 | **10** |
| 71- 80 | 5 | 5 | 6 | **16** |
| 81 and above | 0 | 2 | 4 | **6** |
| Length of survival | | | | |
| 5-7 years | 8 | 8 | 8 | **24** |
| 8-11 years | 2 | 2 | 3 | **7** |
| 12 plus years | 5 | 3 | 1 | **9** |

The majority of the respondents were located in the region covered by the OCIU, and had survived from 5-7 years post-diagnosis. Generally, the interviews lasted between 1 to 1.5

hours. Most respondents were aged between 61 and 80 years at the time of interview. All of the interviewees were White British. The questionnaire which formed the basis of the sampling frame included a question on ethnic background, and while there were 13 respondents who were of non-White background, only 7 indicated an interest in taking part in the qualitative study. In order to attempt to maximize the cultural background of the interviewees, I contacted all 7 ethnic minority respondents with a personal invitation along with the interview study pack explaining why it was important to represent a wide range of ethnicities in the project. Despite these invitations, none of the ethnic minority questionnaire respondents wished to take part in the interview study.

Demographic details of each individual interviewee are provided in Table 5.2. Each respondent was assigned a unique identifier, starting with the letters LBC, which stands for 'Living Beyond Cancer'.

**Table 5.2: Participants in the qualitative interview study**

| Patient identifier | Cancer type | Sex | Age | Years from diagnosis | Region |
|---|---|---|---|---|---|
| LBC01 | Breast | Female | 65 | 6 | OCIU |
| LBC02 | Breast | Female | 64 | 11 | OCIU |
| LBC03 | Breast | Female | 63 | 16 | OCIU |
| LBC04 | Colorectal | Female | 59 | 7 | OCIU |
| LBC05 | Prostate | Male | 70 | 10 | NYCRIS |
| LBC06 | Breast | Female | 68 | 8 | NYCRIS |
| LBC07 | Prostate | Male | 63 | 7 | OCIU |
| LBC08 | Colorectal | Male | 81 | 7 | OCIU |
| LBC09 | Colorectal | Male | 77 | 17 | OCIU |
| LBC10 | Breast | Female | 55 | 8 | OCIU |
| LBC11 | Breast | Female | 58 | 7 | OCIU |
| LBC12 | Colorectal | Female | 68 | 7 | NYCRIS |
| LBC13 | Prostate | Male | 71 | 7 | NYCRIS |
| LBC14 | Colorectal | Female | 46 | 7 | OCIU |
| LBC15 | Colorectal | Male | 85 | 7 | NYCRIS |
| LBC16 | Breast | Female | 60 | 6 | NYCRIS |
| LBC17 | Prostate | Male | 78 | 5 | NYCRIS |
| LBC18 | Breast | Female | 59 | 6 | NYCRIS |
| LBC19 | Prostate | Male | 81 | 12 | OCIU |
| LBC20 | Colorectal | Male | 79 | 11 | NYCRIS |
| LBC21 | Breast | Female | 57 | 7 | NYCRIS |
| LBC22 | Colorectal | Male | 60 | 7 | OCIU |
| LBC23 | Colorectal | Male | 67 | 11 | OCIU |
| LBC24 | Colorectal | Female | 70 | 6 | OCIU |
| LBC25 | Breast | Female | 75 | 17 | OCIU |
| LBC26 | Colorectal | Female | 78 | 15 | OCIU |
| LBC27 | Breast | Female | 71 | 8 | OCIU |
| LBC28 | Colorectal | Female | 73 | 7 | OCIU |
| LBC29 | Breast | Female | 61 | 14 | OCIU |
| LBC30 | Breast | Female | 74 | 12 | OCIU |
| LBC31 | Prostate | Male | 92 | 6 | OCIU |
| LBC32 | Breast | Female | 72 | 11 | OCIU |
| LBC33 | Prostate | Male | 80 | 10 | OCIU |
| LBC34 | Prostate | Male | 81 | 10 | OCIU |
| LBC35 | Prostate | Male | 72 | 8 | OCIU |
| LBC36 | Colorectal | Female | 71 | 22 | OCIU |
| LBC37 | Prostate | Male | 88 | 8 | NYCRIS |
| LBC38 | Prostate | Male | 72 | 8 | NYCRIS |
| LBC39 | Breast | Female | 71 | 16 | NYCRIS |
| LBC40 | Prostate | Male | 73 | 8 | NYCRIS |

OCIU = Oxford Cancer Intelligence Unit, NYCRIS = Northern and Yorkshire Cancer Registry

Analysis of the interview data coded to the themes 'interactions with primary care' and 'unmet needs' are presented in four subthemes: role of the GP, unmet needs, reasons for not using primary care services for cancer-related needs, and follow up care.

### 5.3.1 Role of the GP in long-term care

The majority of cancer survivors interviewed did not see a major role for their GP in their long-term cancer care. In general, they reported having moved on from their illness experience. They spoke of their cancer being 'in the past', and did not assess themselves as unwell:

**LBC04, female colorectal cancer survivor, 7 years post-diagnosis**

*Interviewer: Do you feel that there's anything they [your GPs] could be doing for you now?*

Respondent: Not at all, no, not now at all, no. No. I tend to, these days, go in and tell them what I need [laughs]. Yeah, that's it.

**LBC05, prostate cancer survivor, 10 years post-diagnosis**

*I: Do you do you think that there's anything more that your GP could be doing for you in terms of your cancer related care at this stage?*

R: No, not at all. I think it's in the past now and what's happened has happened and importantly, he knows about it and he's got the record but they've got all that at the [surgery] and I'm sure they take account of it. But it what's done is done and that's it really.

**LBC31, prostate cancer survivor, 6 years post-diagnosis**

*I: So do you go and see your GP or anyone about things related to cancer?*

R: Not now. No, not now. I haven't done for quite a long time because, as I say, I don't feel any adverse effect. If I did I would certainly go because I've got no qualms about going and discussing these things but no, I manage really very well and don't feel any need to go.

A related, and prominent theme expressed by many of the interviewees was of 'moving on' from cancer as they progressed along their cancer journey past the diagnosis and treatment phases. This view was consistent with an impression that ongoing cancer-related primary care services were unnecessary, as many cancer survivors considered themselves well and cured. Respondents felt they could not only move on from their illness, but could deal with any future recurrences when and if they occurred, one saying, 'I think it's [cancer] one of those things I've done and been through but it's not going to haunt me or upset me for the rest of my life, I hope, unless another one recurs and then I can deal with that one' (LBC02, breast cancer survivor, 11 years post-diagnosis). Four other respondents mirrored this view:

**LBC04, female colorectal cancer survivor, 7 years post-diagnosis**

Well, it's [cancer] just receded into the past I think. It's not something that I'm dealing with in the present... it fills your life when you've got it. Now it's way back down the line.

**LBC07, prostate cancer survivor, 7 years post-diagnosis**

I don't think about it [having had cancer] now. I really don't think about it. I went through all the operation[s] and, at this moment in time, I just get on with my life and, without being too smug, it's brilliant...The operation was successful and here I am five or six years later and although I'm aware of it, it's not an issue in my life any more, I've got other things to worry about...or to deal with.

**LBC09, male colorectal cancer survivor, 17 years post-diagnosis**

*I: Is there anything that you want to know about other people's experiences of having been through bowel cancer?*

R: Not now. In a way I suppose you have to remember the actual cancer recovered is seventeen years ago...or it's certainly about twelve years ago since the last time I saw anybody at all in terms of cancer. So it's not something that I think about very often now.

**LBC29, breast cancer survivor, 14 years post-diagnosis**

I mean it's like if you break your foot isn't it, when you're young. You're not going to remember it for the rest of your life are you or keep thinking about it all the time and I don't see that cancer is any different to an injury or an illness like any other. Once you had it and you've had all the treatments, then you tend to move on and not think about it.

Despite ongoing long-term consequences of cancer and its treatment, such as requiring a stoma or dealing with late effects, a number of interviewees nonetheless felt they could integrate the impact of cancer into their lives. One respondent (LBC09) described the impact of having a stoma in the long-term, and another (LBC20) spoke about his ongoing bowel incontinence. Both respondents, however, felt that they could integrate these long-term effects into their lives:

**LBC09, male colorectal cancer survivor, 17 years post-diagnosis**

I don't think I know how to describe it. It was something that happened in my life. I've got over it and let's get on. I don't...just want to sit back and dwell on it. Could have been worse. Could have been better. I've got a constant reminder with the stoma that I've had it but that's as far as it goes.

**LBC20, male colorectal cancer survivor, 11 years post-diagnosis**

*I: It sounds as though it's you feel that it's...something that's happened but you try to just accept it and move on.*

R: Exactly. That's it. You accept it. I keep saying, like old age, there's only one alternative and that's a great deal worse. I accept what it is, certain limitations are inflicted on you but you just move on with the limitations... So, generally speaking it has changed my life to a certain extent but you live with what you've got.

Although many did not feel a need to access long-term cancer related services, some repeated that they felt reassured that their GP would be available and accessible for an episode of acute illness or any concerns about recurrence. One breast cancer survivor who

had experienced a long-term cough spoke about how her GP acted quickly on her symptoms:

**LBC18, breast cancer survivor, 6 years post-diagnosis**
I'd whinge every now and then ...in the end he [my husband] made an appointment with the GP and I went and I said to her, "Look." I said, "I've got this cough, which I've had for weeks and weeks. I know everybody else has but, as you know, I've got breast cancer." And I said, "If I hadn't have had breast cancer I wouldn't have bothered you." And she said, "Well, if you hadn't have had breast cancer I'd have said, 'Don't worry about it. Go home.' But as you have I suggest you go and have an x-ray at the hospital." Which I did and it was fine.

Most respondents did not voice concerns that their needs were being neglected; their GP was available when required. Many described a positive and open relationship with their primary care clinical team, who they felt they could approach when and if any new problems arose in their long-term cancer recovery. For example, one participant stated that he knew 'they're there and I can go any time....I could be up there and be attended to' (LBC15, male colorectal cancer survivor, 7 years post-diagnosis).

Primary care services were viewed as easy to access, and in some cases GPs had encouraged their patients to contact them if they had any ongoing problems, with one respondent describing how his doctor had told him 'if you've got any problems at all, an ache here, and ache there, just come in...even if you want to talk' (LBC23, male colorectal cancer survivor, 11 years post-diagnosis) which he felt was 'very nice'. One woman described her 'wonderful relationship' with her GP, who she couldn't 'praise enough' (LBC21, breast cancer survivor, 7 years post-diagnosis).

### 5.3.2 Unmet needs

A number of respondents spoke about unmet needs and specific services that their primary care team could be providing and which were not offered when they might have been useful. These included psychological services, access to complementary and alternative therapies, and information needs.

**Psychological services**

A desire for long-term counselling for depression was expressed by several respondents who were either unaware that psychological services were provided by their GP, or who noted that these services were not in place around the time of their cancer diagnosis:

**LBC06, breast cancer survivor, 8 years post-diagnosis**

*I: Do you think that there's anything that he [the GP] could be doing more of for you in terms of having lived past cancer?*

R: No, I don't think so. I see now at the surgery they've got a counselling service, which as far as I remember wasn't in place when I was diagnosed. I think if it had been in place at the time I would have gone there maybe earlier than I went to the [cancer centre]. But the way things turned out, the [cancer centre] was perfect for me.

**LBC18, breast cancer survivor, 6 years post-diagnosis**

*I: So you did go to your GP. I mean, do you think that there was something that he could have been doing to help you at that stage?*

R: Yeah, I think it could have been looked into more really because I have wondered whether it was depression, whether some, because when I've read about symptoms of depression I've thought, "Well, yes. That's how I feel." And I did wonder whether there was a depression element to it although I don't sit around feeling miserable or weeping. But I did wonder that and so it might have been helpful really to sit down with a doctor and really talk through it. And just see whether there was something that could be done or whether it was something I was just going to have to adapt to and find coping strategies with.

Although the GP was seen by many as a point of care for physical symptoms, one respondent noted that her wounds were mainly 'emotional and psychological' as a result of cancer (LBC06, breast cancer survivor, 8 years post-diagnosis). Another breast cancer survivor felt that her GP didn't have the best 'bedside manner', saying 'I wouldn't go to him if I had an emotional problem' and that her long-term cancer issues were something she would need to 'struggle along with...on [my] own' (LBC18, breast cancer survivor, 6 years post-diagnosis).

**Complementary and alternative therapies**

A few respondents spoke about their use of complementary and alternative therapies and the lack of availability on the NHS. One breast cancer survivor, who stopped taking long-term hormonal therapies due to the severe side effects, preferred to rely on natural and alternative therapies. She did not see a role for the biomedical care provided by her GP, stating, 'the sort of treatment they would offer, I don't want. I want what's natural and what's organic and that seems to suit me because I am so ultra-sensitive.' (LBC16, breast cancer survivor, 6 years post-diagnosis). This respondent also felt that the NHS was unable to meet her needs for alternative therapies, noting that it was 'a shame that homeopathy isn't offered and advice about diet and what not, because I'm sure it's helped me tremendously'. This respondent was unique in the sense that she wanted to use these therapies as an alternative to her main treatment, while others discussed using natural remedies as an adjunct treatment. For instance, respondents used complementary techniques such as Reiki, hypnotherapy, Bowen technique, shiatsu and acupuncture, which also were not offered by GP or oncology services on the NHS and sometimes required travel to specialist centres. The following quotation, from a woman who felt that she

benefitted greatly from using shiatsu, describes not being able to access this complementary therapy through her GP surgery or via the NHS:

**LBC04, female colorectal cancer survivor, 7 years post-diagnosis**
It seems sensible for the NHS to utilise those aspects of complementary therapy and I mean complementary is the word here. And they were available in London but not in [respondent's local town] I was told so that was a bit disappointing. So I had to ask around and try and get help from contacts and so on.

**Information needs**

Some respondents indicated that they had unmet information needs during the course of their long-term care, particularly relating to effects of cancer treatment. A colorectal cancer survivor spoke about not being ready to receive information on what foods to avoid to prevent bowel dysfunction immediately following his bowel surgery because 'so many things happen…you're depressed and you're worried…you listen but you don't take it all in' (LBC22, male colorectal cancer survivor, 7 years post-diagnosis). Another breast cancer survivor echoed this sentiment, saying 'the average person could do with more information…there was a pack I came away with from the hospital. I never read it…it has to be at the right time. When you come out of hospital all you want to say is, 'I'm out of hospital'. You don't want to read about it and anyway, you're too tired' (LBC27, breast cancer survivor, 8 years post-diagnosis). Another prostate cancer survivor (LBC17, prostate cancer survivor, 5 years post-diagnosis) wanted information on new treatment technologies to help with his ongoing urinary incontinence. Others talked about needing information that was trustworthy and medically correct:

**LBC13, prostate cancer survivor, 7 years post-diagnosis**
*I: If someone could offer you something to make your life easier in terms of your cancer,*

*from the hospital or your GP...what sort of thing would you want from them?*
R: When I first started, I used to look at loads of stuff on the internet but there were so many conflicting pieces of advice, different treatments that in the end I just stopped doing that...I didn't find it helpful. So, to have a...dedicated prostate line or page or something like that somewhere where you know what you're what you're actually reading is medically correct and it's based on good practice. And I think some of the stuff you read, it clearly isn't.

**Other cancer-related unmet needs**

In addition to their unmet psychological, complementary therapy and informational needs, several participants spoke about other cancer related unmet needs. One respondent felt 'let down' about the length of time she would have to wait for her next round of follow-up tests, suggesting that all she needed was the reassurance that the test results were 'alright' (LBC12, female colorectal cancer survivor, 7 years post-diagnosis). A colorectal cancer survivor, who was aged 53 at the time of his initial diagnosis and below the age for free prescriptions on the NHS[1], was frustrated that he had to pay for his numerous and expensive medications following discharge from hospital, saying 'I've paid my taxes due all my life. My father fought and died for this damned country. Why shouldn't I get free prescriptions' (LBC22, male colorectal cancer survivor, 7 years post-diagnosis). Lastly, a single woman who had survived breast cancer felt that more home support and aftercare could have been provided to her, especially in terms of 'somebody to do the shopping', saying, 'no notice was taken of my single state' (LBC27, breast cancer survivor, 8 years post-diagnosis). Many of these respondents suggested that their primary care team could

[1] From 1 April 2009, cancer patients in England have been eligible for free prescriptions via an exemption certificate from their GP or oncology clinic (16). However, this respondent would have been liable for his prescription fees at the time he was diagnosed with colorectal cancer in 2003.

have been a source for these services in the long-term, especially as the acute phase around diagnosis and treatment was too overwhelming a time to focus on their holistic needs.

### 5.3.3 Reasons for not using primary care services for cancer-related needs

Certain respondents had chosen not to discuss their cancer related concerns with a GP. The three main reasons given were that GPs were seen as non-experts in cancer, were too busy to be 'bothered' with cancer related issues, and lastly, that a lack of continuity in primary care hindered discussions about cancer and cancer follow-up.

**GPs are not specialists in cancer**

Many respondents expressed the opinion that GPs were not sufficiently qualified, trained or experienced in cancer to provide cancer related follow-up care or advice. GPs were seen mainly as generalists, and long-term survivors in this study tended to prefer to discuss their cancer related issues with a cancer consultant who had specific expertise:

**LBC08, male colorectal cancer survivor, 7 years post-diagnosis**
The GP, they are only a first port of call aren't they, because...if there's something really wrong with you they will pass you on to a specialist. They won't deal with it themselves. They're not like the old-fashioned family doctor that had to do the lot…I think it's a good thing because, after all, they can't be experienced in every disease there is.

**LBC13, prostate cancer survivor, 7 years post-diagnosis**
Again, you know, a GP has got to be a generalist by nature, you know. "You're ill. You're ill." This has got to be a specialist. I think when something is potentially life threatening you would like to feel a specialist is giving you the answers as opposed to a generalist, although some generalists are very good.

**LBC35, prostate cancer survivor, 8 years post-diagnosis**

*I: And you can have your follow-up from your GP or anything?*
R: No, no. I don't think GPs, I mean what do they know? [laughs] I don't think a GP…would want to look at this sort of thing at all. I think one of the important things is if you've got cancer you need to see a cancer specialist…I showed no symptoms [of the cancer], which is why people normally go to their GP and say, "I've got these problems." And then the GP will say, "Aha, that's probably, I'll send you off to a specialist." So no, I think you need to see a specialist.

**GPs are too busy to be bothered with long-term cancer related problems**

A second reason for not accessing primary care services was an impression that GPs are far too busy to be distracted or bothered by respondents' cancer related concerns; respondents seemed to feel that their GPs would view long-term cancer related worries as minor complaints not worth discussion:

**LBC03, breast cancer survivor, 16 years post-diagnosis**
*I: Do you think that there's anything that your GP could be doing for you in order to help you more?*
R: Well, not any more. Initially, that's when you need reassurance and I suppose it would be nice then to have a nurse or something. You don't want to keep bothering the GP.

**LBC14, female colorectal cancer survivor, 7 years post-diagnosis**
*I: Do you think that your GP could be doing anything [or] offering something ideal for you? I mean could you think of something that he could be doing for you?*
R: Not unless there's something new out there that I wasn't aware of that, you know, whether it was a type of aid, digestion aid or some type of syrup...but to be fair I've not been back to them to complain or to ask about it. Perhaps the next time I'm there, for whatever reason, I could mention it but I wouldn't see that as something that would need a specific appointment to see a doctor because I know they're busy enough.

**LBC38, prostate cancer survivor, 8 years post-diagnosis**

*I: Sometimes it's good to know that it's all going okay.*
R: Yes, aye, if it's like hearing from a doctor, you know, getting your doctor just contacting you and saying, "I'd like you come down and sort of talk about the results." It would, yeah. Not all the time but just to let you know that you're, everything is going fine. That would have been okay. I quite agree on that. But they're always busy, you know.

Because many of the respondents did not feel actively unwell, they did not want to bother their GPs. Others noted that although their GP was busy, there were opportunities for short discussions about long-term cancer related issues. Although it was deemed unnecessary to schedule a separate appointment, it was suggested by several respondents that cancer related issues could be raised in the course of an appointment for something else.

**Lack of continuity of care**

A third reason for not using primary care services for cancer related care was a lack of continuity of care. Respondents in practices without a named GP, or with a high turnover of staff since their initial cancer diagnosis, spoke about their frustrations of not being able to see the same GP from visit to visit:

**LBC09, male colorectal cancer survivor, 17 years post-diagnosis**
There are six or seven doctors in the practice and you see whoever you can…So I had to go and see this lady doctor and spend a few minutes going through the history of the whole cancer and then the duodenal ulcer problem [which was a result of the cancer surgery] and so that she could write a letter to this holiday situation to ensure that we were not legally bound to them in the future [for insurance purposes]. And she was only minimally aware of the cancer.

It seemed difficult for cancer survivors to discuss cancer-related issues if their GP did not have the correct notes or information about their cancer. In practices with numerous GPs

and no named practitioner, respondents were especially frustrated if they had an appointment with a GP who was unaware of the previous cancer or had not read their patient history prior to the consultation. In these cases, a discussion of long-term cancer related issues could not be carried out or instigated by the GP. One interviewee spoke about the high turnover of staff in his primary care practice, which triggered him to bypass his GP and go straight to his cancer consultant for his follow up appointments:

**LBC34, prostate cancer survivor, 10 years post-diagnosis**

One of the problems is the doctor that diagnosed me in the first place, moved on a long time ago. He was a nice enough chap. You could talk to him…but he didn't stay long and the next doctor came in and it coincided, I think, with a change in the general, I don't know what the word is actually, running of the surgery. It's quite a big surgery. There are about fifteen doctors there. It's like going into a mini hospital… they ask you questions and they haven't got a clue and they, obviously, haven't gone back over the records. I've complained to the surgery and I've said to them, "Look. I think it's important in any history with a patient and a doctor that the doctor has some knowledge of what's been going on in the past, preferably through knowing them. But if you keep swapping people about they've got no idea." And you move to the next doctor and you've got to start all over again and tell them everything again and I find that this is not terribly good. And so this is why I go to the consultant [directly]. When I get there he opens his file up and...he knows me and I'm happy with that.

Respondents who were able to continue to see the same GP over time valued the continuity of care, especially if their case history was complicated. One respondent, who was a survivor of Hodgkin's disease from her teenage years and colorectal cancer in her 40s, felt it was important not to move from her local area in order to maintain continuity of care with a GP who was familiar with her medical history:

**LBC14, female colorectal cancer survivor, 7 years post-diagnosis**

I know [with] some GP services...you can't always see the same one but I think it's always

important to try and see the same one so they've got a continuity of your history and what you are going through etcetera. Because otherwise you have to explain it all again... someone can't...read the whole load of [patient notes], I think mine are about this thick so they're not going to go through all those every time. So it's good to try and keep to the same GP and try not shift about...because by moving about you lose that continuity and I think that's really helped me and the service and the support I've got...I think if I'd gone to lots of different hospitals and GPs they'd have all had different ways of dealing with me and I wouldn't have got the consistency.

There was a common feeling, especially amongst the older respondents, that the nature of general practice had changed over time, with less emphasis on personalised care in recent years. Some respondents remembered a time when GPs took the time to phone and follow-up on an appointment, or visit them to check up on them in times of very poor health. The interviewees who did receive personal care such as home visits following discharge from hospital especially appreciated the extra support, and spoke positively about the individualized care provided to them by their GP:

**LBC23, male colorectal cancer survivor, 11 years post-diagnosis**
I came home [from hospital] and I lived downstairs, fortunately, because we've got [toilet] facilities downstairs and [the nurse] visited me...twice in one week and then every week for a month and then the GP came in once or twice until I was able to go down to the surgery. And I feel, my wife pointed out to me, when I go for an appointment to see a doctor I seem to get in very quickly. Other people [have] got to wait a week but she said, "Perhaps your name is on the screen. Perhaps there is some highlight."

**LBC24, female colorectal cancer survivor, 6 years post-diagnosis**
I could get home [from hospital] and I got better at home so the staff from my doctor's surgery were wonderful. They were really good. I didn't need them very often but if anybody was needed, the support I got from everybody in that respect was very good.
*I: So after you had your treatment and things what did you go and see your GP about that was related to your cancer?*

R: Well, in the early days, it was mainly that the nurses came here to clean out my PICC line. I had a PICC line in for the chemotherapy and they came for that and they came to see when I got back from hospital because I'd been discharged early but had to stay in bed...I'm quite pleased with my GPs practice. It's one of the most sought after locally so I'm lucky to be in that one.

### 5.3.4 Follow up services

**Opportunities for providing informal follow up care**

A recurrent theme expressed by respondents was a desire for their GP to briefly follow up on their cancer from time to time, and to assess their cancer recovery despite a lack of acute or ongoing issues. Although some did not feel they required formal follow up through primary care, many noted that there were opportunities for informal care, which could be provided in the course of appointments for other health issues. A long-term colorectal cancer survivor noted that 'the doctors could bring the subject up in conversation with men...when they're visiting them for other reasons' (LBC20, male colorectal cancer survivor, 11 years post-diagnosis). Some wanted a more active, but quick check, with the suggestion that a 'follow-up phone call once a year would be quite nice' (LBC07, prostate cancer survivor, 7 years post-diagnosis). However, while this participant did indicate that a follow-up phone call would be 'nice', he also stressed that he would find it 'slightly disconcerting if they [the GPs] kept ringing me up, you know, "How are you?'. Respondents seemed to appreciate being asked from time to time how they were coping even if there were no active concerns surrounding the cancer. This may have represented a need amongst the cancer survivors in this study for acknowledgement of their cancer experience by a health care professional. One breast cancer survivor felt that a more formalized primary care based follow-up appointment would be useful and reassuring:

**LBC39, breast cancer survivor, 16 years post-diagnosis**

*I: So do you think your GP could be doing anything for you?*

R: I think that perhaps it might be beneficial for women like me to maybe have a yearly visit and a check-up with the GP…But I think, maybe that's something that might be helpful particularly if cancer survivors of all of both gender I suppose, but certainly breast cancer survivors, if we get to the age that I am, a yearly check-up would be beneficial and I think it would be helpful with general health, instead of waiting for something to happen that you might miss.

*I: So what sort of things might be in that check-up, just like a general chat about what's going on and maybe a check-up for your breasts and things?*

R: Yes, and blood pressure and maybe even a simple blood test just to see what's going on...I think it would be reassuring.

In these instances, the respondents suggested that just an occasional chat with the GP could help or act as a reassurance without being too onerous or time consuming for the GP. For instance, a breast cancer survivor who attended her GP surgery for her follow-up Arimidex (hormone therapy) prescription every two months felt that she had 'mentioned these things [her long-term concerns] but he's never...picked up on them but then I don't think he really...understands or maybe he just feels helpless in the face of it' (LBC18, breast cancer survivor, 6 years post-diagnosis).

From speaking to cancer survivors at different stages of survival and in different geographical regions, there appeared to be extensive variation in follow-up services across the country. Respondents in neighbouring geographical areas and localities received very different services and care depending on their GP or practice based policies. This issue especially impacted long-term prostate cancer survivors, many of whom were still attending their GP surgery for follow-up PSA testing to monitor for disease recurrence. There was wide variation in the follow-up procedures and notification of PSA test results

across the different primary care practices. Many prostate cancer survivors wanted more information on their PSA levels, thresholds for starting second line treatment and notification of the test results. A low PSA test level can provide reassurance that the cancer has not recurred, and it was therefore important for survivors to keep track of PSA levels. While some prostate cancer survivors received letters, phone calls or follow-up appointments to discuss their PSA test findings, others described how they were not informed of their test results:

**LBC07, prostate cancer survivor, 7 years post-diagnosis**
I have a PSA test, a blood test, once a year and that goes back to the doctor's and they don't even contact me. So perhaps if they phoned up and said, "We've got your test. It's brilliant." Then I'd think, "Oh, okay." I think once or twice I have phoned them to say, "Is it is it okay? I haven't heard." And they've said, "Yeah, no, it's fine." But obviously they've got a huge workload and I think at the end of the day they're relying on me, if I've got a problem, to speak up and say that, but at this point in time I don't have any problems.

**LBC38, prostate cancer survivor, 8 years post-diagnosis**
My doctor has never got those [PSA test] results and contacted me to say, "Come down and we'll have a talk." No...none of them has ever done that, you know, I've been under them and it may have been a nice thing to have done to give me a bit more confidence.

Many of the prostate cancer survivors remembered receiving notification of their PSA test results when they were under the care of a hospital consultant, and felt that this service should continue now that their follow-up was primary care based, 'I would like I'd like a little letter like the hospital used to do because it's always is it [the PSA level] going up or is it coming down.' (LBC40, prostate cancer survivor, 8 years post-diagnosis). A few prostate cancer survivors maintained hospital follow-up appointments for PSA testing, however, one of these respondents was in a long-term clinical trial and another had private health insurance.

There was some variation amongst cancer survivors in terms of whom they would contact if they had a follow-up question or concern regarding their cancer. Some respondents saw their GP as a first point of contact if they had questions about their cancer, but others were given direct contact information for a consultant or cancer care nurse upon finishing their hospital-based follow up. Many of the cancer survivors in this sample acknowledged the gate-keeping role of their GP even if they did want to speak to their cancer consultant, and accepted that they firstly needed to speak to their GP in order to obtain a referral to hospital cancer services. For these respondents, it was important to know that it was easy to re-access specialist care without delay, therefore, an crucial role for their GP was to efficiently refer back to hospital when a serious problem or concern arose. One respondent, who felt she could directly contact her consultant, acknowledged that she would firstly go to her GP regardless, 'The surgeon did say, I could go straight back to them at the hospital but...as a matter of courtesy, I'd probably go through my GP' (LBC18, breast cancer survivor, 6 years post-diagnosis). Other respondents mirrored the view that GPs were gatekeepers to cancer services in hospital:

**LBC14, female colorectal cancer survivor, 7 years post-diagnosis**

Usually, I go to my GP because to be honest, from the hospital's point of view they don't tend to like to see you without you have been to [see] your GP. They prefer you to have at least acknowledged to the GP that you...have a concern and they want you to go through the blood test, CT scan or whatever it is before they get involved. They're quite happy to talk over the phone and give you advice if they can, but invariably they'll tell you to see your GP anyway so I'll go there.

**LBC28, female colorectal cancer survivor, 7 years post-diagnosis**

*I: Or if you had a question or if, say, you wanted to try and request a colonoscopy where would you [go]?*

R: I'd have to go back to my doctor.

*I: So your GP.*

R: [pause 5 seconds] Well, I don't know where else I would go really. I would think the GP because he has to get in touch with the surgeon, doesn't he. You can't go direct to the surgeon. You've got to go through your GP.

Two respondents agreed that although they would initially contact their GP for any cancer related concerns, it was reassuring and valuable to have a direct contact at the hospital as well. A few of the interviewees spoke of the special relationship they had with their cancer consultant, with whom they had shared the diagnosis and treatment phase of their cancer:

**LBC03, breast cancer survivor, 16 years post-diagnosis**

*I: So if you had a question for instance about your cancer now who would be the first person that you'd approach?*

R: Well, it would probably have to be my GP. My oncologist, who I've been with the whole time, I can also phone her…she's always said that if you have any worries, just make an appointment and come back. So that's very reassuring… I can't imagine anything worse than not having her at the end of the telephone really or her secretary. So I think it's important that everybody has a GP, but I think possibly you do need somebody

that's been through it with you a little bit and she was the one who treated me. So, yes, I think it's very important to have her at the end of a telephone.

**LBC14, female colorectal cancer survivor, 7 years post-diagnosis**
I was contacted by his [previous cancer consultant] replacement who said, "Basically, you know, you've been clear for fifteen, twenty years. I think you're okay but here's my number, here's my details. If you've got any worries please call me and we'll see you."…if I've got any worries I can go straight back to them if I want to. So I have a named contact I can go to, which is super and obviously in the meantime, I have a local doctor that I go to.

Many of the respondents were given direct contact details of a cancer nurse, for instance, a breast cancer survivor describes how 'when I left she [the breast care nurse] gave me her card and she said she'd always been in touch'. This woman continued to say that she would initially get in touch with the breast care nurse who 'could direct me to whoever I needed to talk to'. (LBC06, breast cancer survivor, 8 years post-diagnosis). One respondent was even advised by her consultant to approach secondary care services directly and bypass her GP, 'I think they [her consultants] said, "If you have any problems in the future come back to us...Don't worry about going through your GP"' (LBC02, breast cancer survivor, 11 years post-diagnosis). Not all respondents were provided with direct contact information for their cancer consultant, and there was wide variation in the ability to directly access secondary care. Other respondents did not want to access hospital services in the long-term and preferred to arrange follow-up services in their GP surgeries. A prostate cancer survivor noted that while he was given the option to receive his hormone therapy injections at the hospital, he opted for the convenience of his GP 'because they're very flexible' and he was able to make an appointment to see his GP for an early morning appointment if he so chose (LBC13, prostate cancer survivor, 7 years post-diagnosis).

### 5.3.5 Modelling the pathway of primary care use amongst long-term cancer survivors

The results of this interview study were used to develop a visual framework encompassing the different themes and phases of cancer survivorship and use of primary care services as described by the interviewees. Reflecting a similar cancer trajectory as reported in the focus group study by Kendall et al (1), the respondents in this sample described progressing through different phases of using primary care services as they moved past the diagnosis and treatment stages into a survivorship phase (Figure 5.1, Pathway of use of primary care services amongst long-term cancer survivors in this project). Most, but not all cancer survivors moved into one of two pathways following treatment and discharge from hospital follow-up; either integrating cancer and its after effects into their lives or moving on from cancer.

Those respondents who moved into a phase of learning how to integrate cancer and its long-term impact into their lives spoke of cancer 'staying with you forever'. This concept of 'integration' has been previously discussed in the literature as a natural stage of recovery following the traumatic event of cancer diagnosis. In her model of psychosocial function, Tish Knobf discusses how the majority of breast cancer survivors were 'emotionally distressed...and endured the side effects of therapy but were able to move on with their life, integrating cancer as one component of their life experience' (17). In this interview study, the respondents who integrated cancer into their lives identified specific long-term services they felt that their GP could provide, including follow-up testing, raising the subject of their previous cancer from time to time, psychological services,

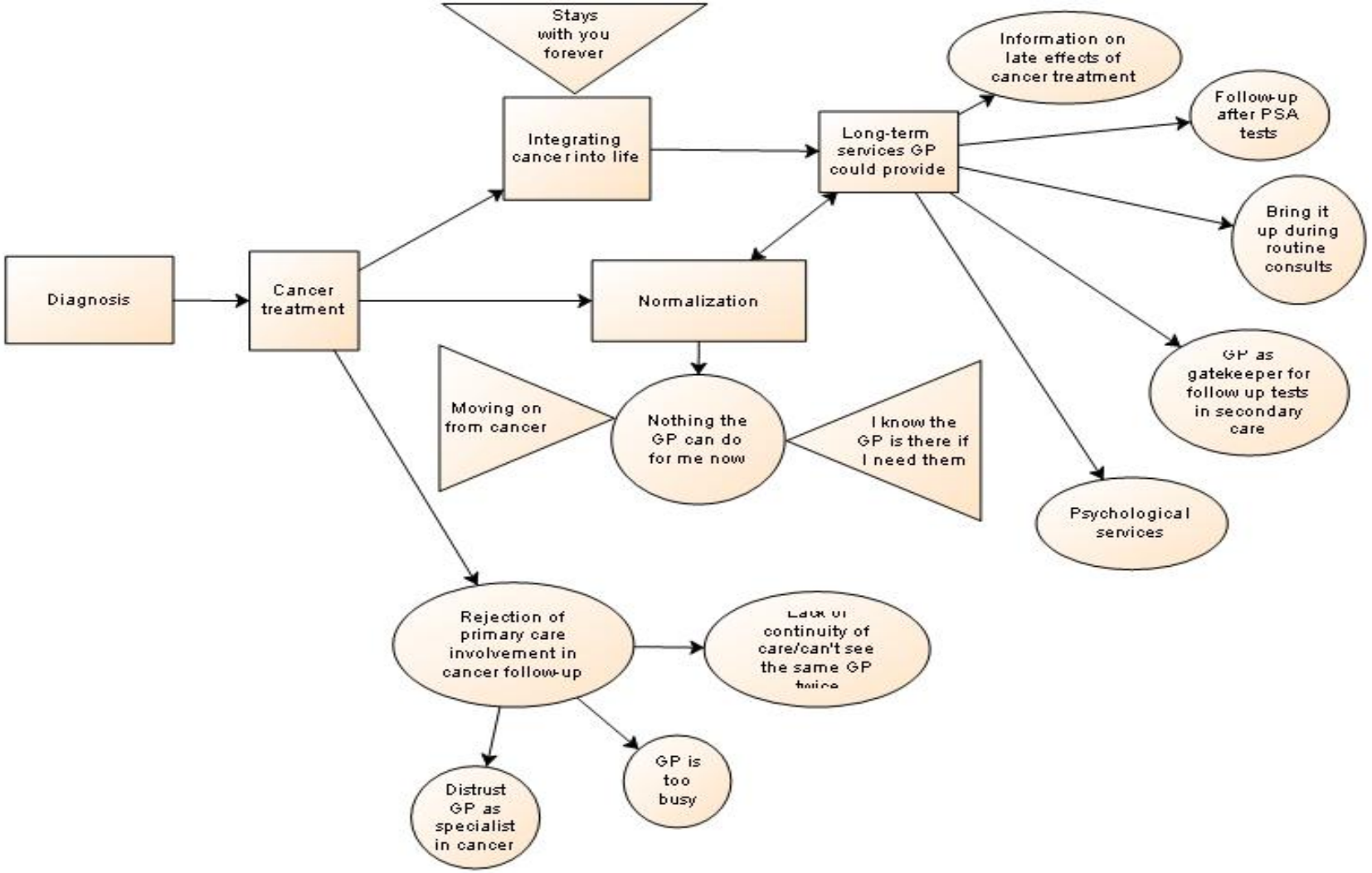
information on late effects of cancer treatments and acting as an efficient gatekeeper to secondary care services if they were needed. Some interviewees with ongoing worries or symptoms regularly re-accessed primary care services in order to get cancer related follow-up tests or referrals to secondary care.

In contrast, other individuals described a normalization or readjustment phase, which indicated 'moving on' from cancer. Although cancer certainly may have played a large role in their life at some point, these interviewees expressed coming to terms with their cancer and a decreasing concern regarding the impact of cancer on their lives. Some of these respondents felt that although there was little their GP could provide to them in terms of long-term care for their cancer, they were reassured by a positive relationship with their GP, who was viewed as easily accessible if they needed to re-access medical care in the future.

The third and final pathway followed those participants who felt that the GP could do nothing for them cited a number of reasons for rejecting primary care involvement in their long-term cancer related care, including a distrust of their GP's expertise in cancer, an impression that GPs were too busy to be 'bothered' with cancer related issues, and dissatisfaction with lack of continuity in primary care.

This model provided a useful tool for organizing the themes emerging from the interviews and my thoughts on the interviews. However, this framework does not represent an inflexible model; respondents did not strictly follow one pathway or the other and some described simultaneously moving on from cancer while integrating long-term cancer related issues into their lives.

**Figure 5.1: Pathway of use of primary care services amongst long-term cancer survivors**



**Review by interview participants**

Three interview participants reviewed this entire chapter; LBC14 (female colorectal cancer survivor, 7 years post-diagnosis), LBC18 (breast cancer survivor, 6 years post-diagnosis) and LBC34 (prostate cancer survivor, 10 years post-diagnosis). The participants were asked to provide written feedback and general thoughts on whether the findings accurately described their experiences, which is summarized in Box 5.2.

**Box 5.2: Feedback from interview participants**

LBC14 'You have expressed and understood my views correctly…thank you for getting our views known.'

LBC18 'I do not think there is anything I disagree with - obviously different people will have had different experiences or if they have had the same ones they will not necessarily react to them the same.'

LBC34 'Having read the summary twice I find that most of the survivors had similar feelings to myself regarding the involvement of their GPs…In summary I would agree that the GP cannot know everything about every disease so all they can do is to recognise a problem and then refer the patient to a specialist, but once they know the outcome they should show more interest in their patient to ensure good continuity of support, but the patient can do a lot for himself if he reads as much as possible about the disease and it would help if he was directed towards the best source of information for this purpose.'

These three respondents broadly supported the findings of this work, and did not report any disagreement with the main themes or results.

## 5.4 Discussion

### 5.4.1 Summary of main findings

Due to the increasing number of cancer survivors in the UK and an increasing movement towards earlier discharge from hospital follow-up, primary care will increasingly play an integral role in the ongoing care of long-term cancer survivors. A summary of the main findings from this interview project relating to how long-term survivors of cancer view their interactions with primary care is presented in Box 5.3.

**Box 5.3 - Summary of main findings from the qualitative study relating to interaction with primary care**

- The majority of cancer survivors talked about moving on from their previous diagnosis
- In general, the respondents agreed that they did not require active GP involvement in their long-term care, and acknowledged that their GPs was available for advice and as a gatekeeper for access to hospital services
- Some long-term cancer survivors had ongoing needs including a need for psychological services, access to complementary therapies and information
- Some cancer survivors did not want to consult with their GP for cancer-specific issues due to a concern about lack of GP skills and expertise for a disease such as cancer
- Where GPs did play an active role, for instance with PSA testing, participants noted deficiencies in the systems such as a lack continuity of care and notification of PSA test results

The majority of long-term survivors in this study indicated that they did not require ongoing or regular follow-up in primary care, while other respondents spoke of specific unmet needs, including a lack of information on late effects of treatment, a need for long-term psychological help, and access to complementary therapies on the NHS. Those cancer survivors who did not require ongoing primary care involvement agreed that GP services were helpful and convenient to re-access if and when an acute need were to arise. A number of these interviewees wanted the opportunity to talk about their cancer with their GP informally and briefly, but some of the cancer survivors in this project discussed why they did not feel that their GP could provide ongoing cancer-related care. The main reasons included a perception that GPs were too busy, that GPs as generalists did not have the necessary expertise to discuss cancer related issues, and a feeling that lack of continuity in primary care did not facilitate discussion of long-term issues like cancer. These results reflect those of a recent survey of breast cancer survivors conducted in the United States, which showed that most items related to primary care provision of cancer care, including symptom diagnosis and management, follow-up and surveillance for late effects of cancer treatment were given low endorsements. This means that a large proportion of the women in this survey study had concerns about the capability of their primary care provider to deliver cancer-specific care in the long-term (18).

In terms of primary care based follow up services, many of the prostate cancer survivors in this study did not receive automatic notification of results from PSA tests conducted by their GP. There was a wide variation in follow-up practices and preferences amongst the long-term cancer survivors in this study. Several prostate cancer survivors who were receiving follow-up PSA testing via their GP received their test results as a matter of routine care. However, other prostate cancer survivors were not notified of their test results, and wanted to

be reassured that their test results were still within the acceptable range. These findings were mirrored in a report of the experiences of follow-up for prostate cancer patients. In their study, O'Brien and colleagues found that men who were only contacted about their PSA test results if there was a problem with the reading were unhappy if they were used to regular updates on their PSA levels as part of their hospital follow-up (19). Notification and information on PSA test results was significant to the prostate cancer survivors in this study because it was important to know whether or not their previous cancer was still in remission. The 'substantial role' of PSA testing and results has been described in a previous qualitative study of unpartnered prostate cancer survivors, and the findings from this project support those findings (20).

Many of the cancer survivors acknowledged the gate keeping role of primary care, but some still preferred to contact their hospital consultant directly to discuss cancer related issues. An American focus group study of breast cancer survivors 10 years post-diagnosis reports a similar finding; women preferred to see their oncologist rather than a general practitioner, while acknowledging the holistic and supportive nature of primary care practitioners (21). The ability to bypass primary care depended on having direct contact information for their consultant or cancer care nurse, which varied considerably across the interviewees.

### 5.4.2 Implications for primary care

While the results of this project suggest that the majority of cancer survivors do not require ongoing care, some may require their GPs to take a proactive approach to identify those who may face long-term cancer related unmet needs. High risk groups may include those patients who are experiencing depression, older cancer survivors, and those with additional comorbid diseases (22;23).

These findings suggest that while the majority of cancer survivors do not require specialized follow up services, many could benefit from a short appointment with a member of their primary care team upon discharge from hospital follow-up. The purpose of this appointment could be two-fold; firstly, to encourage cancer survivors to seek primary care services in the future if a need arose, and secondly, to offer psychological help and information on late effects of treatment at the point of discharge. This initial appointment could additionally allow cancer survivors better understand the services available in primary care and open the dialogue for cancer related issues with their GP. Cancer patients in a Scottish focus group study identified the need for a guide within primary care to 'listen and explain about the course of the illness and treatments, respond quickly to whatever urgent need is felt [and] support them' (1). Potentially, this appointment could be offered by a named practice nurse who could act as a key contact for future issues, which would decrease the burden on general practitioners. Identifying a 'key contact' is an important step in assigning responsibility for cancer survivorship care, as it organizes care, provides a point of contact for information, and reinforces a positive and continuous relationship with one person (24).

Many cancer survivors in this sample suggested that it might be helpful for the GP to briefly raise the previous cancer from time to time in the course of regular care for other conditions. A UK based study of prostate cancer patients undergoing both hospital and primary care based follow-up indicated that it was important for GPs to call them in to see whether they were coping (19). Intermittently raising the issue of their previous cancer may provide the cancer survivors with the reassurance that they could talk about cancer-related issues without the worry that they are 'bothering' their GP.

Despite the importance placed upon feedback of PSA tests, reporting of results was not standardized across the country or even in the same regions. One suggested improvement is to issue or provide a set of guidelines to indicate the appropriate level of PSA feedback if this is deemed necessary as part of prostate cancer follow-up. While GPs may not be able to take on the additional role of contacting patients with test results as some GPs conduct up to 20 blood tests a day[2], there may be some utility in using a practice based, assigned nurse or named key contact to feedback test results to survivors.

Continuity of care was also identified as an important aspect of primary care based follow up by some of the cancer survivors in this study. There are several different aspects to continuity of care, which may include a development of trust (25), patient familiarity with the doctor and a GPs knowledge about the patients through an accumulated knowledge of the patient's medical history (26). Previous research has shown that patients prefer to see the same doctor when dealing with long-term or complex problems, which describes the issues facing many long-term cancer survivors (27). A greater flexibility in appointments based

[2] Personal communication, Dr. Peter Rose

systems and an ability to choose which GP for follow-up appointments may improve continuity of care amongst cancer survivors, and encourage this population to consult with their GP rather than turn to hospital-based consultants.

### 5.4.3 Integrating results from the GPRD and qualitative studies

This thesis has involved two component projects; a database study using the GPRD and a qualitative interview study. Although the two parts of the thesis are independent projects, they both consider how people living at least five years past a diagnosis of breast, colorectal or prostate cancer use primary care services. The GPRD gives a quantitative summary of the use of primary care services by survivors of these three cancers while the qualitative study explores how individual cancer survivors use GP and primary care services and whether there are any unmet needs.

The themes covered in the qualitative interview schedule (see Appendix 7) focussed mostly on cancer-related needs and quality of GP care and did not overlap with the issues arising from the GPRD analysis. One GPRD finding was specifically investigated in the qualitative interviews; the analyses on screening and preventive care highlighted a possible underuse of screening mammography amongst breast cancer survivors more than 10 years post-diagnosis in the GPRD cohort (section 3.3.2). The interview study included 7 women who had survived at least 10 years after a breast cancer diagnosis. In order to investigate reasons for this underuse I asked each of these women whether they attended mammographic screening and how each individual felt about follow-up testing. While some respondents reported feeling anxious before attending cancer screening, the breast cancer survivors I spoke to were aware of the importance of mammography following a cancer diagnosis and attended screening regularly. Therefore, although the GPRD analysis suggests an underuse of

mammographic screening amongst breast cancer survivors more than 10 years post-diagnosis, the small numbers of interviewees meant that it was difficult to come to any sort of insight to explain this finding through this qualitative study.

Some of the interviewees in the qualitative study talked about needing better psychological care, however, analysis of the GPRD showed that cancer survivors were no more likely to consult with a GP for depression compared to controls. It is difficult to interpret the qualitative finding in light of the case-control analysis conducted in the GPRD. There may be people in the general population who have ongoing psychological care needs that are also not being addressed by their GP, however I only spoke to people who were post-diagnosis of cancer and it is difficult to come to any broad conclusions relating the two results.

Results from Chapter 4 (4.3.3) show that people living five or more years past a diagnosis of breast, colorectal or prostate cancer continue to remain at risk of early mortality due to their index cancer. However, in the qualitative study, some people felt that they had been cured of their disease. For instance, one prostate cancer survivor (LBC38) who was 8 years post-diagnosis, stated, 'No, it [the cancer] is all gone and I'm on the up. I'm on the right way. No, it does not worry me that sort of thing. I've got away from it. I'm cured, me, I'm cured. I'll not get cancer again and I'm convinced of that'. This quotation highlights that some cancer survivors may not appreciate the possibility of recurrence or perhaps do not wish to focus on thoughts of cancer recurrence.

Overall, the GPRD analysis and the qualitative studies have provided a comprehensive overview of the use and experience of primary care services amongst long-term survivors of breast, colorectal and prostate cancer.

### 5.4.4 Strength and weaknesses

There are several strengths and weaknesses to this interview study. The strengths of the study include the large sampling frame and in-depth nature of the interviews which allowed the respondents to discuss those issues of most importance to their experience. The majority of health and illness experience studies led by the Healthtalkonline team use a sampling strategy of inviting people to take part through GP practices, hospital consultants and support groups from across the UK. However, this study was different in that only respondents to the initial cancer survivors questionnaire based in two regions of the UK were eligible to take part in the interviews. While these two regions cover a diverse range of socioeconomic and urbanized and rural areas, it is a limitation of this project that the sampling frame did not cover the whole of the United Kingdom. The response rate to the questionnaire was 51% and the sampling frame in this study does not include non-responders to the questionnaire. It is possible that the non-responders to the questionnaire represented a demographically diverse population with a different survivorship experience. Additionally, not all respondents to the survivors questionnaire were interested in taking part in the interviews. Non-responders may have included a higher proportion of individuals with little or no cancer-related needs which may have influenced their interest in completing the questionnaire. However, the sampling strategy purposively considered both those cancer survivors expressing high and low levels of unmet cancer needs as measured by the Cancer Survivors Unmet Needs measure (CaSUN) in order to cover as wide a range of patient experiences as possible within the limited sampling frame.

There were only 7 respondents to the main survivors questionnaire who indicated an interest in the qualitative study and who were not of White British background. In a project of this

nature, where the researcher tries to aim to cover as wide a range of experiences as possible, it is useful to interview members of ethnic minority groups. However, it was not possible to recruit any of the ethnic minority respondents to the questionnaire study. Finally, this qualitative study intends to describe a broad range of experiences rather than a numerically representative sample of long-term cancer survivors. Therefore, the results from this study cannot be used to represent the views of all cancer survivors based on the demographic characteristics of the respondents.

### 5.4.5 Conclusion

The results from this qualitative study suggest that some cancer survivors have specific emotional and physical needs, but not all cancer survivors require active long-term cancer-related care from their GP. Some cancer survivors may benefit from increased continuity of primary care systems and more information and feedback on PSA testing to monitor recurrence.

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# Chapter 6: Discussion and implications for future work

## 6.1 Introduction and recap of the main aims

With over two million cancer survivors now living in the United Kingdom, it is important to understand the long-term impact of cancer on the health and health care needs of this population (1). The majority of patients undergoing curative treatment for cancer will be discharged from hospital-based follow up back to the sole care of their GP. As GPs will become increasingly responsible in the long-term care of this population from between three and five years post cancer-diagnosis, it is important to understand the use and experience of primary care usage amongst cancer survivors (2).

The main aims of this thesis were to examine how survivors of breast, colorectal and prostate cancer use primary care services and to explore their unmet needs for health care in the United Kingdom. The objectives of this thesis were threefold. The first objective was to study the use and quality of primary care services amongst long-term survivors of breast, colorectal and prostate cancer. This involved describing the primary care consultation patterns, use of preventive care and monitoring for chronic diseases, and prescribing patterns for common therapies. The second objective was to study the risk of diseases related to cancer treatment, the risk of second cancers, and the risk of early mortality amongst cancer survivors. Lastly, this thesis has aimed to describe the patient experience of surviving cancer by exploring individual patient views on the use of primary care services and unmet needs for future care.

This final chapter summarizes research described in this thesis, discusses some of the overall strengths and weaknesses of the project and suggests future avenues for research and implications for policy.

## 6.2 Major findings and how this integrates into previous research

There are several new findings emerging from this thesis describing the way in which long-term survivors of breast, colorectal and prostate cancer use primary care services. In particular, attention has focussed on describing the the quality of use of these services, current good practice in British primary care, and areas where services can be improved.

Use of a large, population based database such as the General Practice Research Database (GPRD) has provided the first description of the consultation patterns of British cancer survivors compared to similar patients who have not been diagnosed with cancer, matched on age, sex and general practice. Analysis of the GPRD has shown that cancer survivors consult with GPs and other members of their primary care team more often than controls. The consultation rates of breast and colorectal survivors converge with controls by about ten years post-diagnosis, but prostate cancer survivors continue to see their GP more often than a control population even 15 years post-diagnosis. While research into use of preventive care and management of chronic diseases has been well described in American populations of cancer survivors, there has been no previous work looking at this care amongst survivors of cancer in the UK (3-13). In this thesis, cancer survivors have generally been found to receive the same screening, preventive care and chronic disease monitoring as controls, with the exception of mammography in breast cancer survivors. An investigation of trends in

prescribing for commonly used therapies has shown that cancer survivors use higher rates of anti-depressants and anxiolytics, especially at the end of life, and that cancer survivors use higher volumes of pain relief and treatments for erectile dysfunction. The increased use of pharmacological therapies may represent higher rates of depression, pain and sexual dysfunction amongst the cancer survivors in the GPRD cohort.

Surviving cancer has previously been associated with an increased risk of second cancers, late effects of treatment and early mortality (14-18). By linking the GPRD with data from the National Cancer Intelligence Network cancer registrations and death registrations from the Office for National Statistics, this thesis has quantified the risk of second cancers and cause-specific mortality amongst a population-based cohort of long-term survivors. The results showing prolonged risk of non-cancer related deaths amongst breast, colorectal and prostate cancer survivors in the UK, along with an extended risk of dying from colorectal cancer after five years, have not been shown before. Analyses in section 4.3.1 have shown an overall increase in the risk of developing treatment-related diseases such as heart failure, dementia and coronary artery disease amongst cancer survivors receiving any treatment.

The analyses of incidence of new diagnoses have also found that breast, colorectal and prostate cancer survivors are at a significantly increased risk of osteoporosis and osteoporotic fractures. Prostate cancer survivors in the GPRD cohort were especially at risk, with two and a half times the risk of developing osteoporosis compared to controls. This increase in risk is likely due to the long-term effects of using androgen deprivation therapy (ADT), which increases bone turnover and decreases bone mineral density (19-22). All three groups of

cancer survivors were more likely to have received a bone density scan at least once during the three year analysis period, with prostate cancer survivors almost 60% more likely to receive a scan. It is unclear whether these tests are being conducted as part of follow-up procedures as there are currently no guidelines in primary care or use of bone density scans amongst cancer survivors.

Results from the qualitative study of 40 long-term survivors of breast, colorectal and prostate cancer have found that the majority of cancer survivors feel that they have moved on from their cancer diagnosis, and do not see a large role for their GP in their long-term care. Some cancer survivors acknowledged ongoing needs including a need for psychological services, access to information on complementary services and late effects of treatment. Some participants noted deficiencies in primary care in terms of their cancer follow-up, including a lack of continuity of care and notification of PSA test results.

## 6.3 Strengths and limitations of the research methodology

This thesis has considered the use of primary care services by survivors of breast, colorectal and prostate cancer through both quantitative and qualitative studies. By using these two distinct methodologies, it has been possible to comprehensively describe how cancer survivors use GP services and detail areas where care is deficient and needs are unmet.

Additional strengths of this research include the large size of the GPRD cohort and the ability to compare results from the quantitative analysis against a representative control population. This thesis also represented the first published use of the GPRD and NCIN/ONS linked

datasets. The qualitative study was also large and involved individuals across a wide range of ages and length of survival post-diagnosis of cancer.

One of the strengths of the study design is that it has allowed for comparisons within matched groups of cancer survivors and controls. National data on cancer survival and mortality tend to measure relative survival with the general population as the baseline (23). Relative survival measure may not take deprivation measures into account despite the fact that cancer incidence and mortality are linked to socioeconomic status. Using the primary care practice as one of the matching criteria between cancer survivors and controls means that this study has accounted for practice level deprivation scores (24).

The GPRD data for this study was provided in early 2007, and with exception of the ONS linked data which runs until 2009, the last date of GPRD follow-up data was 1 September 2006. It is important to remember that this is a retrospective analysis conducted on data that is now five years out of date. However, there have been no major changes or developments in the way that cancer survivors are cared for within primary care since 2006 and it is reasonable to expect that many of the results could be replicated in a more recent GPRD dataset.

Recent research has demonstrated that different researchers may have conflicting interpretations of which codes are relevant to the medical condition and that the selection of codes for case definitions should be transparent (25). Using our own code lists to identify clinical diagnoses in the GPRD may mean that other researchers could use a different code set and produce differing results. Because the initial Read code searches were over inclusive, it is

unlikely that any frequently used codes were excluded from the code lists used for case identification.

Recent work from our group has shown that up to one-third of cancer survivors were not discharged from hospital follow-up even 5-16 years post-diagnosis. While the analyses in this thesis have focused on use of primary care services, it is possible that some cancer survivors are continuing to receive support and care through hospital-based services, especially if they are still undergoing regular hospital-based follow-up. In the qualitative study, some of the individuals talked about having a direct phone number for cancer care nurses or their consultant. A more comprehensive analysis would have taken into account the hospital-based care that these long-term survivors may have still been receiving. It is possible that underuse of care, such as use of mammography or psychological services, may reflect underestimation of services in the cancer survivors cohort by not including hospital-based procedures or services.

One of the objectives of this thesis was to investigate the risks associated with surviving cancer, including late effects of cancer treatment. The main limitation in achieving this objective was the lack of detailed treatment information, which prevented analysis of treatment effects amongst the cancer survivors cohort. This is due to poor historical recording of treatment in cancer registries and low coverage of the GPRD linkage scheme amongst practices contributing data to the GPRD data warehouse. There is a strong need for improvements in capturing cancer treatment at cancer registries and cancer treatment data needs to be incorporated into patient electronic medical records in primary care.

Many of the analyses in the GPRD project involved multiple statistical tests. However, the analyses in this thesis were planned a priori using an analysis plan based on pre-defined hypotheses. I have not used adjustments such as Bonferonni corrections for multiple comparisons as these do not necessarily improve interpretation of the findings and can produce misleading results (26;27). Instead, I tried to use my judgement to assess which findings were relevant; often the associations reaching statistical significance were more numerous than would be expected due to chance. Finally, due to the size of the GPRD cohort, many of the statistical tests reached significance at the $p<0.05$ level. The size of the p-value and the precision of the 95% confidence interval is dependent on the size of the sample; the larger the sample size, the narrower the confidence interval and the smaller the p-value (28). In this large study, in order to avoid making judgements on small differences with a high level of statistical significance, I avoided use of p-values and instead reported 95% confidence intervals along with rate or odds ratios, which indicate the strength of the effect as well providing an estimate of the clinical relevance of the findings (29). All statistically significant results are reported, the focus remained upon discussing the statistically significant results in terms of size of the effect and clinical relevance.

## 6.5 Future avenues of the research

The findings from this thesis have provided an overview of how long-term survivors of three common cancers use primary care services and long-term health risks associated with surviving cancer. The results have both implications for future research projects and for policy in the UK related to the National Cancer Survivorship Initiative.

### 6.5.1 Future research

Future research could entail examining the findings reported in this thesis in more detail, expanding the research more widely, or testing interventions to improve the care of cancer survivors using randomised control trials within a primary care setting.

Overall use of mammography was lower amongst long-term breast cancer survivors when compared to a matched control population. Use of a large, anonymised database means that it is impossible to investigate individual decisions or factors influencing uptake of cancer screening, and the size and distribution of the qualitative sample meant that there were too few women to fully explore this finding. Future research should identify reasons and explanations for lower uptake of mammographic screening with a view to developing interventions for improving rates amongst breast cancer survivors.

This work has found an increased risk of morbidity and early mortality amongst cancer survivors compared to controls. Some of these health outcomes can be prevented by modifying unhealthy lifestyle choices. There are several ongoing studies examining the adherence and long-term outcomes associated with increasing physical activity, promoting smoking cessation and improving diet amongst cancer survivors. Proponents of these lifestyle changes amongst cancer survivors indicate that it can improve quality of life and lessen the impact of long-term and late effects of treatment, such as lymphoedema, loss of bone density, depression, cardiovascular morbidity and even early mortality (30-34). While the results of this thesis quantify the risks associated with cancer in a population-based cohort, future work

could test the impact of physical activity, smoking cessation and dietary interventions to reduce these risks in the long-term.

This thesis has described potential long-term risks and early mortality associated with cancer survivorship status. A lack of consistent and validated data on original cancer treatment means that it has not been possible to stratify these risks upon treatment modality or intensity. Future work should use improved and more comprehensive data sources to provide more information on risks of late effects and early mortality associated with specific cancer treatments.

The three groups of cancer survivors investigated in this thesis are examples of cancers with good survival rates and represent the majority of prevalent cancers in the UK. However, each cancer has its own specific risk factors, survival and treatment characteristics and not all of the results from this thesis will be applicable to other tumour types. Further research may be necessary to explore similar outcomes amongst other cancer types.

### 6.5.2 Implications for primary care

Primary care will be the main point of contact for long-term cancer survivors and their comprehensive care needs following discharge from hospital. Chapter 1 described the cancer care trajectory (Section 1.5.6, Figure 1.6) and the role of primary care in managing chronic or intermittent disease in the cancer-free survival stage. This thesis has described aspects of this care, and considered how the growing population of cancer survivors uses and experiences primary care services in the United Kingdom.

Although there is little previous research relating to the individual experience of using primary care services amongst cancer patients, cancer is increasingly viewed as a chronic disease. It is possible to draw parallels between the experiences of cancer patients with those who have other long-term health conditions, and while the primary care model for chronic diseases such as diabetes and congestive heart failure has been shown to improve patient outcomes, this model is not currently applied to long-term cancer survivors (35;36). The chronic care model is based on an understanding that the majority of chronic illness care is performed in the primary care setting (37). A main focus of the model is an increasing emphasis on self-management support, whereby patients themselves become the principal caregivers. Because people live with chronic diseases for many years, they are encouraged to work with their primary care team to collaboratively acquire the skills to manage their chronic disease and routinely self assess and solve their own problems with the appropriate information (38). An initial appointment with a GP upon discharge from hospital follow-up may facilitate this shift towards supportive self management within the long-term cancer survivors population. Therefore, the chronic care model, as applied to this population, would not result in active monitoring by GPs, but would require GPs to equip cancer survivors with the tools and information to look after themselves in the long-term.

### 6.5.3 Implications for policy

With over 1.2 million cancer survivors living at least five years past a cancer diagnosis in the UK, understanding the issues facing this population and their use of primary care services is becoming increasingly relevant to policy makers. This thesis has coincided with national

initiatives to assess the health service usage of cancer survivors and to improve their care. Since work on this thesis began, the National Cancer Survivorship Initiative (NCSI) has developed a research agenda to address the long-term needs of people living after cancer to answer 'priority questions on survivorship' in order to 'improve the ongoing services and support for those living with, and beyond, cancer' (39;40).

A main focus of the NSCI is to provide risk stratification tools to guide surveillance and screening amongst groups of cancer survivors receiving specific treatments. An NSCI document summarizing research priorities states that 'the highest priority for research in cancer survivorship is to understand the natural history of survivorship and to create risk stratification tools for all cancers and for survivors of all ages to assess the most appropriate after care for each individual' (41). This thesis has provided information on the natural history of surviving cancer but without addressing the question of treatment or pre-existing risk factors such as diet, exercise or family history for morbidity or early mortality. Future work should use additional treatment information and patient characteristics in order to predict morbidity and early mortality and to guide individualized risk stratification as recommended by the NCSI.

In order to ensure that primary care physicians are aware of patient cancer treatment and potential late effects, an Institutes of Medicine report recommended use of a Survivorship Care Plan (SCP) entailing an individualized follow-up plan (35). The results of from this thesis have highlighted several areas where care for cancer survivors is poorer than the general population and the risks associated with long-term survival from a cancer diagnosis. Some of

these areas can be used to guide future SCP development and areas for active surveillance, for instance screening for osteoporosis, amongst cancer survivors.

Since 2003, one of the indicators included in the British Quality and Outcomes Framework (QOF) is for each cancer patient to have a 'cancer care review' within 6 months of diagnosis. QOF guidance defines the purpose of this review as an opportunity to discuss 'an assessment of support needs, if any, and a review of co-ordination arrangements with secondary care' (42). The content of the cancer care review meeting is currently left to the discretion of the GP. Some respondents to the qualitative study described in this thesis described unmet needs such as psychological support and information about long-term effects of treatment. These services should be sign-pointed more effectively during the cancer care review appointment.

Recognizing the limitations of the current cancer care review, Macmillan Cancer Support developed a submission for the 2010 QOF to support the introduction of additional indicators and expansion of the content of the six month cancer care review. This was not adopted and the feedback from the QOF panel was that the evidence base was presently lacking to support the inclusion of the more robust review (43). In the future, it might be possible to amalgamate an appointment the cancer care review at the point of discharge from hospital follow up which could include use of a survivorship care plan issued from secondary care. The majority of patients in a recent study in Oxfordshire felt that a designated appointment with their GP to discuss their cancer-related concerns would be valuable. The preferred timing of the appointment varied amongst respondents; some stated that the end of active treatment would be the best time while others wanted several specific appointments with their GP over the

course of their cancer journey (44). The authors recommend that 'an invitation to a specific review appointment following completion of active treatment would promote continuity of care and legitimise the raising of any concerns'. While there is nothing stopping cancer survivors from making appointments themselves to speak to their GPs at their own initiative, the authors of this paper felt that it would 'validate' the concerns of the cancer survivors who are invited to attend an appointment to discuss any concerns (44). An expansion of the current six month cancer care review to a second review appointment under QOF may ensure that patients are not 'lost in the transition' between secondary and primary care at the end of active treatment (35).

## 6.6 Conclusion

This thesis has aimed to describe the use of primary care services amongst cancer survivors, risks associated with cancer survivorship and the individual experience of using primary care services. These aims have been achieved through a large cohort study of the GPRD and an in-depth qualitative interview study of 40 long-term survivors of breast, colorectal and prostate cancer. Analysis of the GPRD has shown that these long-term survivors are at increased risk of early mortality and morbidity. It is good that more people are surviving cancer than before, however, the current challenge is now to maximize the health experiences of those living beyond their cancer diagnosis. The next steps are to use the findings of this thesis to focus interventions and policy towards those cancer patients who may be at risk of poorer health in the long-term, and to consider how primary care can provide this care.

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# Appendices

# Appendix 1

Validity of diagnostic coding within the General Practice Research Database: a systematic review. Khan NF, Harrison SE, Rose PW. British Journal of General Practice. 2010 Mar;60(572):e128-36 .

# Validity of diagnostic coding within the General Practice Research Database: a systematic review

*Nada F Khan, Sian E Harrison and Peter W Rose*


## ABSTRACT

### Background
The UK-based General Practice Research Database (GPRD) is a valuable source of longitudinal primary care records and is increasingly used for epidemiological research.

### Aim
To conduct a systematic review of the literature on accuracy and completeness of diagnostic coding in the GPRD.

### Design of study
Systematic review.

### Method
Six electronic databases were searched using search terms relating to the GPRD, in association with terms synonymous with validity, accuracy, concordance, and recording. A positive predictive value was calculated for each diagnosis that considered a comparison with a gold standard. Studies were also considered that compared the GPRD with other databases and national statistics.

### Results
A total of 49 papers are included in this review. Forty papers conducted validation of a clinical diagnosis in the GPRD. When assessed against a gold standard (validation using GP questionnaire, primary care medical records, or hospital correspondence), most of the diagnoses were accurately recorded in the patient electronic record. Acute conditions were not as well recorded, with positive predictive values lower than 50%. Twelve papers compared prevalence or consultation rates in the GPRD against other primary care databases or national statistics. Generally, there was good agreement between disease prevalence and consultation rates between the GPRD and other datasets; however, rates of diabetes and musculoskeletal conditions were underestimated in the GPRD.

### Conclusion
Most of the diagnoses coded in the GPRD are well recorded. Researchers using the GPRD may want to consider how well the disease of interest is recorded before planning research, and consider how to optimise the identification of clinical events.



### Keywords
database management systems; meta-analysis; sensitivity and specificity; and systematic review.


## INTRODUCTION

Information collected routinely from primary care can provide a cost-effective source of data for epidemiological research.[1] One of the main benefits of using automated databases for research lies in the ability to access data from large patient populations across a wide population coverage. While these datasets represent a valuable tool for conducting research, it is important to remember that the data are collected primarily for clinical and routine use rather than specifically for research purposes. Data quality and reliability must be considered by researchers using these resources.

The General Practice Research Database (GPRD) is a widely used UK-based database of clinical primary care records, and has been extensively used in both primary care and pharmacoepidemiological research. It is the world's largest source of anonymised longitudinal data from primary care, and currently contains information on 3.6 million active patients from 450 general practices in the UK.[2,3] Practices participating in the GPRD are remunerated for recording data on clinical diagnoses, test results, prescriptions, and referral data. Clinical data are captured using the Read/OXMIS (Oxford Medical Information System) coding framework, which is based


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on the International Classification of Diseases, (Ninth Revision, Clinical Modification: ICD-9-CM) and is widely used in British primary care. Each practice is issued with a set of GPRD recording guidelines, describing how to record all significant morbidity events in each patient's medical history.[4] The raw data provided from each practice undergo extensive quality control and validity checks by a research team based at the Medicines and Healthcare products Regulatory Agency before release. These data are assessed by an 'up to standard' audit, confirming data recording in several key areas. Practices meeting this standard are included in the GPRD data warehouse. Patient-level data are also assessed, with patients considered 'acceptable' for inclusion in the GPRD if recorded details are internally consistent in four areas: age, sex, registration details, and event recording.[5]

While the checks conducted by the GPRD team may provide an overall evaluation of which practices are providing good-quality data meeting certain standards, they do not specifically assess the validity and completeness of individual patient records. Quality of data in disease registers can be assessed by considering two issues. First, are the data accurate; do the codes on the register represent the diagnosis under question? Second, are the data complete; what proportion of all true cases are recorded on the database?[6]

As the GPRD is increasingly used for academic research, it is important to consider the quality of the data available for study. The aims of this paper are to conduct a systematic review of the literature to present a description of the accuracy and completeness of recording in the GPRD. Specifically, the paper will consider both the recording of clinical diagnoses and comparisons between the GPRD and other databases or national statistics.

## How this fits in

The UK General Practice Research Database (GPRD) is increasingly used for academic primary care researchers. Data collected for automated databases such as the GPRD are subject to a number of quality checks, but the validity and accuracy of specific disease coding may vary. This paper describes a systematic review of studies that conducted validation of diagnoses in the GPRD or compared rates of disease in the GPRD against other databases. The majority of diagnoses were reliably coded; however, investigators conducting research using the GPRD should consider how information is captured in primary care and how the variation in recording practices for different diseases and prevalent conditions may affect research.

## METHOD

### Literature search

Six electronic databases were searched (MEDLINE, Embase, British Nursing Index, PsycINFO, Health Management Information Consortium, Social Sciences Citation Index) from inception to May 2009, using search terms relating to the GPRD in association with terms synonymous with validity, accuracy, concordance, and recording. See Appendix 1 for an example of the MEDLINE search. Two reviewers screened the titles and abstracts of all papers in the initial search, and excluded citations that did not meet the inclusion criteria. Disagreements at this stage were resolved through discussion; however, the full-text paper was ordered when either reviewer was uncertain about inclusion. One reviewer independently assessed the retrieved full-text papers for relevance and inclusion, and hand searched the reference lists of all retrieved papers. The same reviewer also conducted a hand search of the GPRD bibliography provided on the GPRD website,[7] and included any potentially relevant papers in the review process.

### Inclusion criteria

Studies that specifically considered the accuracy of recording of data in the GPRD were included, and those that looked at the accuracy of recording of data as part of a larger study. Papers written in English and non-English languages were considered for inclusion. Papers that did not look specifically at the GPRD were excluded, as well as those that were not original research and papers that did not conduct validation or comparison of information held on the GPRD. Database comparison studies were also excluded if the study compared prevalence rates over different time periods. Two investigators independently reviewed articles meeting the inclusion criteria and abstracted relevant data onto a standardised data extraction form. A third reviewer resolved any uncertainties in relation to the main outcomes.

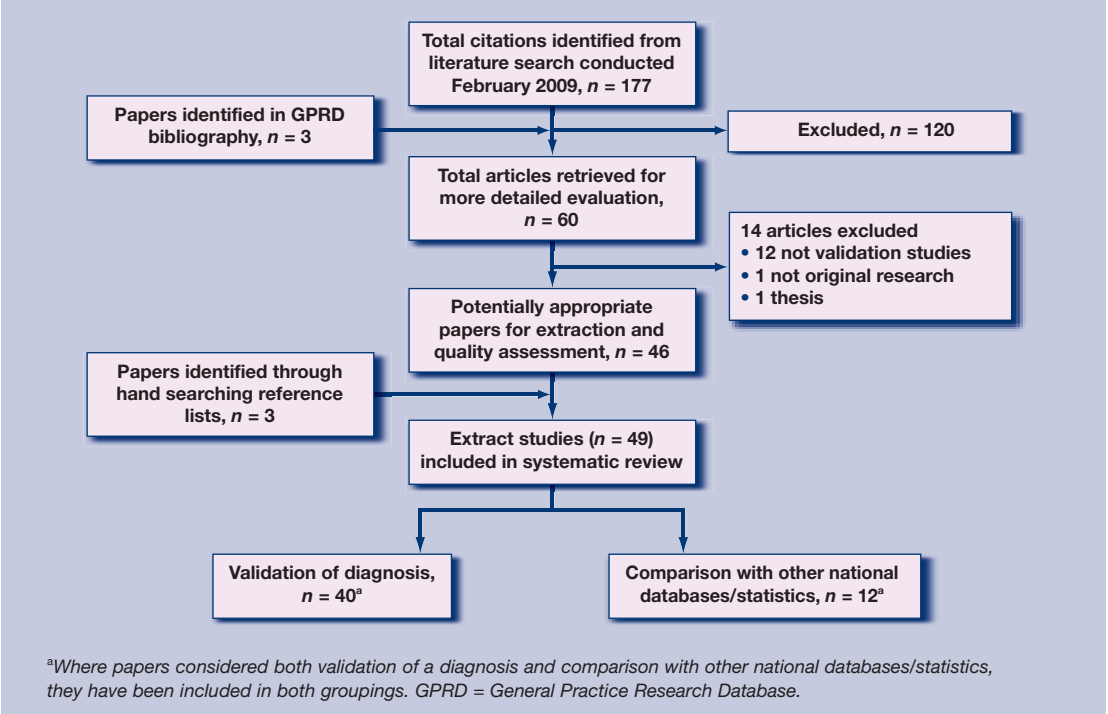
### Assessment of accuracy and completeness of data

This review considers both the accuracy and completeness of data recording in the GPRD. The accuracy of diagnoses was achieved by comparing the GPRD-coded data in the electronic patient record against the gold standard defined in each paper. Assessing the completeness of data was achieved by comparing disease prevalence and prescription rates between the GPRD and other national datasets and determining the level of under-reporting or over-reporting in the GPRD.

### Statistical analysis

Positive predictive value (PPV) was defined as the proportion of GPRD-coded diagnoses validated as true cases against a gold standard (GP questionnaire, primary care medical records, or hospital letters). Where the investigators used a GP questionnaire or request for hospital notes, the percentage validated

*Figure 1. Flowchart of literature search results.*




[a]*Where papers considered both validation of a diagnosis and comparison with other national databases/statistics, they have been included in both groupings. GPRD = General Practice Research Database.*

was calculated using the returned questionnaires as the denominator. Stata (version 10.0) was used to calculate binomial exact 95% confidence intervals (95% CIs) for each PPV, and to produce a forest plot of PPVs for correct coding of clinical diagnoses. A pooled PPV was not calculated, due to the variability in the included studies.

## RESULTS

### Literature search

A total of 46 papers were identified through the literature search and included in this review. Three additional papers were identified through hand searching the reference lists of the final 46 papers.[8–10] Therefore, a total of 49 papers entered the review (Figure 1). Results are presented in the following main groupings: (1) validation of clinical diagnoses and (2) comparisons between GPRD and other national statistics or databases.

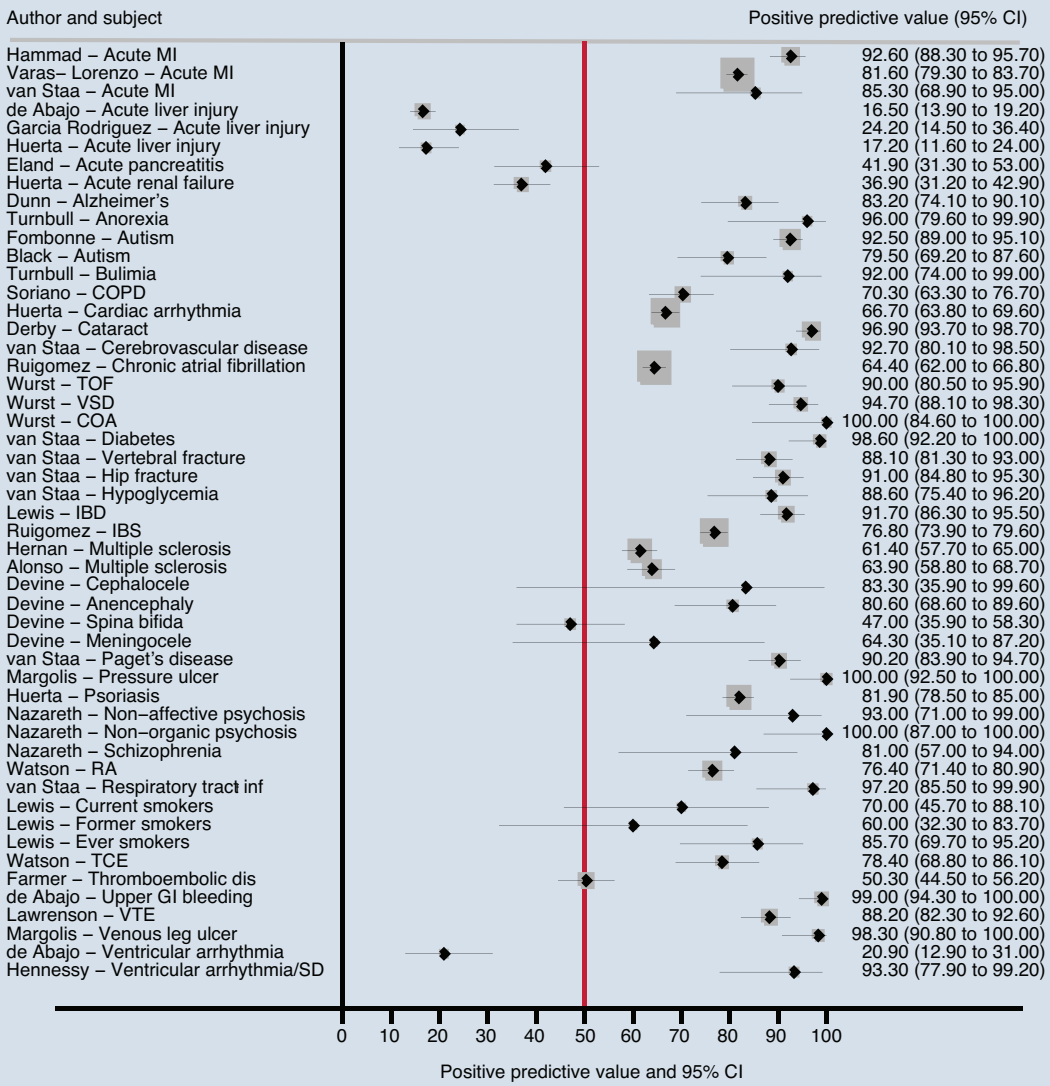
### Papers validating a diagnosis or patient characteristic

A total of 40 papers conducted validation of a diagnosis or patient characteristic coded in the GPRD database. Most of these validation exercises involved sending a questionnaire to the patients' GPs ($n$ = 19) and conducting independent verification of diagnoses against hospital letters or medical records in practice ($n$ = 16). Some studies involved both sending a GP questionnaire and conducting verification against medical records ($n$ = 5). The PPV of the accuracy of GPRD clinical codes from these validation exercises is summarised in Figure 2. The majority of papers report PPVs over 50%, and simply required patients' GPs to confirm the diagnosis on the GPRD database. Five of the seven papers reporting a PPV under 50% considered acute outcomes including drug-induced liver injury, pancreatitis, or renal failure.[11–15] The studies considering acute conditions all used strict diagnostic criteria to validate cases, which included confirmation of the diagnosis via biochemical tests or specialist confirmation.

Studies in this review reported high PPVs over 90% for the recording of anorexia, bulimia,[16] cataract,[17] congenital heart defects (including ventricular septal defects, tetralogy of Fallot, and coarctation of the aorta),[18] inflammatory bowel disease,[19] cerebrovascular disease, diabetes, respiratory tract infection,[19] Paget's disease,[20] hip fracture,[21] upper gastrointestinal bleeding,[22] non-affective and non-organic psychosis,[23] venous leg ulcer,[24] and pressure ulcer.[25]

Recording of psoriasis,[26] venous thromboembolism,[27] schizophrenia,[23] dementia, and Alzheimer's disease[28] was relatively accurate, with PPVs between 80% and 90%. Other diagnoses, including cardiovascular events and thromboembolic disease,[10,29] irritable bowel syndrome,[30] chronic obstructive pulmonary disease,[31] chronic atrial fibrillation,[32] and cardiac arrhythmia,[33] were not as accurately recorded, with reported PPVs lower than 80%.

Several papers validated the same diagnosis. Two papers considered the recording of autism in the GPRD.[8,34] Both studies validated the diagnosis directly against hospital and patient medical records, and report that autism is well recorded in the GPRD.




*COA = coarctation of the aorta. COPD = chronic obstructive pulmonary disease. GI = gastrointestinal. IBD = inflammatory bowel disease. IBS = irritable bowel syndrome. MI = myocardial infarction. RA = rheumatoid arthritis. SD = sudden death. TCE = thromboembolic cardiovascular events. TOF = tetralogy of Fallot. VSD = ventricular septal defect. VTE = venous thromboembolism.*

***Figure 2. Forest plot reporting positive predictive values of diagnoses in the General Practice Research Database.***

However, the electronic record was not detailed enough to provide sufficient differentiation between subtypes of pervasive developmental disorders. Acute myocardial infarction was also well recorded in the GPRD, with three studies reporting PPVs above 80%.[9,35,36] There was good agreement in two papers that validated the recording of incident multiple sclerosis against hospital and medical records; however, both papers reported relatively low PPVs of around 60%.[37,38]

Two papers considering the validity of coding for ventricular arrhythmia reported markedly different PPVs.[39,40] Using a GP questionnaire as the standard for validation resulted in a PPV of 93% (95% CI = 78 to 99%) for cases of sudden death or ventricular arrhythmia, whereas more stringent criteria requiring objective evidence of ventricular arrhythmia from specialist clinics and absence of recent angina or myocardial infarction resulted in a PPV of only 20.9% (95% CI = 13 to 31%). However, the investigators using a GP questionnaire to validate ventricular arrhythmia also report that only 23% (95% CI = 10 to 42%) of these diagnoses originated from outpatient events, which was their main outcome of interest. Two papers consider the validity of coding for rheumatoid arthritis; however, one study reported four validation categories (valid, invalid, possible, and unclassifiable) from which a PPV could not be derived.[10,41]

Two studies assessed the completeness of GP recording of diagnoses made by hospital consultants. In these studies, diagnoses were transcribed from the hospital discharge letter onto patients' electronic medical files in a high proportion (~90%) of cases.[42,43]

Devine *et al* conducted a validation study using an algorithm to identify children with neural tube defects. They reported an overall PPV of 71% (95% CI = 63 to 78%); however, the PPV varied considerably according to the specific neural tube defect diagnosis.[44] While anencephaly and cephalocele were generally well recorded, spina bifida was not. The Read Code algorithm used by the authors located spina bifida in the mother and not the child in 37% of cases.

One paper considered the recording of smoking status in the GPRD.[45] Although current smoking is generally well recorded, former smoking is not as well recorded. Appendectomy is also under-recorded in the GPRD; in a study of ulcerative colitis, the self-reported rate of appendectomy was 13% in the random sample of patients; however, the GPRD-coded rate of appendectomy in the same study was only 3.5%.[46]

Three papers reported results relating to accuracy of the date of diagnoses. There were discrepancies in date recording in 45/95 (47%) of dementia cases.[28] The differences were generally small, with an interquartile range (IQR) of –7 to 0 weeks. In a study of the validity of inflammatory bowel disease recording, the median difference in the first date reported by the GP and the first inflammatory bowel disease diagnosis in the electronic record was –8 days (IQR = –81 to 0 days). However, for 33 of the 53 patients included in the study, the first recorded diagnosis of inflammatory bowel disease in the electronic record was within 30 days of the date reported by the GP.[19] Recording of the date of acute myocardial infarction was also generally reliable; only 31/201 (15%) of confirmed cases had a GP-reported date that was inconsistent with the electronic record. The differences in dates were generally small; 28/31 (90%) of the GP-reported dates were within 15 days of the date in the electronic record.[35]

### The GPRD compared with other databases or statistics

In total, 12 papers compared GPRD database prevalence or consultation rates with other primary care databases or national statistics registers. All compared the GPRD with UK data, except for one comparison with a US-based database.[47]

Three papers compared GPRD consultation or prevalence rates against the Morbidity Statistics from General Practice 1991–92 (MSGP4), a UK-wide survey of consultation patterns in primary care.[48–50] The MSGP4 itself has been evaluated;[48] 96% of all consultations in the GP surgery were recorded, suggesting it contains good-quality data on consultation patterns in the UK. There was good agreement between the GPRD and MSGP4 for 11 common respiratory conditions. However, consultation rates and prevalence of diabetes and musculoskeletal conditions were underestimated in the GPRD compared with the MSGP4.[49,50]

Three studies compared the GPRD with the Doctors' Independent Network (DIN), a UK-based primary care database that has been collecting routine data from over 300 practices distinct from the GPRD since 1989.[51–53] Generally, there was good agreement between the two databases for common childhood conditions, hay fever, ischaemic heart disease, and prescribing for skin emollients.

The six remaining papers compare the GPRD with a variety of other primary and secondary care databases. Three papers report similar rates of disease among the GPRD and other databases. The UK-based MediPlus primary care database, which covers about 150 practices across the UK, provided similar crude incidence rates to the GPRD for venous thromboembolic disease.[54] Derby *et al* compared rates of suicide in the GPRD to a US-based database held by the Group Health Cooperative, and report that the overall rate of suicide among users of antidepressants was similar to the rate in the Group Health Cooperative.[47] A comparison of the GPRD with the Hospital Episodes Statistics demonstrates comparable overall and age-specific incidence of Guillain-Barré syndrome.[55]

There were some differences between disease coding in the GPRD and other datasets. A comparison of the GPRD and the Living in Britain National Household Survey from 1996 suggests that current smoking rates in the GPRD are 79% of the expected rate. The rates for ex-smokers were substantially underestimated; the GPRD rate for ex-smoking was 29% of what was expected according to the National Household Survey.[45] Frischer *et al* describe under-reporting of drug misuse recording in the West Midlands Regional Drug Misuse Database compared to the GPRD.[56] The prevalence of congenital heart defects was higher in the GPRD than in the National Congenital Anomaly System.[57] The same authors also validated heart defect diagnoses using a GP questionnaire, and reported an overall PPV of 0.935, suggesting that the GPRD is a good source of information on congenital heart defects.[18]

## DISCUSSION

### Summary of main findings

A systematic review of literature was carried out to validate the accuracy and completeness of the UK GPRD. The studies included in this review considered the accuracy of diagnostic codes in the GPRD and the completeness of data compared with other databases and national statistics.

Most of the diagnoses coded in the GPRD electronic record were well recorded when compared against GP questionnaire responses, medical records held at the

GP practice, or hospital letters. However, it seems that acute diagnoses were not as well recorded. The studies in this review used a variety of 'gold standard' references to ascertain the accuracy of diagnoses, which may explain some of the differences in accuracy of diagnosis recording, especially in the validation of acute conditions.

When a questionnaire is sent to a GP to support the accuracy of a diagnosis, the GP has several options for verifying the diagnosis, including checking through the computerised medical record or free-text information, looking for supporting evidence for a diagnosis from test results or hospital discharge letters, or relying on memory alone. Investigators conducting independent validation of a diagnosis can also request copies of patient medical records, hospital discharge letters, or correspondence or biochemical test results. This extra information can be used to find key words relating to a diagnosis, or conduct expert validation of a diagnosis.

Several studies assessed the accuracy of recording against an objective standard as defined by an external body; for instance, acute liver injury defined as an increase of more than two times the upper limit of normal in alanine aminotransferase by international consensus statement, or evidence of specific behavioural or cognitive symptoms as described in the Diagnostic and Statistical Manual of Mental Disorders.[15,23,34] The number of patient records validated may depend on the level of evidence required to assess the accuracy of recording.

Smoking status is an important risk factor and confounder in many epidemiological studies, and although current smoking may be recorded well enough for the purposes of epidemiological research, data on former smoking may need to be independently validated.[45]

Only three papers looked specifically at the differences between the date of onset of disease in the GPRD electronic medical record and the GP-reported date.[19,28,35] Although there were some inconsistencies in date recording, the differences were small. Investigators who require precise dates of onset of disease may need to be aware that there could be a slight difference in the date recorded in the electronic record and, if necessary, conduct further validation.

Generally, there is good agreement in disease prevalence rates between the GPRD and other national databases and statistics; however, there were some differences identified in this review. There is no 'gold standard' measure against which data from one database can be compared, or to suggest which database contains the most accurate measure. Discrepancies between two data sources do not necessarily mean that one database is right and one is wrong. There may be geographical differences or disease coding system variability that will lead to systematic differences in disease prevalence or data recording.[48] It is important to consider these differences when conducting research using these datasets.

There are two reasons why the GPRD may be systematically different from other datasets. First, not all consultations for chronic diseases need to be recorded in the GPRD; the GPRD recording guidelines state that the GP should make at least one entry in the medical history for each episode of illness or new occurrence of a symptom.[4] The requirement to record only the first instance of disease may partially explain why consultation rates and prevalence of diabetes and chronic musculoskeletal conditions were underestimated in the GPRD compared with the MSGP4.[49,50] Second, it is important to consider that practices supplying early years of data to the GPRD provided OXMIS-coded data. Other databases may use different coding systems; for instance DIN practices have always used Read Codes for recording diagnoses and prescriptions under a problem-orientated medical record, which presents each medical record as a set of intertwined but separate problems.[51,52] Investigators attributed many of the differences between DIN and the GPRD to the Read and OXMIS coding systems used in the respective databases.[53]

### *Strengths and limitations of the study*

This is the first study to search for studies systematically and to combine studies that consider the accuracy and completeness of the GPRD. By using broad search terms it was possible to find a wide range of literature covering a range of diagnoses. This review provides vital information to aid researchers and clinicians who are planning to conduct research using the GPRD. However, very few of the papers in this review gave results that were directly comparable. A wide range of diagnoses were considered and many of the investigators used different criteria to assess the validity of diagnoses, making it difficult to compare directly PPVs across studies even when diagnoses were the same. There was often a lack of an objective standard for comparison of data recording, and the papers in this review often used a variety of methods to judge the accuracy of clinical diagnoses in the patient electronic records. Finally, many of the studies included in this review only validated a small number of patient records, due to the expense of conducting validation of diagnoses via GP questionnaire or independent evaluation of hospital letters or medical records.

### *Comparison with existing literature*

Several UK-based studies consider the quality of morbidity coding in general practice, and a

systematic review of these studies shows that morbidity coding in general practice is variable. However, the investigators suggest that conditions with clear diagnostic features are better recorded than conditions with more subjective criteria.[58] In their paper, Jordan *et al* include eight GPRD studies which are also assessed in the current review. The sensitive search strategy used in this study, which specifically considered the GPRD, made it possible to find and consolidate information from a larger number of papers validating a diagnosis in the GPRD. Thiru *et al* investigated the quality of data in primary care; however, their review focused more on how well GPs record the outcome of a consultation on electronic patient records.[59] Their review also found that studies report consistently high PPVs, indicating that data on the patient record were valid. As noted in the present review, the authors point out that variability in the assessment of data quality made it difficult to compare results directly between studies.

### *Implications for future research*

Investigators conducting research using the GPRD need to consider carefully how information is recorded in primary care, and how GPs may use different Read/OXMIS codes to represent the same diagnosis. Some diagnoses may be recorded differently from others. This review suggests that researchers can be confident about case validity when using the GPRD for research into most chronic conditions. However, research into acute conditions may need additional validation. It may not be feasible to conduct validation studies of diagnoses in the GPRD for every project, as this can be expensive; current prices start at £60 per patient for a questionnaire or request for additional information from a practice.

One approach to ensure better identification of cases is to construct Read/OXMIS code diagnostic algorithms comprising several codes to identify events and diagnoses in the GPRD. Often, these diagnoses can then be internally validated using evidence within the GPRD to support the diagnosis; for instance, a Read/OXMIS code for an acute myocardial infarction may be followed by a referral to cardiology, details of a discharge letter from hospital, and relevant medication.

A study validating the recording of neural tube defects found that in some cases, the diagnosis represented a condition in the mother and not in the child. Birth defect researchers using the GPRD may wish to search the mother's medical history to determine whether the code relates to a diagnosis in the mother or the child. This supplemental information can be obtained from within the GPRD to improve the reliability of diagnostic codes.

Prescription data are well recorded in the GPRD because prescriptions for patients are generated directly from the computer, and details on drug type and dosage are digitally recorded in this automated process. Therefore, prescribing data can be used to verify clinical diagnoses, or to capture additional cases. For instance, use of inhalers was used as a proxy for asthma diagnoses.[48] However, investigators should be cautious about using drug prescribing as a proxy for disease, and ensure that the prescribed drug is specific to the diagnosis of interest.

One of the future strengths of the GPRD lies in planned linkages with other national databases, including the Hospital Episodes Statistics, and Office for National Statistics databases, and the National Cancer Intelligence Network. These linkages will allow investigators to access more detailed clinical information relating to inpatient and outpatient hospital attendances and diagnoses, death registration, cause of death, and cancer diagnoses and treatment. This additional information will be a source of accurate and complete information on many of the clinical outcomes occurring outside of primary care.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### Competing interests

The authors have stated that there are none.


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## Appendix 1. Sample search strategy used in MEDLINE.

MEDLINE search: 1950 to week 3, May 2009

| | | |
|---|---|---|
| 1. | "general practice research database".ti,ab | |
| 2. | GPRD*.ti,ab | |
| 3. | "Value added medical products".ti,ab | |
| 4. | FF-GPRD.ti,ab | |
| 5. | ffGPRD*.ti,ab | |
| 6. | 1 or 2 or 3 or 4 or 5 | GPRD or VAMP |
| 7. | valid*.ti,ab | Accuracy and completeness |
| 8. | consisten*.ti,ab | |
| 9. | sensitiv*.ti,ab | |
| 10. | specificity*.ti,ab | |
| 11. | reliab*.ti,ab | |
| 12. | "positive predictive value*".ti,ab | |
| 13. | PPV*.ti,ab | |
| 14. | concordance*.ti,ab | |
| 15. | miss*.ti,ab | |
| 16. | accura*.ti,ab | |
| 17. | variation*.ti,ab | |
| 18. | variab*.ti,ab | |
| 19. | replica*.ti,ab | |
| 20. | note*.ti,ab | |
| 21. | verify*.ti,ab | |
| 22. | recording*.ti,ab | |
| 23. | 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 | Accuracy and completeness of data |
| 24. | 6 and 23 | Accuracy and completeness of data in the GPRD |

*GPRD = General Practice Research Database. VAMP = Value Added Medical Products.*

# Appendix 2

Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. Khan NF, Perera R, Harper S, Rose PW. BMC Family Practice 2010 Jan 5;11:1.

BMC Family Practice

RESEARCH ARTICLE Open Access

# Adaptation and validation of the Charlson Index for Read/OXMIS coded databases

Nada F Khan[1*], Rafael Perera[1], Stephen Harper[2], Peter W Rose[1]

## Abstract

**Background:** The Charlson comorbidity index is widely used in ICD-9 administrative data, however, there is no translation for Read/OXMIS coded data despite increasing use of the General Practice Research Database (GPRD). Our main objective was to translate the Charlson index for use with Read/OXMIS coded data such as the GPRD and test its association with mortality. We also aimed to provide a version of the comorbidity index for other researchers using similar datasets.

**Methods:** Two clinicians translated the Charlson index into Read/OXMIS codes. We tested the association between comorbidity score and increased mortality in 146 441 patients from the GPRD using proportional hazards models.

**Results:** This Read/OXMIS translation of the Charlson index contains 3156 codes. Our validation showed a strong positive association between Charlson score and age. Cox proportional models show a positive increasing association with mortality and Charlson score. The discrimination of the logistic regression model for mortality was good (AUC = 0.853).

**Conclusion:** We have translated a commonly used comorbidity index into Read/OXMIS for use in UK primary care databases. The translated index showed a good discrimination in our study population. This is the first study to develop a co-morbidity index for use with the Read/OXMIS coding system and the GPRD. A copy of the co-morbidity index is provided for other researchers using similar databases.

## Background

Studies of patient health should take into consideration any independent predictors that will affect the outcome of interest. Individual disease status is an important predictor of mortality and health care usage especially in studies of older patients, and in many cases, subjects may have more than one co-existing illness at the same time. Investigators may wish to conduct risk adjustment for the additional health effects of these co-morbid diseases.

Previous research has led to the development of summary comorbidity measures which classify patients according to their disease burden [1-4]. The most widely used and validated index of comorbidity was developed by Charlson and colleagues in the late 1980s [5,6]. The Charlson index includes 17 categories of comorbid disease weighted based on their association with 1 year all-cause mortality. Because the Charlson index is weighted and allows for additive scoring, it can take into account both the number and the severity of comorbidity to provide a summary of disease burden for each individual patient [6]. The index has been validated in several different populations, and has been widely used in studies involving cancer patients and survivors [7-11].

Recognizing the potential for its use in large database studies that require risk adjustment for individual patients, the Charlson index has previously been adapted for use with administrative data [12-15]. These adaptations involve searching individual level hospital claims data for codes corresponding to the Charlson index categories. However, these adaptations generally apply only to ICD-9-CM coded data, an international coding system for classification of diseases, symptoms and signs. There is no current translation of the Charlson index for Read and OXMIS coded data, two systems which are based on ICD-9-CM and are widely used in British primary care. Data using the Read and OXMIS coding system has recently been made more readily available from the General Practice Research Database

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(GPRD), a UK-based database of clinical primary care records. The GPRD is the world's largest source of anonymised longitudinal data from primary care, and currently contains information on 3.6 million active patients from 450 general practices in the UK [16]. With increasing use of the GPRD for academic and epidemiological research, there is a need for a GPRD-compatible research tool that will allow categorization and adjustment for patient comorbidity.

The main aim of this paper is to develop a comorbidity index based on the Charlson index for use with Read/OXMIS coded data. We also describe the performance of the new measure by testing whether comorbidity is associated with increased mortality in a cohort of patients from the GPRD. It is our hope that the newly developed and tested translation of the Charlson score can be used by other researchers working with Read/OXMIS coded data and the GPRD.

## Methods

### Development of Read/OXMIS codes lists

The original Charlson index consists of 17 diagnostic categories which provide the basis for assigning weighted scores to each comorbid disease. Deyo et al [12] describe a validated translation of each diagnostic category of the Charlson index to ICD-9-CM codes. We used the ICD-9-CM codes suggested by Deyo et al to guide development of the Read/OXMIS code lists used in this comorbidity index. Figure 1 summarizes our process for translation of the index to Read/OXMIS codes using one of the Charlson diagnostic categories, myocardial infarction, as an example.

Using definitions provided by Deyo et al for each Charlson diagnostic category, we searched the General Practice Research Database Medical Dictionary (Version 0.3.7, Copyright © 2004) for potentially relevant Read/OXMIS codes. This dictionary includes the GPRD medical code for the type of event, the Read/OXMIS code for the event and a description of the medical term. We identified potential Read/OXMIS terms using two search strategies. Firstly, we used specific terms in the ICD-9-CM description of the event to search the GPRD dictionary. Read codes have a hierarchical structure, with a top level code for a disease category branching into more precise and specific codes. Therefore, our second strategy involved identifying relevant top level Read codes and including all lower level codes. By using the wild card (*), and hierarchies of Read codes, we generated a list of all potentially related codes. We conducted these Read/OXMIS searches for 16 of the diagnostic categories used in the Charlson index. We treated the cancer codes separately, and included all Read codes starting with 'B', but excluding all codes for benign cancer (B7), cancer in situ (B8) and neoplasms of uncertain behaviour (B9). We tried to be over-inclusive in the searching and used broad search terms when possible.

Two clinicians experienced in the use of Read codes (PWR and SH) independently reviewed the list of all Read/OXMIS codes identified through searches of the GPRD medical dictionary. The clinicians selected relevant Read/OXMIS codes and rejected codes not corresponding to ICD-9-CM codes used in the Deyo adaptation of the Charlson index. A third clinician resolved any disagreement on coding. We calculated the degree of inter-rater agreement between the two clinicians reviewing Read/OXMIS code lists using the kappa score, which provides an estimate of the level of agreement between the two raters above that occurring due to chance. The final list of Read/OXMIS codes in this adaptation of the Charlson index is available in Additional file 1.

13 Read/OXMIS codes were used in more than one diagnostic category. These overlaps only occurred between diabetes and peripheral vascular disease (i.e. 'gangrene diabetic' was coded as both 'diabetes' and 'peripheral vascular disease'), and between diabetes and diabetes with complications. One clinician (PWR) determined that the codes should be classified as diabetes codes.

### Data source

The GPRD is the world's largest anonymised database of primary care records [16]. Practices participating in the

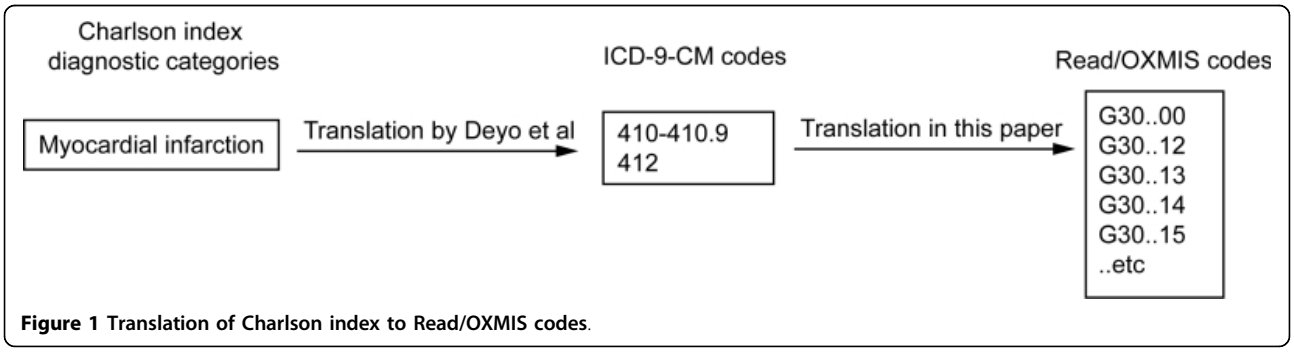


**Figure 1 Translation of Charlson index to Read/OXMIS codes**.

GPRD record data on clinical diagnoses, test results, prescriptions and referral data from primary care. Clinical data is coded using Read/OXMIS codes, along with the date of original onset for chronic or recurrent conditions. GPRD Recording Guidelines direct practices to provide a record of all significant morbidity events in the patient's medical history, including a summary of events that occurred before the patient joined the practice [17]. The data from practices undergoes quality control procedures and several validation studies have shown a high level of data completeness within the GPRD [18].

### Validation dataset

As part of a study looking at the unmet needs of long-term survivors of cancer, we received a dataset containing primary care records between 01/01/1987 and 30/06/2006 for all patients in the GPRD with a diagnosis of breast, colorectal or prostate cancer and more than five years survival. We also received data on a control population of patients with no record of breast, colorectal or prostate cancer, matched to the cancer survivors by age, gender and practice on a ratio of 1:4. The dataset included data on 18707 breast cancer survivors, 5773 colorectal cancer survivors, 4856 prostate cancer survivors, and 117105 control patients (total $n$ = 146 441 patients). We used individual level clinical data in this dataset to test the adapted Charlson index.

### Assessing the comorbidity measure

Following translation of the Charlson index to Read/OXMIS codes, we tested whether an increasing comorbidity score was associated with increased patient mortality. To achieve this, we applied the adapted weighted Charlson index to the patient cohort obtained from the GPRD. Our adapted comorbidity score used the original Charlson score which does not include age, however, Charlson and colleagues have also developed a combined age-comorbidity index [19].

Cox proportional hazards models were fit with mortality from July 1 2001 to 31 August 2006 as the dependent variable. Charlson score was coded as a continuous ordinal indicator variable, and was included along with age as explanatory variables. Survival was measured in days and associations are reported using hazard ratios with Charlson score of 0 as the referent group. All analyses were conducted using Stata MP (Version 10, College Station, TX).

### Discriminatory power of the model

The area under a receiver operating characteristic (ROC) curve, or c-statistic, can be used to quantify how well a predictor based on a number of variables discriminates a dichotomous outcome [20]. We used a logistic model to estimate the relationship between death (dichotomous outcome coded 0/1) and the Charlson index, after adjusting for age, quintiles of the the Index of Multiple Deprivation (IMD) and gender, before producing the ROC curve. Model discrimination was assessed by the area under the ROC curve.

### Adjusting variables

We included age in 2001, gender and socioeconomic status in the models for adjustment. Age was categorized in 5 groups of similar sizes (30-49, 50-59, 60-69, 70-79, 80+). The GPRD dataset includes an Index of Multiple deprivation (IMD) score to estimate socioeconomic status at practice level. The IMD covers a range of indicators including income, employment, health deprivation and disability, education, skills and training, housing, and geographical access to services for each small area in the UK [21]. IMD scores were grouped into quintiles based on the spread of scores within each country in the UK.

## Results

### Coding exercise

The inter-rater agreement between the two clinicians for including Read/OXMIS codes in the Charlson index was 84.6%, with a kappa of 0.45, indicating a moderate level of agreement [22]. Including the cancer codes, a total of 3156 Read/OXMIS codes were included in this adaptation of the Charlson index.

### Characteristics of the cohort

The mean age of the cohort was 73.7 (SD 12.5), and 73.5% of the patients were female. The high percentage of female patients is due to the high proportion of breast cancer survivors and gender matched controls in the cohort. Table 1 shows the frequency and percentages of patients with each of the diagnoses included in the comorbidity index.

The original Charlson index weights each disease category on the strength of its association with mortality. Using the original Charlson weights for each disease category, the breakdown by index score in our dataset is shown in Figure 2.

Most of the patients in the validation dataset had no comorbid disease (n = 60585). There were a few patients with a very high Charlson score above 5. There was a strong positive association between increasing Charlson score and increasing age ($p < 0.0001$).

### Patient mortality

In total, 11,490 patients died during the five-year period from July 1 2001 to August 31 2006. Figure 3 shows the survival curves for the population stratified according to Charlson score.

Mortality was significantly associated with a Charlson score of 1 or more, with a positive increasing association as Charlson score increases (Table 2). There was an increased risk of death amongst older patients and amongst males.

**Table 1 Frequency of comorbid disease in validation cohort**

| Charlson Diagnostic category | Weighted score in Charlson index [6] | Number of patients in our dataset |
|---|---|---|
| AIDS | 6 | 8 (0%) |
| Cerebrovascular disease | 1 | 9,028 (4.4%) |
| Chronic pulmonary disease | 1 | 27,698 (13.5%) |
| Congestive heart disease | 1 | 9,217 (4.5%) |
| Dementia | 1 | 3,624 (1.8%) |
| Diabetes | 1 | 14,418 (7.0%) |
| Diabetes with complications | 2 | 2,544 (1.2%) |
| Hemiplegia and paraplegia | 2 | 505 (0.25%) |
| Mild liver disease | 1 | 416 (0.2%) |
| Moderate or severe liver disease | 3 | 96 (0.05%) |
| Myocardial infarction | 1 | 6,512 (3.2%) |
| Peptic ulcer disease | 1 | 6,943 (3.4%) |
| Peripheral vascular disease | 1 | 6,731 (3.3%) |
| Renal disease | 2 | 12,624 (6.1%) |
| Rheumatological disease | 1 | 8,140 (3.9%) |
| Cancer | 2 | 34,750 (16.9%) |
| Metastatic tumour | 6 | 2,116 (1.0%) |
| No comorbid disease | - | 60,585 (29.4%) |
| Total | | 205,955 |

* Patients can be counted more than twice if they have more than one comorbid disease, therefore the total will not equal 146 441 (the number of patients in the cohort)

### Discrimination of the model

The discrimination of the logistic regression model was good, with an area under the curve (AUC) of 0.853 (Figure 4). This indicates that the adaptation of the Charlson index is a good predictor of mortality in the validation dataset.

## Discussion

We have translated a commonly used comorbidity index into Read/OXMIS codes for use with UK primary care databases. In a cohort of cancer survivors and matched controls, a higher comorbidity score in this adaption of the Charlson index was associated with an increased risk of mortality after adjusting for age, deprivation scores and gender. The translated comorbidity index showed a good discrimination our study population. To our knowledge, this is the first study to develop a comorbidity index for use with this disease coding system.

Although this adaptation of the Charlson index can be applied to any Read/OXMIS coded dataset, we hope that our adapted version of the Charlson index will be especially useful to the increasing number of researchers conducting work using the GPRD. GPRD data provides

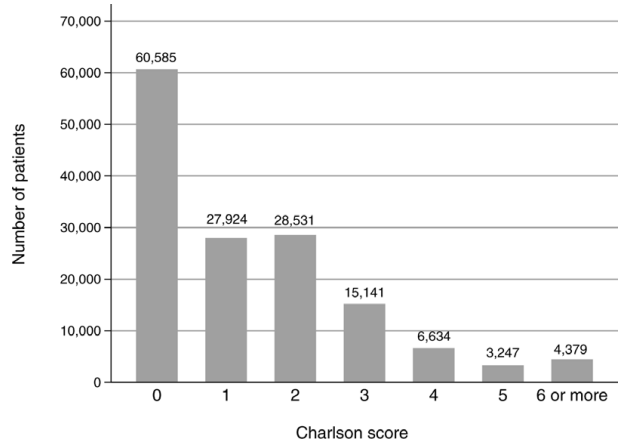


**Figure 2 Breakdown of Charlson score in patient dataset**.

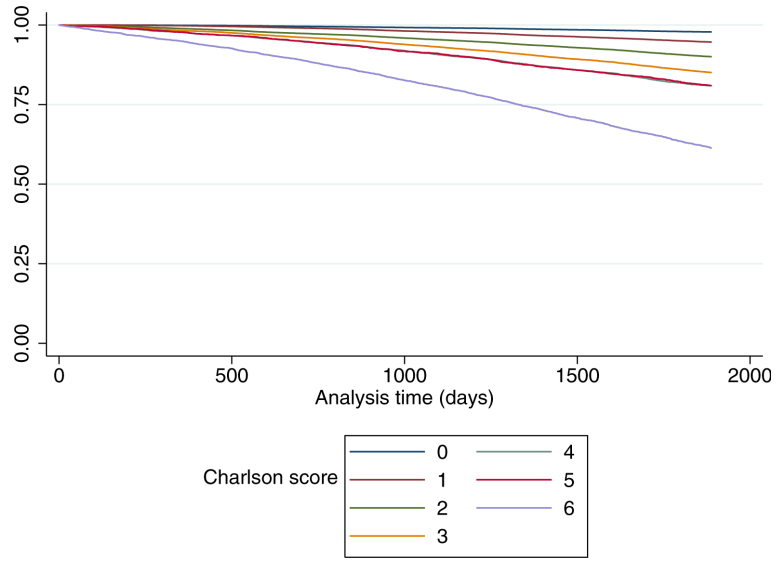


**Figure 3 5 year mortality stratified by Charlson score**.

an opportunity to conduct large scale epidemiological research in primary health care use, health outcomes and pharmacology. The Medicines and Healthcare products Regulatory Agency (MRHA), which manages the GPRD, has recently announced plans to link GPRD data with Hospital Episodes Statistics (HES), cancer registrations and Office for National Statistics databases. These linkages will increase the value of conducting research using the GPRD, as researchers will be able to trace patient pathways through primary and secondary care. Our adaptation of the Charlson index is available in Additional file 1, and can be imported into statistical software for use with other datasets. This index can be used to quickly categorize patients into different comorbidity levels, and will add explanatory power when conducting analyses using Read/OXMIS coded datasets and the GPRD.

We tested the association between increasing Charlson score and mortality, which was the primary outcome used in the development of the original score. Our results confirm the hypothesis that patients with a greater burden of disease will die sooner. One unexpected result was a large jump in the risk of mortality in patients with a Charlson score of 6 or above. This is likely due to the number of patients in our cohort with metastatic cancer, which generally has a very poor prognosis in the small but high risk group of patients with a score of 6 or more [23].

### Limitations

This comorbidity index performed well in our validation exercise, however, there are several areas where the model may be inadequate. Firstly, it is possible that some codes were not included when developing the Read/OXMIS code lists for assessment. By using broad search terms, hierarchical searches of Read codes, and two reviewers to independently assess records, fewer potentially relevant Read/OXMIS codes were excluded from the final adaptation of the Charlson index. Secondly, we used the original disease weights developed by the authors of the original Charlson index almost twenty years ago. One recent criticism of the Charlson index is that certain diseases have an improved prognosis since the original score was developed. For instance, according to the original Charlson weighting, a positive AIDS disease status carries an equivalent mortality risk to a diagnosis of metastatic cancer. Only eight patients in our dataset were diagnosed with AIDS, therefore, this issue is unlikely to affect our validation results. In studies where a larger proportion of individuals are HIV/AIDS positive, investigators may wish to use updated weights for HIV/AIDS taking into account that the burden of disease and mortality is lower now than in the 1980s [24].

Thirdly, recording of clinical outcomes in primary care settings may be incomplete; a recent study demonstrated that even major outcomes such as cancer may not be recorded in patient electronic records [25]. Although the GPRD data is subject to a number of quality checks, it is possible that disease recording is incomplete. However, many of the previous adaptations of the Charlson index have used administrative data, where patient history and comorbid disease may not be as recorded as accurately as the clinical data available in datasets such as the GPRD [26,27]. Omissions of major comorbid diseases can result in an incorrect final Charlson score in any study. These omissions are not an intrinsic

**Table 2 Adjusted risk of death and 95% CI for 5 year mortality**

| | Adjusted Hazard ratio* | 95% Confidence Interval |
|---|---|---|
| Charlson score | | |
| 0 | 1 | |
| 1 | 1.87† | 1.74 - 2.02 |
| 2 | 3.68† | 3.45 - 3.93 |
| 3 | 4.71† | 4.40 - 5.05 |
| 4 | 5.47† | 5.06 - 5.91 |
| 5 | 5.25† | 4.77 - 5.78 |
| 6 or more | 14.21† | 13.21 - 15.28 |
| | | |
| | | |
| 30-49 | 1 | |
| 50-59 | 1.07 | 0.885 - 1.29 |
| 60-69 | 1.39† | 1.16 - 1.66 |
| 70-79 | 2.98† | 2.51 - 3.53 |
| 80+ | 10.51† | 8.89 - 12.43 |
| | | |
| IMD quintile‡ | | |
| 0* | 1 | |
| 1 | 1.00 | 0.94 - 1.06 |
| 2 | 1.04 | 0.98 - 1.09 |
| 3 | 1.05 | 1.00 - 1.12 |
| 4 | 0.97 | 0.91 - 1.03 |
| | | |
| Gender | | |
| Female | 1 | |
| Male | 1.16† | 1.12 - 1.21 |

* Adjusted for age, gender, and quintile of IMD
† Significant at the $p < 0.0001$ level
‡ A low rank indicates the least deprived, and a high rank indicates the most deprived

limitation in the tool that we have developed, but may affect its functional ability in datasets such as the GPRD. Future work should continue to validate the accuracy of disease coding in administrative datasets and the GPRD.

Our validation population of long-term cancer survivors is unusual; these patients are older and sicker than the general population. The cancer survivors have a Charlson score of at least 2 and a high proportion are female owing to the high number of breast cancer survivors. Other patient cohorts using this adapted comorbidity index will likely have different trends in mortality and consultation behaviour. Future studies should apply this Charlson adaptation to other study populations to measure mortality and use of primary care services. We were also unable to consider race or ethnicity in the analysis as this information is not routinely collected in the GPRD. These limitations, however, do not affect the development and translation of the Charlson index to Read/OXMIS codes, but may affect the results of the validation exercise.

## Conclusions

In conclusion, we have developed an adaptation of the Charlson comorbidity index for use in Read/OXMIS databases and the GPRD which predicts 5-year mortality in a cohort of patients. Our adaptation is provided in a downloadable format (Additional file 1) for other researchers using similar databases. With increasing use of large datasets for epidemiological research, researchers must consider how disease status will affect their outcomes of interest. Tools such as the Charlson index can provide a summary of comorbidity for use in large studies, and this paper demonstrates the utility of an

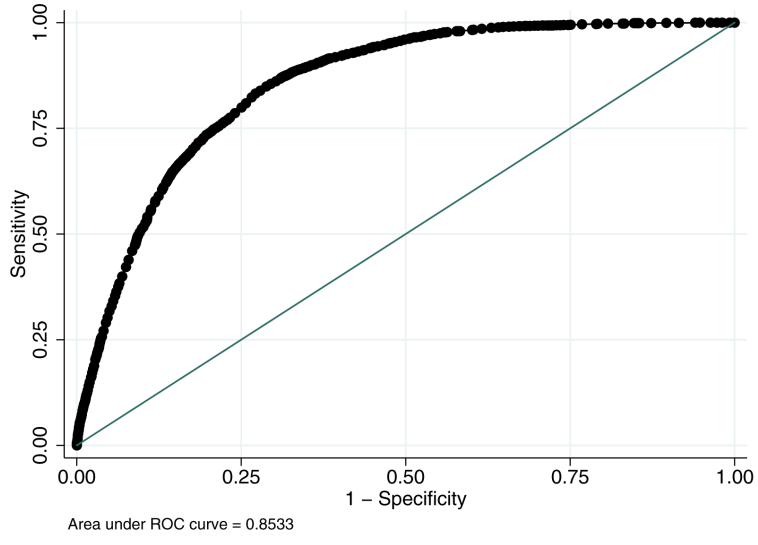


**Figure 4 ROC curve for logistic regression model**.

adaptation of the Charlson score in primary care coded data.

**Additional file 1: Adapted Charlson score**. This file contains the Read/OXMIS codes relating to this adaptation of the Charlson index.
Click here for file
[ http://www.biomedcentral.com/content/supplementary/1471-2296-11-1-S1.xls ]

### Abbreviations

ICD-9: International Classification of Diseases; IMD: Index of Multiple Deprivation; GPRD: General Practice Research Database; ROC: Receiver operating characteristic

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### Authors' contributions

NFK conceived the study, carried out all analyses and drafted the manuscript. PWR participated in the design and coordination of the study, and along with SH reviewed all codes. RP provided expert statistical advice. All authors read and approved the final manuscript.

### Competing interests

The authors declare that they have no competing interests.

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## Appendix 3

Primary care consultation behaviours of long-term, adult survivors of cancer in the UK. Khan NF, Watson E, Rose PW. British Journal of General Practice. 2011 Mar;61(584):e197-99.

# Primary care consultation behaviours of long-term, adult survivors of cancer in the UK

*Nada F Khan, Eila Watson and Peter W Rose*


## ABSTRACT

The population of cancer survivors is growing, and GPs have an increasing role in their care. The General Practice Research Database was used to compare consultation rates between cancer survivors and controls. Breast and colorectal cancer survivors had one more consultation per year compared with controls up to 5 years after diagnosis; rates then converged at 10 years post-diagnosis. Prostate cancer survivors consistently consulted up to three more times per year than controls. These increased consultation rates are leading to an impact on service capacity.



**Keywords**

family practice; long-term care; neoplasms; primary health care; survivors.



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## INTRODUCTION

The prevalence of cancer survivors has increased due to demographic changes, increasing incidence of cancer, and improvements in cancer diagnosis and treatment. Current estimates indicate that 2 million people in the UK are cancer survivors; and at the current rate of growth, there will be 4 million cancer survivors in the UK by 2030.[1] GPs are responsible for the majority of cancer-related and comprehensive healthcare needs in this population after discharge from hospital follow-up. However, little is known about how cancer survivors use primary care services. The aims of this research are to describe the consultation patterns of adult survivors of breast, colorectal, and prostate cancer in British primary care at different points of survival, and to explore whether there are differences in the consultation rates between cancer survivors and a matched control population.

## METHOD

This analysis uses the UK General Practice Research Database (GPRD). Cancer survivors were defined as those aged 30 years or over at the time of diagnosis of breast, colorectal, or prostate cancer, with at least 5 years of survival post-diagnosis. Controls were matched on the basis of age (within 1 year), sex, and primary care practice, and the analysis was undertaken for a time period from 1 September 2003 to 31 August 2006. A more detailed description of the data source and patient inclusion and exclusion criteria has been reported previously.[2] Descriptive statistics were used to describe consultation rates according to length of survival, and regression analysis to compare the number of consultations between survivors and controls matched by age, sex, and primary care practice. All analyses were performed using Stata MP (version 10.1).

First, the total number of consultations for each patient over the analysis period was counted. Follow-up was censored upon death or transfer out of the GPRD primary care practice; therefore, the consultation rate was standardised to the number

## How this fits in

Little is known about the primary care consultation patterns of the increasing population of cancer survivors in the UK. This study shows that breast and colorectal cancer survivors have higher rates of GP consultations in the first 10 years post-diagnosis, while prostate cancer survivor consultation rates are elevated past this point.

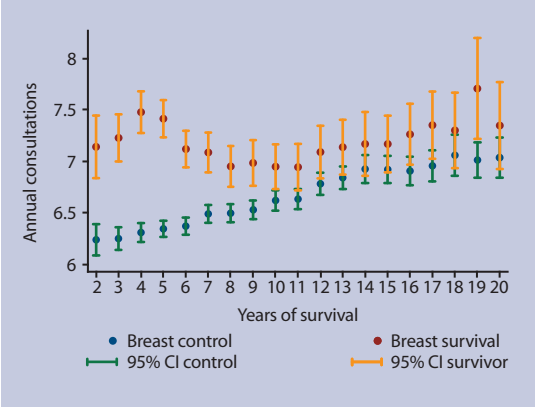


*Figure 1. Annually standardised consultation rate, breast cancer survivors and controls, 2003–2006.*

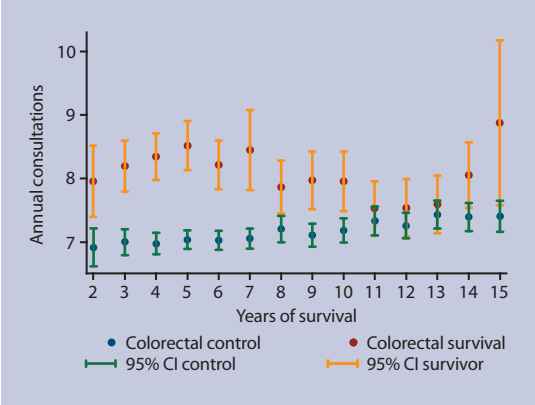


*Figure 2. Annually standardised consultation rate, colorectal cancer survivors and controls, 2003–2006.*

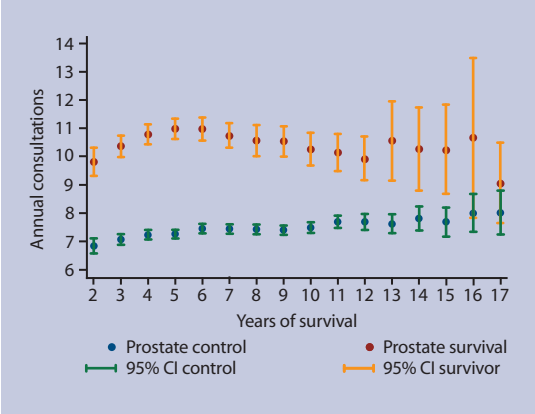


*Figure 3. Annually standardised consultation rate, prostate cancer survivors and controls, 2003–2006.*

of years each patient contributed data to the follow-up. Face-to-face consultations in the practice with a member of the primary care team and home visits were counted, excluding events such as patient correspondence, claim payments, and other administrative events. The 'stsplit' command in Stata was used to account for the fact that patients moved through survival periods during the 3-year period; for instance, a person diagnosed with cancer in 1998 was counted as a 5-year survivor in 2003 and a 6-year survivor in 2004.

To compare the total number of consultations between cancer survivors and matched controls over the analysis period, multivariate fixed-effects negative binomial regression was used.[3] Differences in the number of consultations are expressed as incidence rate ratios (IRRs). The analysis adjusted for comorbidity using an adaptation of the Charlson comorbidity index.[4]

## RESULTS

The dataset contains longitudinal primary care data on 18 612 breast, 5764 colorectal, and 4868 prostate cancer survivors, and 116 418 control patients. The cohort had a median age of 72 years in 2003 (interquartile range 61 to 80 years). Just over half (52%) of the cancer survivors had a Charlson score greater than zero, indicating at least one additional comorbidity in their electronic medical record.

Descriptive results show that breast and colorectal cancer survivors have a significantly increased consultation rate up to 10 years from diagnosis, with one extra consultation per year up to 5 years for breast cancer and up to 9 years for colorectal cancer (Figures 1 and 2). The multivariate, matched analysis showed a slight increase in the overall number of consultations between breast cancer survivors (IRR 1.11, 99% confidence interval [CI] = 1.09 to 1.12) and colorectal survivors (IRR 1.12, 99% CI = 1.08 to 1.14) versus controls. In comparison, prostate cancer survivors consulted up to three more times annually compared to controls, and this trend persisted even 15 years post-diagnosis (Figure 3). Compared to matched controls, prostate cancer survivors had 39% more consultations over the 3-year follow-up period (IRR 1.39, 99% CI = 1.35 to 1.43).

It is possible that patients who died contributed disproportionately to the excess consultation rate. However, after excluding patients who died during the analysis period, there was still an increase in consultations among breast (IRR 1.07, 95% CI = 1.06 to 1.09), colorectal (IRR 1.08, 95% CI = 1.05 to 1.11), and prostate (IRR 1.33, 95% CI = 1.29 to 1.37) cancer survivors compared to controls.

## DISCUSSION

### Summary of main findings

The analysis of consultation rates among cancer survivors in the GPRD has shown a significant difference in the number of consultations between survivors and matched controls, with the greatest difference for prostate cancer survivors. Breast and colorectal cancer survivors have higher consultation rates than a control population, until rates converge 10 years post-diagnosis. The increase in consultation rates for prostate cancer survivors persists for many years post-diagnosis.

A major contribution to the increased consultation rate in prostate cancer will be the monitoring and administration of hormonal treatments; this will apply to breast cancer patients as well, but to a lesser extent. Half of cancer survivors have unmet needs relating to ongoing health conditions, which include secondary effects from the disease and its treatment, risk of second cancers, and emotional responses such as depression and anxiety.[5–6] The early peak in consultation rates among all groups of survivors may reflect the need to address in primary care aspects of ongoing morbidity related to the cancer.

### Strengths and limitations of the study

This is the first study of primary care consulting behaviours among cancer survivors in the UK. The study used data from a large, representative database, and explored consultation behaviour among a community-based group of cancer survivors, with a robust comparison population. It was not possible to confirm the reasons for increased consultation rates, due to the multitude of possible reasons for GP visits, and further research could clarify this point.

### Comparison with existing literature

Surveys of long-term cancer survivors in Norway and France have indicated an increase in the use of GP services compared to a control population, but there is little previous research looking at the primary care consultation patterns of survivors of cancer in the UK.[7–8] Future research should consider reasons for increased health services use in this growing population.

### Implications for future research and clinical practice

These trends in increased consultation behaviours are impacting on the workload in British primary care, and this impact will increase as the population of cancer survivors continues to grow. As many as one in six adults over the age of 65 years seen by a GP is likely to be a cancer survivor, and a significant proportion of these will be breast, colorectal, or prostate cancer survivors.[9] It is estimated that an average GP with a list size of 2000 patients would provide 60–180 extra consultations per year for all cancer patients, assuming a cancer prevalence of 3% in the UK, and the extra consultation rate for all cancers mirrors the one to three extra consultations per year of the three cancers in this study.[1] Additionally, for some cancers, such as breast, colorectal, and prostate, the current trend is towards earlier discharge to primary care. Many of these long-term cancer survivors will not require specialist disease management, and this paper quantifies the likely effect on GP workload.


### Funding body

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### Ethical approval

The GPRD Group has obtained ethical approval for all observational research using GPRD data. This study has been approved by the Independent Scientific Advisory Committee (ISAC) of the GPRD (ISAC protocol No. 06_051R).

### Competing interests

The authors have stated that there are none.

### Discuss this article

Contribute and read comments about this article on the Discussion Forum: http://www.rcgp.org.uk/bjgp-discuss

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# Appendix 4

Cancer screening and preventative care among long-term cancer survivors in the United Kingdom. Khan NF, Carpenter L, Watson E, Rose PW. British Journal of Cancer. 2010;102(7):1085-1090.

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# Cancer screening and preventative care among long-term cancer survivors in the United Kingdom

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BACKGROUND: Long-term cancer survivors in the United Kingdom are mostly followed up in a primary care setting by their general practitioner; however, there is little research on the use of services. This study examines whether cancer survivors receive adequate screening and preventative care in UK primary care.

PATIENTS AND METHODS: We identified a cohort of long-term survivors of breast, colorectal and prostate cancer with at least a 5-year survival using the General Practice Research Database, with controls matched for age, gender and practice. We compared adherence with cancer screening and the use of preventative care between cancer survivors and controls.

RESULTS: The cancer survivors' cohort consisted of 18 612 breast, 5764 colorectal and 4868 prostate cancer survivors. Most cancer survivors receive cancer screening at the same levels as controls, except for breast cancer survivors who were less likely to receive a mammogram than controls (OR = 0.78, 95% CI: 0.66–0.92). Long-term cancer survivors received comparable levels of influenza vaccinations and cholesterol tests, but breast (OR 0.81, 95% CI: 0.74–0.87) and prostate cancer survivors (OR = 0.70, 95% CI: 0.57–0.87) were less likely to receive a blood pressure test. All survivors were more likely to receive bone densitometry.

CONCLUSIONS: The provision and uptake of preventive care in a primary care setting in the United Kingdom is comparable between the survivors of three common cancers and those who have not had cancer. However, long-term breast cancer survivors in this cohort were less likely to receive a mammogram.

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**Keywords:** primary care; cancer screening; preventative care; cancer survivors

There are increasing numbers of cancer survivors in the United Kingdom. Current estimates indicate that there are now more than 2 million people living past a diagnosis of cancer in the United Kingdom, a number that is projected to increase by 3% annually (Maddams *et al*, 2009). With increasing numbers surviving many years after a diagnosis, it is important to identify and control adverse sequelae of cancer and its treatment, effectively manage comorbid conditions and optimise the health of this population (Aziz, 2002; Aziz and Rowland, 2003).

Cancer survivors are at increased risk of ill health because of a number of factors, including second cancers, late effects related to treatment and other comorbidities, including those unrelated to cancer (Curtis *et al*, 1985; Orel *et al*, 1993; Sankila *et al*, 1995). The risk of adverse health can be reduced through the use of preventative services that can have an important part in ensuring the long-term health of this population at risk (Carver *et al*, 2007). However, cancer survivors have previously been shown to report poorer health than the general population (Yabroff *et al*, 2004). Previous research into the use of preventative care provided to cancer survivors in the United States has provided mixed results. Although the use of preventive services was better in some cancer survivors, some breast cancer survivors had poorer uptake of measures such as cholesterol screening and influenza vaccination compared with non-cancer controls (Yeazel *et al*, 2004; Trask *et al*, 2005; Duffy *et al*, 2006; Snyder *et al*, 2009). In contrast, others found that although breast cancer survivors received adequate care, the uptake of preventative health in long-term colorectal cancer survivors was worse than in those without cancer (Earle *et al*, 2003; Earle and Neville, 2004). These disparities in health care in the United States may result partly from a focus on cancer follow-up at the expense of routine preventative care for other diseases.

Despite the long-term risks in this population, there has been very little research on the use of primary care services, and specifically on the cancer screening and preventative health behaviours, of cancer survivors in developed health economies other than the United States (Khan *et al*, 2008). This paper aims to fill this gap by examining the use of cancer and non-cancer-related preventative health practices in a primary care-based cohort of cancer survivors in the United Kingdom. In particular, we examined whether screening is affected by a previous cancer diagnosis, and whether cancer survivors receive similar preventative health care compared with individuals who have not had cancer.

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## METHODS

### The source of data

The General Practice Research Database (GPRD), which currently contains information on 3.6 million representative patients from 450 primary care practices in the United Kingdom, was used to identify the patients enrolled in this study (Walley and Mantgani, 1997). The GPRD includes records on individual-level clinical diagnoses, test results, prescriptions, referrals and all significant morbidity events in the patient's medical history (MHRA, 2004). The data undergo quality control procedures, and several validation studies have shown a high level of data completeness within the GPRD (Khan *et al*, 2010). Screening and preventative care events were identified if a medical or investigation code corresponding to the event was present in the patient medical record. Clinical and investigation code lists are available on request.

### Definition of preventative services

We examined adherence to three national cancer screening guidelines as outlined by the National Health Service (NHS) cancer screening programme and the use of services for routine screening of disease and disease prevention (Table 1). There are no British guidelines on frequency of blood pressure testing, bone density scanning or cholesterol tests; therefore, we examined the receipt of one test every 3 years.

### Description of participants

This study focuses on adult survivors of three cancer types: breast, colorectal and prostate cancer. We defined cancer survivors (cases) as those aged $\geqslant$30 years at the time of diagnosis, with at least a 5-year survival after diagnosis. Controls were patients with no record of breast, colorectal or prostate cancer. For each case, up to four controls were selected from the same primary care practice and matched on the basis of age (within 1 year) and gender.

### Inclusion and exclusion criteria for the use of screening and preventative services

We only included patients who were within the age range and eligible for cancer screening, or who did not have a history of previous disease that would indicate the need for monitoring. We excluded women with a history of hysterectomy in the analysis of cervical smear, women with a history of bilateral mastectomy in the analysis of mammography, prostate cancer survivors in the PSA test analysis and breast cancer survivors $<$10 years after diagnosis in the use of mammography. For preventative services, we excluded patients with hypertension from blood pressure monitoring; patients with a clinical history of diabetes, cerebrovascular disease/stroke, hypertension and myocardial infarction from cholesterol testing; and patients with a clinical history of osteoporosis from bone density scanning. These patients will receive regular disease monitoring as directed by the Quality and Outcomes Framework, an incentive programme for payments to primary care practices from the English government (Department of Health, 2006).

### Statistical analyses

We compared the use of screening and preventative services between cancer survivors and their matched controls over a 3-year period between 1 September 2003 and 31 August 2006, which represented the most recent data available in our data set. We extended this analysis window to 5 years starting from 1 September 2001 for the analysis of cervical smear screening in women aged 50–64 years to capture events corresponding to the national cervical cancer screening programme guidelines (see Table 1 for screening recommendations). Cancer survivors entered the analysis along with their matched controls only when they achieved a 5-year survival. In addition, cancer survivors and their matched controls were censored from the analysis if the cancer survivor died, was diagnosed with a second cancer or was transferred out of the practice.

We first described the characteristics of the patients included in each analysis and examined the percentage of cancer survivors and controls receiving cancer screening and preventative services. To determine the association between cancer survivor status and use of preventative services compared with matched controls, we used conditional logistic regression to calculate odds ratios and 95% CIs, which accounts for the matching by comparing cases with the controls for whom they were selected (Kirkwood and Sterne, 2003). All analyses were carried out using Stata MP statistical software, version 10.1 (StataCorp LP, College Station, TX, USA).

### Explanatory variables

We assigned each patient a Charlson comorbidity score on the basis of their clinical history. The original Charlson score assigns patients with cancer a weighted score of 2; however, we excluded cancer as a comorbid disease when calculating individual Charlson scores for both cancer survivors and their controls (Charlson *et al*, 1987). We included the number of consultations during the study period as an explanatory variable for preventative care outcomes, as patients who consult more frequently are more likely to have incidental measurements, such as blood pressure. Information on mastectomy was particularly important when considering receipt of mammography. Therefore, we also linked the GPRD data set to

**Table 1** Summary of UK guidance for cancer screening and preventative health services

| | National guidance | Age range (years) | Frequency of test |
|---|---|---|---|
| *Screening test* | | | |
| Mammogram | NHS Breast Cancer Screening Programme (2007–2008) | 50–69 | Once every 3 years |
| Cervical smear | NHS Cervical Cancer Screening Programme (2007–2008) | 25–49 | Once every 3 years |
| | | 50–64 | Once every 5 years |
| PSA test | Prostate Cancer Risk Management Programme (PCRMP) (UK National Screening Committee, 2001) | 50+ | Patient request |
| *Preventative health* | | | |
| Influenza vaccination | National Institute for Health and Clinical Excellence (NICE) (2008c) | 65+ | Annually |
| Blood pressure test | None | — | — |
| Bone density scan | None | — | — |
| Cholesterol test (HDL, LDL, serum cholesterol) | None | — | — |

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein; PSA = prostate-specific antigen.

treatment data obtained from the English national cancer registry network. A breast cancer patient was considered to have a history of bilateral mastectomy if there was a clinical record for bilateral mastectomy in GPRD records or cancer registration, or if there were two clinical codes for mastectomy more than 1 year apart. Not all mastectomy codes allowed us to distinguish between unilateral and bilateral mastectomy; hence, we included a history of mastectomy as a dichotomous covariate in the remainder of women without a specific code for bilateral mastectomy. We included a history of hormone therapy as identified through prescription records in the GPRD as a covariate in the analysis for bone density scanning. Body mass index was included in multivariate models that considered blood pressure, cholesterol testing and bone density scanning. As patients nearing the end of their life may be treated differently in primary care, we also included a dichotomous variable indicating whether the patient died during the analysis period, and tested for interactions between death and receipt of screening and preventative care.

## RESULTS

### Patient characteristics and univariate analysis

The data set included 18 612 breast cancer survivors, 5764 colorectal cancer survivors, 4868 prostate cancer survivors and 116 418 controls (total $n = 145\,662$ patients). A summary of patient characteristics is shown in Table 2. Colorectal and prostate cancer survivors were quite elderly, and correspondingly a high proportion had at least one comorbid disease.

Table 3 shows the prevalence of screening and preventative service use among cancer survivors and controls. Rates of cervical smear were much lower than expected, but similar in all cancer survivors and controls, and a similar proportion of colorectal cancer survivors and controls underwent mammography according to the national guidelines. A lower proportion of breast cancer survivors underwent a mammogram compared with controls.

In general, cancer survivors were more likely to receive bone density scans, flu vaccination and cholesterol testing preventative care than the control population. However, breast cancer survivors were less likely to receive a blood pressure or cholesterol test compared with controls. We examined these differences in multivariate models.

### Cancer screening

After adjusting for a history of mastectomy ($n = 885$), comorbid disease and death, breast cancer survivors were 22% less likely to receive a mammogram as indicated by the national screening programme, compared with their matched controls (Table 4). There was no difference in the receipt of mammography between

**Table 2** Patient demographics

| | Breast | | Colorectal | | Prostate | |
|---|---|---|---|---|---|---|
| | **Survivor** | **Control** | **Survivor** | **Control** | **Survivor** | **Control** |
| *Numbers in analysis* | | | | | | |
| Male | — | — | 2912 | 11 515 | 4868 | 19 288 |
| Female | 18 612 | 74 284 | 2852 | 11 331 | — | — |
| Age in years (s.d.) | 67.65 (12.65) | | 75.13 (11.2) | | 76.86 (8.31) | |
| Charlson score >0 | 8594 (46.2%) | 31384 (42.3%) | 3418 (59.3%) | 12022 (52.6%) | 3189 (65.5%) | 11008 (57.1%) |

**Table 3** Univariate analysis, with numbers eligible for analysis

| | Breast | | Colorectal | | Prostate | |
|---|---|---|---|---|---|---|
| | **Survivor** | **Control** | **Survivor** | **Control** | **Survivor** | **Control** |
| *Screening exam* | | | | | | |
| Mammogram | 54.4% | 59.5% | 60.5% | 58.5% | | |
| Number in analysis | 2317 | 9974 | 513 | 2055 | — | — |
| Cervical smear | | | | | | |
| Aged 25–49 years | 43.6% | 40.1% | 13.9% | 15.2% | — | — |
| Number in analysis | 755 | 3085 | 65 | 263 | | |
| Aged 50–64 years | 45.7% | 44.4% | 41.6% | 41.9% | — | — |
| Number in analysis | 3419 | 14 061 | 178 | 855 | | |
| PSA test | — | — | 22.1% | 19.0% | — | — |
| Number in analysis | | | 2489 | 9859 | | |
| *Preventative health* | | | | | | |
| Influenza vaccination | 75.8% | 74.4% | 74.9% | 73.2% | 74.6% | 70.2% |
| Number in analysis | 9488 | 37 803 | 4118 | 16 325 | 3854 | 15 275 |
| Blood pressure | 68.0% | 69.2% | 70.1% | 70.4% | 70.7% | 68.7% |
| Number in analysis | 9771 | 38 815 | 2531 | 10 668 | 2105 | 9252 |
| Bone density scan | 14.1% | 10.3% | 13.2% | 10.5% | 17.1% | 9.3% |
| Number in analysis | 14 574 | 59 471 | 4455 | 17 954 | 3928 | 16 026 |
| Cholesterol test | 31.9% | 33.1% | 37.8% | 36.2% | 39.9% | 36.7% |
| Number in analysis | 9072 | 35311 | 2306 | 9235 | 1720 | 7563 |

Abbreviation: PSA = prostate-specific antigen.

**Table 4** Multivariate model for receipt of screening and preventative care (odds ratios from conditional logistic models)

| | Breast cancer | Colorectal cancer | Prostate cancer |
|---|---|---|---|
| *Screening*[a] | | | |
| Mammogram | 0.78, 95% CI 0.66–0.92 | 1.11, 95% CI 0.77–1.61 | — |
| Cervical smear | | | — |
| Aged 25–49 years | 1.37, 95% CI 1.11–1.68 | 0.66, 95% CI 0.21–2.15 | — |
| Aged 50–64 years | 1.14, 95% CI 1.03–1.25 | 1.13, 95% CI 0.72–1.75 | — |
| PSA testing | | 1.19, 95% CI 1.06–1.34 | — |
| *Preventative care* | | | |
| Influenza vaccination[b] | 1.15, 95% CI 1.07–1.23 | 1.15, 95% CI 1.03–1.28 | 1.39, 95% CI 1.22–1.59 |
| Blood pressure test[c] | 0.81, 95% CI 0.74–0.87 | 0.97, 95% CI 0.81–1.17 | 0.70, 95% CI 0.57–0.87 |
| Bone density scan[c] | 1.26, 95% CI 1.10–1.44 | 1.23, 95% CI 1.05–1.43 | 1.59, 95% CI 1.23–2.06 |
| Cholesterol testing[c] | 0.93, 95% CI 0.87–1.00 | 1.01, 95% CI 0.85–1.18 | 0.83, 95% CI 0.69–1.01 |

Abbreviations: BMI = body mass index; CI = confidence interval; PSA = prostate-specific antigen. Cancer controls were used as the baseline comparison. [a]Adjusted for Charlson comorbidity score and death. Mammography analysis also adjusted for history of mastectomy. [b]Adjusted for total number of consultations over analysis period, Charlson comorbidity score and death. [c]Adjusted for total number of consultations over analysis period, BMI, Charlson score and death. Bone density scan analysis also adjusted for hormone treatment in breast and prostate cancer.



female colorectal cancer survivors and matched controls. All breast cancer survivors were more likely than controls to have a cervical smear according to screening guidelines. There was no evidence for a difference in the utilisation of cervical smear among female colorectal cancer survivors compared with controls. As some women receiving mammography or cervical smear may have received screening just before or after the period of analysis, we conducted a sensitivity analysis allowing for a 3-month interval before and after the period of interest. The results were similar, and are therefore not presented.

Colorectal cancer survivors over the age of 50 years were 19% more likely to have a PSA test compared with controls. There was no evidence for a difference in screening behaviours among cancer survivors who died during the analysis period.

### Preventative care

A summary of the multivariate models that consider preventative care among cancer survivors and matched controls is presented in Table 4 (full multivariate models are included in Appendix 1). Each group of cancer survivors was more likely to receive bone density scanning than their matched controls. In addition, cancer survivors over the age of 65 years were more likely to receive an influenza vaccination. In contrast, there were no differences in cholesterol testing between cancer survivors and their matched controls. Although colorectal cancer survivors were as likely to receive a blood pressure test as their matched controls, both breast and prostate cancer survivors were less likely to receive a measurement of blood pressure over the analysis period. An increasing number of primary care visits was the strongest predictor of preventative care delivery.

## DISCUSSION

This is the first paper reporting on the use of primary care services in a large population of cancer survivors outside the United States. In general, most cancer survivors in the United Kingdom receive similar cancer screening and preventative health compared with individuals who have not had cancer. All cancer survivors were more likely to receive influenza vaccination and bone density scans. However, in this cohort, long-term breast cancer survivors were less likely to receive mammography, and breast and prostate cancer survivors were less likely to receive a blood pressure test.

Second cancers can be detected at an earlier stage when appropriate screening guidelines are met (Adami *et al*, 2001). Colorectal cancer survivors in this cohort were more likely to receive a PSA test, and breast cancer survivors were more likely to receive a cervical smear than their matched controls. This finding is understandable; individuals who have previously had cancer may be motivated to identify second cancers at an early stage. However, it is of concern that long-term breast cancer survivors in this study are significantly less likely to receive breast cancer screening than women without a history of breast cancer. Breast cancer survivors are at risk of recurrence and primary cancer in the contralateral breast; therefore, even women who have a unilateral mastectomy should receive regular mammography (Burstein and Winer, 2000). This is the not the first paper to report the underuse of breast cancer screening; previous research has shown the underuse of mammography in breast cancer survivors and childhood cancer survivors despite an increased risk of mortality (Andersen and Urban, 1998; Schapira *et al*, 2000; Keating *et al*, 2006; Lash *et al*, 2007; Oeffinger *et al*, 2009). Although lack of access to mammographic services contributes to the underuse of breast screening amongst certain populations in the United States, this is unlikely to explain cancer screening practices in the United Kingdom, as all eligible women are invited for free breast cancer screening through a national programme. It is difficult to explore the reasons behind attendance at national cancer screening programmes in a large, anonymised database study. However, to increase screening rates, it is important to understand why the use of mammography is lower in long-term survivors.

The results from this analysis indicate that that in UK primary care, cancer survivors generally receive similar preventative care compared with matched controls, and indeed in some cases, receive better care. It seems that the bone health of cancer survivors is well managed in the United Kingdom; our analysis shows that breast and prostate cancer survivors, who are at a greater risk of osteoporosis after hormonal treatment, are significantly more likely to receive a bone density scan than matched controls (Chen *et al*, 2005). This is a large study with a greater propensity for significant results, and although there are deficiencies in the receipt of blood pressure testing among breast and prostate survivors, the differences are small and may not be clinically significant.

It is important to consider the results from this UK-based paper and previous US-based studies in the context of differences in national health-care delivery. In the United States, patients who consulted their oncologist only in the long-term received poorer preventative care for other diseases, but those who consulted both primary and secondary care physicians received the best care (Earle *et al*, 2003; Earle and Neville, 2004; Snyder *et al*, 2008, 2009). Earle and colleagues suggested that a lack of clarity of the roles of secondary and primary care in the United States may lead to fragmentation of care, with cancer survivors unclear about whom

to consult for different aspects of their health care. Long-term cancer survivors in the United Kingdom are unlikely to maintain contact with oncologists, and will rely on their GP to provide care for their cancer and other comorbidities after discharge from hospital follow-up. Compared with the United States, the role of primary care in the general health care of cancer survivors in the United Kingdom is well defined, and this difference may explain why cancer survivors in this cohort received preventative care at similar levels to a non-cancer population. With the exception of mammography for breast cancer survivors, there is certainly no suggestion that cancer survivors are penalised by their status.

Several potential limitations of this study should be considered. First, the data source was collected primarily for clinical use rather than for research, and it is possible that some tests and diagnoses were not fully recorded. However, because the analysis was conducted as comparisons between cases and controls, completeness of recording should not affect this analysis; it is unlikely that the services considered in this paper would be coded preferentially in either population. One proxy of the completeness of recording in the GPRD is a comparison of rates of screening and preventative care with national data. Rates of mammography through the national screening programme are currently 73%, and hence may be slightly underestimated in this GPRD cohort (2009). However, rates of influenza captured in the GPRD closely mirror those of national influenza vaccination, as estimated by the Department of Health (NHS Immunization Information, 2005). This difference in completeness of recording may reflect the fact that influenza vaccination is likely to take place in primary care; however, breast cancer screening occurs in specialised screening centres, and GPs may record the event differently in the GPRD electronic patient record. However, cervical screening, which does occur in UK primary care, was not well captured in this GPRD cohort. National coverage of cervical screening is $\sim$78%; therefore, the rates of cervical smear are drastically underestimated in this study (2008). This underestimate is a recognised problem in the GPRD because of underrecording of cervical smear results in computerised patient medical records before the widespread use of electronic transfer of cervical smear results from laboratories.

Second, it has been suggested that research using administrative data may underestimate rates of bilateral mastectomy (Nissen *et al*, 2008). However, the analysis in this paper was conducted using surgery data from both cancer registries and primary care. Some of the clinical codes used to identify mastectomy in the GPRD were not precise enough to determine whether the procedure was bilateral or unilateral. This may be a limitation, as patients receiving a bilateral mastectomy will not be eligible for breast screening. However, to account for this, we excluded any women with a specific primary care code for bilateral mastectomy, or two mastectomy codes more than a year apart. This definition of bilateral mastectomy resulted in an overall rate of 4.2% in the cohort of breast cancer survivors, which corresponds to rates in the SEER (Surveillance, Epidemiology and End Results) database (Tuttle *et al*, 2007). We also conducted a sensitivity analysis excluding all women with any clinical code for mastectomy. The results were similar and therefore not presented.

Finally, because we are using a primary care database, we are unlikely to account for preventative care or screening occurring in hospital or in specialised clinics. However, in the United Kingdom, the majority of cancer survivors are discharged to the care of their GP 3 to 5 years after diagnosis. Therefore, the majority of their care will occur in primary care and is likely to be coded in the GPRD.

As cancer survivors are living longer, the current challenge in primary care is to maximise the quality and duration of life after cancer. This can be achieved through screening, preventative services and advice to patients, which can reduce the risk of second cancers and other potential comorbidities. There are now guidelines for risk-based surveillance among childhood cancer survivors; management of bone loss among breast cancer survivors; and identification of cardiac and pulmonary late-effects in long-term survivors; however, more work is required in this area to direct GPs who will be responsible for the long-term health care of this population (Carver *et al*, 2007; Reid *et al*, 2008; Hudson *et al*, 2009). There is a need for evidence-based guidelines to direct case finding and preventative care in primary care for elderly cancer survivors, who require care of general health and comorbid disease, as well as potential late effects of cancer and its treatment. A further understanding of the factors that contribute to late effects and the appropriate risk-based surveillance will help towards maintaining the good health of this population.

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## Appendix 5

Quality of care for chronic diseases in a British cohort of long-term cancer survivors. Khan NF, Mant D, Rose PW. Annals of Family Medicine. 2010;8:418-424.

# Quality of Care for Chronic Diseases in a British Cohort of Long-Term Cancer Survivors

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## ABSTRACT

**PURPOSE** Previous research has shown that long-term cancer survivors with other chronic diseases may receive poorer care for those diseases compared with the general population. We sought to establish the quality of care for chronic diseases among cancer survivors in the United Kingdom.

**METHODS** From the UK General Practice Research Database, we identified 21,366 adult patients who had survived 5 or more years after a diagnosis of breast, colorectal, or prostate cancer with a diagnosis of hypertension, coronary artery disease, diabetes, or cerebrovascular disease. For each patient, an age-sex matched noncancer control patient was selected from the same general practice and with the same chronic disease. We compared the chronic disease care in cancer survivors and their matched controls.

**RESULTS** The proportion of patients meeting quality standards for chronic disease care was high in both cancer survivors and control patients. Although cancer survivors were slightly less likely to receive blood pressure monitoring and cholesterol tests, this difference was no longer apparent if patients who died during the study period were excluded. For instance, 93% of breast cancer survivors received blood pressure monitoring compared with 94% of matched control patients. Similarly, control of disease was comparable among all patients, with the exception of diabetic prostate cancer survivors, who had fewer cholesterol readings under the control limit (17% reduction, 95% CI, 7%-26%) and diabetic colorectal survivors, who had fewer calendar quarters of glycated hemoglobin control (12% reduction, 95% CI, 2%-23%).

**CONCLUSIONS** Care of comorbidities is not neglected in the United Kingdom because people have had a previous diagnosis of cancer. One explanation is that in the United Kingdom, such care is provided through a robust primary care system.

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## INTRODUCTION

Cancer is primarily a disease affecting an older population. Currently, 1 in 8 people aged 65 years and older are living beyond a diagnosis of cancer in the United Kingdom.[1] Chronic disease management is an important issue for older, long-term survivors, many of whom will have 1 or more comorbid diseases.[2] Research from the United States has highlighted, however, the underuse of chronic disease monitoring in individuals with cancer.[3-8] Furthermore, cancer survivors with a comorbid condition have a substantially higher likelihood of poor health and disability than those without a history of cancer.[9,10] Now that more than one-half of all individuals with a diagnosis of cancer will live more than 5 years after the diagnosis, these chronic illnesses, not cancer, will contribute to a substantial proportion of the long-term morbidity and mortality in this population.[11]

*Conflicts of interest: none reported*

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Previous research has highlighted problems in delivering coordinated health care to cancer survivors. Patients and physicians report different beliefs about the role of primary and secondary care in the long term, resulting in uncertainly among patients wondering where to turn to for their routine preventative care.[12] In the United Kingdom, most cancer survivors are referred back to the care of their primary care physician 3 to 5 years after the diagnosis, and it is in primary care that these long-term cancer survivors will receive the bulk of their health care. It is unknown whether this population receives adequate care in the British primary health care system.[13]

The main aims of this work are to extend upon previous research and to investigate monitoring of chronic disease in a British primary care setting. Our purpose is to investigate whether cancer survivorship influences primary care physicians in the United Kingdom to deliver less-adequate disease monitoring for other chronic diseases compared with control patients who did not have cancer. One of the advantages of this study includes the ability to not only investigate receipt of care, but also to use individual monitoring test results to determine whether long-term cancer survivors have adequate disease maintenance.

## METHODS

### Source of the Data

This study used the General Practice Research Database (GPRD), which is the world's largest source of anonymous longitudinal data from primary care. The GPRD currently contains information on a representative group of 3.6 million patients from more than 400 general practices in the United Kingdom.[14] Practices participating in the GPRD record data on individual-level clinical diagnoses, prescriptions, and quantitative results from tests and examinations conducted in primary care. The data undergo quality control procedures, and several validation studies have shown a high level of data completeness within the GPRD.[15]

### Participants and Inclusion and Exclusion Criteria

This report is part of a larger study that aims to examine the use of primary health care services by long-term survivors of breast, colorectal, and prostate cancer.[16] Cancer survivors were defined as those aged 30 years or older at the time of diagnosis with at least 5 years of postdiagnosis survival. The main cohort from which the participants for this analysis were chosen consists of 18,707 breast cancer survivors, 5,773 colorectal cancer survivors, and 4,856 prostate cancer survivors matched to 4 control patients who did not have cancer. This analysis included only those patients with a chronic disease requiring monitoring; therefore, we included cancer survivors and matched controls with diabetes, hypertension, stroke or transient ischemic attack (TIA), myocardial infarction (MI), or coronary artery disease (CAD) diagnosed before the start of the analysis period. Because cancer survivors and control patients were not originally matched by chronic disease, for the purposes of this study, we restricted cases to those cancer survivors with a chronic disease, then randomly sampled within all available control patients on the basis of age, sex, primary care practice, and chronic disease on a one-to-one ratio to make comparisons between survivors and control patients with the same condition. Clinical codes for identification of disease status can be provided upon request. Survivors and control patients entered the analysis on September 1, 2003, with at least 1 day of follow-up until the end of the study period on August 31, 2006. Cancer survivors entered the analysis along with their matched controls only when they achieved 5 years survival, and the matched groups were censored from the analysis if the cancer survivor died or transferred out of the GPRD primary care practice.

### Statistical Analysis

We used national guidelines to determine whether patients with chronic disease achieved adequate levels of disease control. The English Quality and Outcomes Framework (QOF) is an incentive program with annual monetary rewards for primary care practices achieving nationally set indicators for clinical care.[17] We used levels for monitoring as indicated in QOF to define adequate control of disease for the indicators used in this study. Adequate control of blood pressure was defined as a measurement of 150/90 mm/Hg or less for patients with hypertension or 145/85 mm/Hg for patients with diabetes. We also used the QOF guidelines for total cholesterol levels, which defines less than 5 mmol/L (200 mg/dL) for patients with a history of coronary artery disease, diabetes, and cerebrovascular disease (stroke and transient ischemic attack). Adequate control of diabetes was defined as a glycated hemoglobin ($HbA_{1c}$) reading of less than 7.5%. Cancer survivors with more than one chronic condition requiring monitoring were included in each of the relevant analyses. For instance, a cancer survivor with hypertension and diabetes was included twice, in both analyses examining blood pressure and $HbA_{1c}$ monitoring.

We initially compared receipt of monitoring in cancer survivors and control patients from September 1, 2003, to August 31, 2006, using $\chi^2$ tests and binomial exact 95% confidence intervals for the proportions. Because patients at the end of life may be treated differently, we also compared the proportion of patients

receiving monitoring after excluding all matched pairs where either the survivor or control patient died during the study period. To account for the matched groups in multivariate models, we also used conditional logistic regression to report receipt of monitoring over the 3-year analysis window.

To examine disease control, we produced mean systolic and diastolic blood pressure, total cholesterol, and $HbA_{1c}$ measurements for each patient receiving monitoring based on readings in 3-month periods (quarterly) from September 1, 2003, to August 31, 2006. When a monitoring test was not conducted or not recorded, we assumed no change and used the same value as the previous time period. We compared the number of quarters with a test reading in the control range using *t* tests, and univariate associations ($P < .05$) were explored in multivariate models using conditional fixed-effects regression to account for the matched groups. All analyses were carried out using Stata MP statistical software, version 10.1 (StataCorp LP, College Station, Texas).

### Explanatory Variables

We adapted the Charlson comorbidity index and assigned each patient a comorbidity score based on their clinical history in the GPRD.[16] The original Charlson score assigns patients with cancer a weighted score of 2; however, we excluded cancer as a comorbid disease.[18] This score was added as an explanatory variable to all multivariate analyses. We also included the number of consultations during the study period, along with body mass index and a dichotomous variable indicating whether the patient died during the analysis period. Because patients nearing the end of their life may be treated differently in primary care, we tested for interactions between death and receipt of monitoring in all multivariate models.

## RESULTS

The final analysis was conducted on 15,800 patients with hypertension, 1,346 patients with diabetes, 1,066 patients with a history of cerebrovascular disease, including stroke and TIA, and 3,154 patients with a history of coronary artery disease (Table 1). Reflecting national trends in cancer incidence and survival, breast cancer survivors comprised the largest group of cancer survivors. The patient population was elderly, and most breast and colorectal cancer survivors were more than 10 years after their diagnosis. A significantly higher proportion of all cancer survivors died during the 3-year study period. Most patients in this study had only 1 of the chronic diseases indicating monitoring ($n = 17,254$, 89.7%), however, a small proportion of patients ($n = 1,974$, 10.3%) had more than 1 of the chronic conditions under investigation.

### Proportion of Patients Receiving Monitoring

We first examined the proportion of individuals who received at least 1 monitoring test during the 3-year period (Table 2). Almost all cancer survivors were significantly less likely to receive any monitoring tests. Compared with the control population, however, a considerably higher proportion of cancer survivors died during the study period. Because patients at the end of life may receive different levels of disease monitoring, we also considered the receipt of monitoring among matched pairs when neither the survivor nor

**Table 1. Patient Characteristics in Each Analysis**

| Characteristic | Breast | | Colorectal | | Prostate | |
|---|---|---|---|---|---|---|
| | Survivor | Control | Survivor | Control | Survivor | Control |
| History of hypertension | | | | | | |
| No. of patients | 4,624 | 4,624 | 1,732 | 1,732 | 1,544 | 1,544 |
| Patients who died, % | 14.7 | 2.6 | 18.2 | 3.2 | 25 | 5.1 |
| Age in 2003, years | 73.7 | 73.7 | 77.1 | 77.1 | 77.0 | 77.0 |
| Years from diagnosis | 11.4 | – | 10.8 | – | 5.9 | – |
| History of diabetes | | | | | | |
| No. of patients | 334 | 334 | 167 | 167 | 172 | 172 |
| Patients who died, % | 20.1 | 3.6 | 23.4 | 5.9 | 27.9 | 6.9 |
| Age in 2003, years | 73.3 | 73.3 | 75.7 | 75.7 | 76.3 | 76.3 |
| Years from diagnosis | 10.4 | – | 10.5 | – | 5.6 | – |
| History of coronary artery disease, myocardial infarction | | | | | | |
| No. of patients | 499 | 499 | 478 | 478 | 600 | 600 |
| Patients who died, % | 25.2 | 7.4 | 24.5 | 8.8 | 27.3 | 6.2 |
| Age in 2003, years | 78.9 | 78.9 | 79.0 | 79.0 | 78.1 | 78.0 |
| Years from diagnosis | 12.4 | – | 10.6 | – | 6.4 | – |
| History of cerebrovascular disease (eg, stroke or transient ischemic attack) | | | | | | |
| No. of patients | 229 | 229 | 156 | 156 | 148 | 148 |
| Patients who died, % | 34.5 | 10.5 | 33.3 | 11.5 | 39.2 | 15.5 |
| Age in 2003, years | 81.5 | 81.5 | 81.6 | 81.5 | 80.8 | 80.8 |
| Years from diagnosis | 12.9 | | 11.1 | | 6.2 | |

**Table 2. Proportion of All Patients Receiving a Monitoring Test**

| | Blood Pressure | | Total Cholesterol | | | $HbA_{1c}$ |
|---|---|---|---|---|---|---|
| Type of Cancer | History of Hypertension % (95% CI) | History of Diabetes % (95% CI) | History of CAD/MI % (95% CI) | History of Diabetes % (95% CI) | History of Cerebrovascular Disease % (95% CI) | History of Diabetes % (95% CI) |
| Breast | | | | | | |
| Survivor | 91.6[a] (90.8-92.4) | 90.7[a] (87.1-93.6) | 78.6[a] (74.7-82.0) | 84.4[a] (80.0-88.1) | 62.4[a] (55.8-68.7) | 86.2 (82.1-89.7) |
| Control | 95.2 (94.5-95.8) | 95.2 (92.3-97.2) | 86.9 (83.7-89.8) | 91.0 (87.4-93.9) | 81.7 (76.0-86.4) | 88.9 (85.1-92.1) |
| Colorectal | | | | | | |
| Survivor | 91.8[a] (90.4-93.1) | 89.8 (84.2-93.9) | 79.1[a] (75.2-82.6) | 79.6[a] (72.7-85.4) | 66.0[a] (58.0-73.4) | 83.2 (76.7-88.6) |
| Control | 95.4 (94.3-96.4) | 92.2 (87.0-95.8) | 87.5 (84.1-90.2) | 89.8 (84.2-93.9) | 80.7 (73.7-86.6) | 87.4 (81.4-92.0) |
| Prostate | | | | | | |
| Survivor | 88.9[a] (87.2-90.4) | 86.6[a] (80.6-91.3) | 79.2[a] (75.7-82.3) | 79.7[a] (72.9-85.4) | 64.2[a] (55.4-71.5) | 80.2[a] (73.5-85.9) |
| Control | 93.4 (92.0-94.6) | 94.2 (89.6-97.2) | 88.7 (85.8-91.1) | 89.5 (83.9-93.7) | 78.4 (70.9-84.7) | 90.1 (84.6-94.1) |

CAD = coronary artery disease; CI = confidence interval; $HbA_{1c}$ = glycated hemoglobin; MI = myocardial infarction.

[a] $P < .05$ for univariate $\chi^2$ comparison between cancer survivors and controls.

**Table 3. Proportion of All Patients Receiving a Monitoring Test, Excluding Patients Who Died**

| | Blood Pressure | | Total Cholesterol | | | $HbA_{1c}$ |
|---|---|---|---|---|---|---|
| Cancer Type | History of Hypertension % (95% CI) | History of Diabetes % (95% CI) | History of CAD/MI % (95% CI) | History of Diabetes % (95% CI) | History of Cerebrovascular Disease % (95% CI) | History of Diabetes % (95% CI) |
| Breast | | | | | | |
| Survivor | 93.3 (92.5-94.1) | 94.7 (91.2-97.7) | 89.0 (85.3-91.9) | 90.5 (86.3-93.8) | 76.0 (68.3-82.7) | 91.3 (87.2-94.4) |
| Control | 94.8 (94.1-95.5) | 95.8 (92.7-97.9) | 89.5 (85.9-92.4) | 92.1 (88.1-95.0) | 84.2 (77.3-89.7) | 88.6 (84.1-92.2) |
| Colorectal | | | | | | |
| Survivor | 93.9 (92.5-95.1) | 93.5 (87.7-97.2) | 86.2 (82.2-89.6) | 84.7 (77.1-90.5) | 74.7 (65.2-82.8) | 86.3 (78.9-91.8) |
| Control | 95.3 (94.1-96.4) | 91.9 (85.7-96.1) | 90.1 (86.6-93.0) | 89.5 (82.7-94.3) | 85.4 (77.1-91.6) | 88.7 (81.8-93.7) |
| Prostate | | | | | | |
| Survivor | 92.5 (90.8-93.9) | 90.2 (83.6-94.9) | 88.7 (85.3-91.5) | 86.9 (79.7-92.4) | 77.0 (66.8-85.4) | 83.7 (76.0-89.8) |
| Control | 92.1 (90.3-93.6) | 93.5 (87.6-97.2) | 89.6 (86.3-92.3) | 86.9 (79.7-92.4) | 79.3 (69.3-87.3) | 86.9 (79.7-92.4) |

CAD = coronary artery disease; CI = confidence interval; $HbA_{1c}$ = glycated hemoglobin; MI = myocardial infarction.

the control patient died during the analysis window (Table 3). After excluding individuals who died, all cancer survivors and controls received at least the same level of disease monitoring.

We explored all associations further in conditional multivariate models accounting for the matched groups. After adjusting for the matching, number of consultations, Charlson score, body mass index, and death, there were no significant differences between any cancer survivors and control patients in the odds of receiving chronic disease monitoring. There was no formal evidence for an interaction between death and delivery of care; however, the numbers of patients who died and had a chronic disease were few in each separate analysis.

## Control of Disease

To investigate disease control, we compared the proportion of quarterly periods when cancer survivors and control patients had test readings in the indicated

**Table 4. Proportion of Calendar Quarters With Adequate Control of Disease**

| Cancer Type | Blood Pressure | | Total Cholesterol | | | $HbA_{1c}$ |
|---|---|---|---|---|---|---|
| | History of Hypertension % (95% CI) | History of Diabetes % (95% CI) | History of CAD/MI % (95% CI) | History of Diabetes % (95% CI) | History of Cerebrovascular Disease % (95% CI) | History of Diabetes % (95% CI) |
| Breast | | | | | | |
| Survivor | 69.0 (68.1-70.1) | 62.8 (58.9-66.6) | 58.3 (54.1-62.6) | 64.2 (59.7-68.8) | 50.2 (43.0-57.4) | 69.6 (59.6-68.7) |
| Control | 68.1 (67.2-69.1) | 57.9 (54.1-61.8) | 56.5 (52.6-60.6) | 70.4 (66.1-74.6) | 49.5 (43.2-55.8) | 64.1 (59.6-68.7) |
| Colorectal | | | | | | |
| Survivor | 69.6 (67.9-71.3) | 63.7 (57.7-69.7) | 74.4 (70.6-78.2) | 75.3 (69.1-81.6) | 65.4 (57.4-73.5) | 63.7[a] (57.2-70.4) |
| Control | 68.3 (66.7-69.9) | 63.6 (57.9-62.3) | 73.1 (69.3-76.8) | 78.6 (73.0-84.1) | 69.4 (62.3-76.4) | 73.3 (67.7-78.9) |
| Prostate | | | | | | |
| Survivor | 74.4 (72.7-76.1) | 67.9 (61.7-74.0) | 78.0 (74.7-81.3) | 74.6[a] (68.2-80.9) | 66.7 (58.1-75.4) | 72.5 (66.0-79.1) |
| Control | 72.8 (71.1-74.5) | 65.1 (59.7-70.5) | 81.5 (78.7-84.2) | 83.7 (78.6-88.7) | 76.9 (70.4-83.3) | 68.5 (62.1-74.9) |

CAD = coronary artery disease; CI = confidence interval; $HbA_{1c}$ = glycated hemoglobin; MI = myocardial infarction.

[a] $P < .05$ for univariate $\chi^2$ comparison between cancer survivors and control patients.

control range. The univariate analysis shows that most cancer survivors had similar adherence to the QOF clinical indicators for blood pressure, cholesterol, and $HbA_{1c}$ levels compared with control patients (Table 4). There were 2 exceptions, however; diabetic colorectal cancer survivors had significantly fewer quarterly periods with $HbA_{1c}$ levels under 7.5%, and diabetic prostate cancer survivors had significantly fewer periods with a total cholesterol reading under 5 mmol/L. These associations persisted after adjusting for the matching and covariates; diabetic prostate cancer survivors had a 17% (95% confidence interval [CI], 7%-26%) reduction in the proportion of cholesterol readings in the control range compared with matched controls. Colorectal cancer survivors also had a lower proportion of controlled $HbA_{1c}$ readings (12% reduction; 95% CI, 2%-23%). There was no evidence for effect modification for differential control of disease among patients who died within the study period.

## DISCUSSION

This study is the first of this type in the United Kingdom and the first to report comparisons between individual patient-monitoring results in cancer survivors and in control patients. Chronic disease is well managed in UK primary care; most cancer survivors who are not at the end of life receive the same level of care as noncancer patients. Of those who did receive monitoring, disease was generally controlled at the same level in both populations.

### Possible Mechanisms and Implications for Clinicians or Policy Makers

The results of this study show that in British primary care, history of cancer is not associated with poorer management of hypertension, diabetes, cerebrovascular disease, or coronary artery disease. There seem to be some differences in the receipt of monitoring among patients at the end of life; however, there were not enough patients to conduct formal subgroup analyses in the multivariate models. Changes in disease maintenance strategies are likely to be appropriate in patients receiving palliative care.

These findings differ from previous research from the United States, which has shown deficiencies in care for long-term cancer survivors.[4,8,19] This divergence in quality of care is likely a result of differences in health care delivery in the United States and the United Kingdom. Specifically, the introduction of incentives for chronic disease monitoring, universal health care, and a clear role for primary care in the United Kingdom may play a role in ensuring appropriate provision of comprehensive care in older age.

The quality of British primary care has been improving steadily since the late 1990s as a result of the introduction of national initiatives and guidelines for the provision of improved health services.[20,21] The launch of the QOF in England in 2004 helped to accelerate and standardize clinical performance for many of the indicators included in the incentive program.[22-24] Under QOF, primary care practices can claim financial rewards upon meeting clinical indicators relating to

monitoring 10 chronic conditions, including coronary artery disease, stroke, hypertension, and diabetes.[24] These incentives have helped standardize delivery of care in England, and are likely to play a part in ensuring adequate chronic disease care for cancer survivors. The effect of incentivizing indicators for some conditions and not others means that the quality of care for some conditions not covered in QOF have not improved. Patients with conditions that are not indicated for financial incentives under QOF are at risk of poorer quality of care.[25]

The roles of primary care and specialist physicians can be unclear to both long-term cancer survivors and health care professionals in the US health care setting. Many patients expect both primary care physicians and oncologists to provide a proportion of care of other medical problems, and almost all studies comparing uptake of noncancer health care report that cancer survivors who see both a primary care physician and an oncologist received the best quality care.[4-6] The clearer role of primary and secondary care physicians in the United Kingdom means that fewer cancer survivors requiring monitoring should slip through the net. Long-term cancer survivors in the United Kingdom are unlikely to have regular contact with an oncologist; most are discharged from hospital follow-up 3 to 5 years after the diagnosis. Primary care physicians are the first point of contact for patients in the United Kingdom and act as gatekeepers to secondary care. Cancer survivors in the United Kingdom are therefore likely to receive most of their long-term comprehensive health care solely from a primary health care team experienced in the care of chronic conditions. As research from the United States suggests, however, individuals seeing an oncologist as well as a primary care physician will receive better care for cancer-related issues. It is possible that only being able to access a primary care physician in the first case may mean that fewer oncology issues are monitored in long-term cancer survivors in the United Kingdom. Our study did not specifically consider this issue.

## Strengths and Weaknesses

The strengths of this study include the large number of cancer survivors and control patients, and the representative nature of the population. Some of the limitations of this research are common to other studies using large administrative databases. First, because patient records were not primarily collected for research purposes, it is possible that some tests and diagnoses were not accurately or fully recorded. Because this analysis was conducted as case-control comparisons, completeness of recording should not affect our results; it is unlikely that the services considered in this report would be coded preferentially in either population. Second, because we are using a primary care database, we are unlikely to account for disease monitoring provided in the hospital or in specialized clinics. In the United Kingdom, however, most cancer survivors are discharged to the care of their primary care physician by 5 years after the diagnosis. Most of their care will therefore occur in primary care and is likely to be captured in this cohort of long-term survivors in the GPRD.

There are 2 main methodological limitations to this research. Although some of the individuals had a history of more than 1 of the chronic diseases considered in this report, we have treated them separately in each analysis. A higher proportion of all cancer survivors had more than 1 chronic disease, which possibly may have introduced a bias, as patients with multiple morbidities may receive better care.[26,27] Even so, we believe that it was appropriate to analyze the patients with 2 or more chronic diseases similarly to those with only 1 chronic disease, as the QOF guidelines that were used as the benchmark of care are specific to each condition regardless of multimorbidity. Second, although we have conducted numerous statistical tests for the proportion of individuals receiving monitoring and quarterly control of disease, we have not adjusted for multiple comparisons. It is not always necessary to make adjustments for multiple comparisons, especially as these results are based on observed, and not random data.[28]

## Unanswered Questions and Future Research

There are several unanswered questions arising from this research. Our results suggest that primary care physicians may change disease-monitoring practices in dying cancer survivors. It was not possible, however, to access additional information to determine which patients were specifically receiving end-of-life care. The GPRD will soon be linked to death registration data from the Office for National Statistics (ONS), which will allow us to investigate cause of death and primary care provision in those cancer survivors dying from cancer. We also considered chronic disease care in cancer survivors at least 5 years after the diagnosis only, when their disease monitoring was likely to be reported in a primary care database. Further work should be conducted to explore whether shorter-term cancer survivors in the United Kingdom, who are seeing a cancer specialist on a regular basis, are receiving adequate care of other health concerns.

In an aging and growing population with increasing cancer survival rates, it is important to manage not only the cancer-specific needs of long-term survivors, but also to ensure the adequate management of comorbid disease. This research shows that care

of these specific comorbidities is not neglected in the United Kingdom because people have had a previous diagnosis of cancer.

Previous research showing disparities in chronic disease care among long-term cancer survivors in the United States may possibly be due to health system effects. Our research adds to the existing literature in this area, but is the first study to examine use of primary care services in a UK setting.

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# Appendix 6

Consulting and prescribing behaviour for anxiety and depression in long-term survivors of cancer in the UK. Khan NF, Ward A, Watson E, Rose PW. European Journal of Cancer. 2010;46(18):3339-3344.

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# Consulting and prescribing behaviour for anxiety and depression in long-term survivors of cancer in the UK

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ABSTRACT

*Introduction:* Cancer survivors may experience long-term depression or anxiety, however, there is little previous research on the use of services in this area. We explored consultation and prescribing behaviour for depression and anxiety amongst cancer survivors in British primary health care.

*Methods:* This study uses data on 26,213 survivors of breast, colorectal and prostate cancer at least 5 years post-diagnosis, matched to four controls without cancer, from the UK General Practice Research Database. We compared consultations for depression and anxiety, and prescribing for anti-depressants and anxiolytics between cancer survivors and controls.

*Results:* Multivariate, matched regression models showed no difference in consulting for depression or anxiety between any cancer survivors and matched controls. However, breast cancer (odds ratio (OR) 1.16, 95% confidence interval (CI) 1.10–1.22) and prostate cancer survivors (OR 1.31, 95% CI 1.16–1.47) were more likely to receive a prescription for an antidepressant. Breast cancer survivors (IRR 2.49, 95% CI 1.82–3.42) and prostate cancer survivors (IRR 2.84, 95% CI 1.94–4.17) who died received significantly more antidepressants than controls who died. There were no differences in anxiolytic prescribing for colorectal and prostate cancer survivors compared to controls. However, breast cancer survivors nearing the end of life received a greater number of anxiolytic prescriptions compared to controls (IRR 1.84, 95% CI 1.36–2.49).

*Conclusions:* In this cohort of cancer survivors, there were no differences in consultation behaviour for depression and anxiety compared to controls. However, breast and prostate cancer survivors access more antidepressants, and those nearing the end of life received the highest volume of prescriptions. Breast cancer survivors at the end of life also receive more anxiolytics.



## 1. Introduction

### 1.1. Context

Survival rates for cancer have been improving over the last 20 years due to improvements in diagnosis and treatment. Once perceived as a fatal condition, cancer has become a treatable disease, with half of all British cancer patients living for at least 5 years past a diagnosis.[1] Until recently, cancer care and research has focused on the acute physical needs associated with a life threatening disease. However, as survival rates for many of the common cancers have improved, cancer

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is increasingly viewed as a chronic illness. This paradigm shift has refocused cancer survivorship research from the acute phase to a long-term disease model covering physical, social and psychological health.[2,3]

It has been suggested that ongoing medical and psychosocial effects of cancer and its treatment can lead to long-term psychological morbidity in cancer survivors.[2] Surveys of long-term breast and prostate cancer survivors have highlighted ongoing depression, anxiety and need for psychological support.[4–6] A recent systematic review considering the long-term psychological consequences of cancer survivorship suggested that while levels of psychological distress are similar to the general population in most cancer survivors, a proportion of cancer survivors consistently report long-term depression and anxiety.[7] Cancer survivors at risk of long-term psychological distress may include those with multiple comorbid diseases or advanced disease, and individuals receiving cancer treatments with long-term side effects.[8]

Psychological care is an important component of health provision immediately following a cancer diagnosis. However, there has been little research on the use of services amongst long-term survivors of cancer. In the UK, primary care is the first point of contact for cancer survivors seeking medical care following discharge from routine follow-up. The purpose of this work is to explore the use of primary care psychological services amongst long-term survivors of cancer, and to compare their consultation behaviour and prescribing behaviours with a non-cancer control population. Specifically, we aimed to investigate whether cancer survivors were more likely to consult for depression and anxiety-related problems and receive prescriptions for antidepressants or anxiolytics. We also considered the effect of comorbidity and proximity to end of life on consultations and prescribing for psychological problems.

## 2. Methods

### 2.1. Source of the data

We used data from the General Practice Research Database (GPRD), which contains information on 4.5 million actively consulting patients from 450 general practices in the United Kingdom (UK).[9] The GPRD includes records on individual level clinical diagnoses, test results and prescriptions from primary care. Each consultation is coded using a Read or OXMIS code for each episode of illness or new occurrence of a symptom.[10] Several validation studies have shown a high level of data completeness within the GPRD.[11]

### 2.2. Description of participants

This study focuses on a cohort of adult survivors of breast, colorectal and prostate cancer. The three cancers were selected because they are the three most prevalent cancers in the UK and represent a significant proportion of all long-term survivors in primary health care. We defined cancer survivors (cases) as those aged 30 or over at the time of diagnosis, with at least 5 years of survival post-diagnosis. Controls were patients with no record of breast, colorectal or prostate cancer at the start of the analysis period. For each case, up to four controls were selected from the same primary care practice and matched on the basis of age (within 1 year) and gender. Survivors and matched control patients were censored from follow-up if the cancer survivor died, was diagnosed with a second cancer, or transferred out of the GPRD primary care practice.

### 2.3. Antidepressant and anxiolytic prescription definition

We defined antidepressant drugs as tricyclics, selective serotonin re-uptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs), and anxiolytics as benzodiazepines and busipirone, respectively, listed in Sections 4.3 and 4.1.2 of the British National Formulary.[12] See Appendix 1 for further details.

### 2.4. Statistical analyses

We compared consultation behaviour for depression, anxiety and prescribing for antidepressants and anxiolytics between cancer survivors and their matched controls over a 3 year period from 1 September 2003 to 31 August 2006. A full list of codes used to identify consultations can be provided upon request.

We firstly compared the percentage of cancer survivors and controls consulting for the first time for depression or anxiety, or receiving prescriptions for antidepressants or anxiolytics between 1 September 2003 and 31 August 2006. Secondly, we used conditional logistic regression to determine whether or not cancer survivors were more likely than their matched controls to have a consultation for depression or anxiety, or receive at least one prescription for an antidepressant or anxiolytic during the same analysis period. Thirdly, we compared the volume of prescribing for antidepressants and anxiolytics using World Health Organization defined daily doses to assign each of the prescribed drugs in the GPRD, a defined daily dose (DDD).[13] We used conditional fixed-effects negative binomial regression, offset by follow- up time for each individual, to compare the number of defined daily doses for antidepressants and anxiolytics between cancer survivors and matched controls. This method accounts for the matching by firstly making comparisons within each matched set and then averaging across all the matched sets. All analyses were carried out using Stata MP, version 10.1.

### 2.5. Explanatory variables used in the regression analyses

We assigned each patient a Charlson comorbidity score based on their clinical history.[14] We did not count cancer as a comorbid disease.[15] We included history of depression and anxiety (defined as a previous consultation for depression or anxiety prior to the start of the analysis period, not as depression prior to cancer in the survivors), respectively, in the corresponding analyses for depression and anxiety consultation behaviour. The number of overall consultations over the 3 year period was also included in the prescribing analysis, as patients consulting more frequently are more likely to receive pharmacological interventions. Because patients nearing the end of their life can be treated differently in primary care, we included a variable indicating whether or not the patient died during the analysis period, and tested for interactions between death and all outcomes.

## 3. Results

The final dataset included data on 16,938 breast cancer survivors, 5068 colorectal cancer survivors, 4207 prostate cancer survivors, and 104,486 control patients (total $n = 130,699$ patients, see Table 1). Most cancer survivors and controls were elderly, and correspondingly many had at least one comorbid disease. A substantially higher proportion of cancer survivors died within the analysis period.

### 3.1. Clinical consultations for depression

The majority of patients in this cohort did not consult for depression during the 3 year period (Table 2).

After adjusting for comorbidity score, history of depression and death, there were no significant differences between any cancer survivors and matched controls in terms of consultations for depression over the analysis period (Table 2). Previous history of depression and increasing Charlson comorbidity score were the strongest predictors of consultations for depression in all patients. Full multivariate models are provided in Appendix 2.

### 3.2. Clinical consultations for anxiety

Only a small proportion of cancer survivors and controls saw their GP for anxiety-related reasons between 2003 and 2006 (Table 2). The univariate, matched analysis for anxiety consulting behaviour suggested an increase in the likelihood of having at least one primary care visit for anxiety amongst breast and prostate cancer survivors compared to controls. However, after adjusting for Charlson score, history of anxiety and death, there was no significant increase in the odds of consulting for an anxiety amongst any of the long-term cancer survivors compared to the control population (Table 2).

### 3.3. Prescribing for antidepressants

The proportion of cancer survivors and controls receiving at least one prescription for an antidepressant from 2003 to 2006 is shown in Table 3.

After adjusting for Charlson score, death, number of consultations and stratifying on matched groups, both breast cancer survivors (OR = 1.16, 95% CI 1.11–1.22) and prostate cancer survivors (OR = 1.38, 95% CI 1.25–1.54) were more likely to receive at least one prescription for an antidepressant compared to matched controls (Table 3).

There were no differences in the number of defined daily doses of antidepressants amongst colorectal survivors and controls during the 2003–2006 period, conversely, there were significant differences amongst breast and prostate cancer survivors and controls. Breast cancer survivors were prescribed 76.1 defined daily doses (95% CI 72.3–79.8), compared to 71.3 DDDs (95% CI 69.4–73.2 DDDs) prescribed to breast cancer controls. Prostate cancer survivors were prescribed 41.8 DDDs (95% CI 36.9–46.7) versus 29.1 DDDs (95% CI 26.9–31.4) prescribed to controls.

There was evidence for an interaction between increased defined daily doses and death; cancer survivors who died had substantially more doses of antidepressants than cancer survivors who did not die. Therefore, we conducted a subgroup analysis which showed that both breast cancer survivors who survived past 2006 (IRR = 1.15, 95% CI 1.10–1.19), and breast cancer survivors who died (IRR = 2.00, 95% CI 1.61–2.48) received significantly more doses of antidepressants (as defined by DDDs) than their respectively matched controls. Similarly, prostate cancer survivors who remained alive throughout the analysis period (IRR = 1.29, 95% CI 1.16–1.43) and prostate cancer survivors who died before 2006 (IRR = 2.80, 95% CI 2.07–3.78) received more antidepressants than matched controls.

Differences in defined daily doses amongst cancer survivors may be due to increased dosage. We considered prescribing for fluoxetine (Prozac) and tested whether cancer survivors received more pills compared to controls as a proxy for differences in dosage. There were significant differences between the number of pills prescribed to breast cancer survivors compared to controls (31 pills versus 28, $p < 0.0001$) and between prostate survivors and controls (28 pills versus 25, $p < 0.0001$) within patients who received a monthly prescription.

### 3.4. Prescribing for anxiolytics

The majority of cancer survivors and controls did not receive an anxiolytic between 2003 and 2006 (Table 3). After adjusting for matching and covariates, there was no evidence for a difference in anxiolytic prescribing between colorectal or prostate cancer survivors and their matched controls. In contrast, breast cancer survivors were slightly more likely to receive a prescription for an anxiolytic (OR = 1.08, 95% CI 1.01–1.15) than matched controls. There was no evidence for interactions between the receipt of anxiolytics and death. The strongest predictor of receipt of anxiolytics was an increasing number of consultations.

**Table 1 – Patient characteristics.**

| | Breast | | Colon | | Prostate | |
|---|---|---|---|---|---|---|
| | Survivor | Control | Survivor | Control | Survivor | Control |
| Male | – | – | 2569 | 10,178 | 4207 | 16,709 |
| Female | 16,938 | 67,649 | 2499 | 9950 | – | – |
| Mean age in 2003 (SD) | 66.9 (12.3) | | 74.1 (10.9) | | 76.1 (8.1) | |
| Number of patients with Charlson score > 0 | 7551 (44.6%) | 27,999 (41.4%) | 2942 (58.1%) | 10,343 (51.4%) | 2693 (64.0%) | 9345 (55.9%) |
| Number of patients who died | 1964 (11.6%) | 1242 (1.8%) | 798 (15.7%) | 658 (3.3%) | 958 (22.8%) | 794 (4.8%) |

**Table 2 – Depression and anxiety consultation behaviour and multivariate models, 2003–2006.**

| | At least one consultation for depression during 2003–2006 | | Odds of consulting for depression[a] | At least one consultation for anxiety during 2003–2006 | | Odds of consulting for anxiety[a] |
|---|---|---|---|---|---|---|
| | Yes | No | | Yes | No | |
| *Breast* | | | | | | |
| Survivor | 1617 (9.6%) | 15,321 (90.5%) | 1.06, 95% CI 1.00–1.14 | 908 (5.4%) | 16,030 (94.6%) | 1.06, 95% CI 0.97–1.16 |
| Control | 5985 (8.9%) | 61,664 (91.2%) | Reference | 3383 (5.0%) | 64,266 (95.0%) | Reference |
| *Colorectal* | | | | | | |
| Survivor | 416 (8.2%) | 4652 (91.8%) | 1.07, 95% CI 0.94–1.22 | 178 (3.5%) | 4890 (96.5%) | 0.90, 95% CI 0.74–1.10 |
| Control | 1596 (7.9%) | 18,532 (92.1%) | Reference | 718 (3.6%) | 19,410 (96.4%) | Reference |
| *Prostate* | | | | | | |
| Survivor | 393 (9.3%) | 3814 (90.7%) | 1.12, 95% CI 0.98–1.34 | 133 (3.2%) | 4074 (96.8%) | 1.25, 95% CI 0.98–1.59 |
| Control | 1356 (8.1%) | 15,353 (91.9%) | Reference | 399 (2.4%) | 16,310 (97.6%) | Reference |
| | 11,363 | 119,336 | | 5719 | 124,980 | |

[a] Adjusted for Charlson comorbidity score, previous history of depression or anxiety, respectively, and death. Cases and controls were matched on the basis of age, gender and primary care practice.

**Table 3 – Antidepressant and anxiolytics prescribing behaviour and multivariate models, 2003–2006.**

| | Prescribed an antidepressant least once between 2003 and 2006 | | Odds of being prescribed an antidepressant[a] | Prescribed an anxiolytic at least once between 2003 and 2006 | | Odds of being prescribed an anxiolytic[a] |
|---|---|---|---|---|---|---|
| | Yes | No | | Yes | No | |
| *Breast* | | | | | | |
| Survivor | 4007 (23.7%) | 12,931 (76.3%) | 1.16, 95% CI 1.11–1.22 | 1531 (9.0%) | 15,407 (91.0%) | 1.08, 95% CI 1.01–1.15 |
| Control | 13,681 (20.2%) | 53,968 (79.8%) | Reference | 5194 (7.7%) | 62,455 (92.3%) | Reference |
| *Colorectal* | | | | | | |
| Survivor | 874 (17.3%) | 4194 (82.8%) | 1.06, 95% CI 0.96–1.17 | 333 (6.6%) | 4735 (93.4%) | 0.96, 95% CI 0.81 – 1.12 |
| Control | 3166 (15.7%) | 16,962 (84.3%) | Reference | 1122 (5.6%) | 19,066 (94.4%) | Reference |
| *Prostate* | | | | | | |
| Survivor | 757 (18.0%) | 3450 (82.0%) | 1.38, 95% CI 1.25 – 1.54 | 235 (5.6%) | 3972 (94.4%) | 0.87, 95% CI 0.72 – 1.05 |
| Control | 1823 (10.9%) | 14,866 (89.1%) | Reference | 713 (4.3%) | 15,996 (95.7%) | Reference |

[a] Adjusted for Charlson comorbidity score, number of consultations, and death. Cases and controls were matched on the basis of age, gender and primary care practice.

There was a small but significant difference between the number of defined daily doses for anxiolytics between breast cancer survivors and their matched controls (IRR = 1.09, 95% CI 1.02–1.16) and strong evidence for effect modification by death. While breast cancer survivors who survived past the end of the analysis period in 2006 had the same anxiolytic prescribing behaviours as matched controls (IRR = 1.04, 95% CI 0.97–1.12), breast cancer survivors who died had an 84% increase in prescribed defined daily doses (IRR = 1.84, 95% 1.36–2.49).

## 4. Discussion

### 4.1. *Statement of principal findings*

This study examined primary care consultation and prescribing behaviours in a large cohort of long-term cancer survivors in the UK. Long-term survivors of cancer were no more likely to consult for depression or anxiety related reasons compared to a control population. The main predictor for a primary care consultation for depression was not history of cancer, but other comorbid diseases and history of depression.

In terms of pharmacological interventions, long-term breast and prostate cancer survivors were more likely to receive at least one prescription for an antidepressant during the analysis period. Those nearing the end of life received significantly more doses of antidepressants, and proximity to death also influenced prescribing for anxiolytics in breast cancer survivors. Colorectal cancer survivors used all psychological services and pharmacological interventions at the same rate as their corresponding matched control population.

These results suggest that while long-term survivors of three common cancers do not consult with their GPs for depression and anxiety more than the general population, those patients who do see their GPs may access more pharmacological interventions. This was an unexpected finding, and we explored several hypotheses to explain the results. It is possible that cancer survivors are more likely to receive long-term and persistent treatment for depression. However, there were no clear differences in the rates of repeat

prescribing for antidepressants between any of the cancer survivors and control groups. Secondly, it is possible that cancer survivors were receiving certain tricyclic drugs for neuropathic pain relief. We conducted a sensitivity analyses to determine whether removing tricyclic drugs from the analyses would affect these findings, however, the results were similar whether or not tricyclic prescriptions were included or excluded. Our third hypothesis was that long-term cancer survivors receive higher dosages of pharmacological interventions for depression and anxiety due to increased severity of depression. When we considered prescribing for fluoxetine, which is administered at a single strength, we found that cancer survivors received a greater number of doses compared to controls, which supports this final hypothesis but is not definitive. With increased use and scoring of the Hospital Anxiety and Depression score (HADS) in primary care, our hypothesis that depression is more severe in some cancer survivors can be tested in GPRD datasets with more recent follow-up.

### 4.2. *Comparison with existing literature and meaning of the study: possible mechanisms and implications for clinicians or policy makers*

Depression is a commonly recognised disorder in the acute phase of cancer following diagnosis and treatment.[16] Although rates of major disorder vary by population and diagnostic criteria, depressive disorder may be up to four times higher in cancer patients compared to the general population.[17] However, people closer to diagnosis may experience higher levels of depression and anxiety, compared to people who are further from a diagnosis. This study suggests that while most longer-term cancer survivors do not access their GP for depression or anxiety related services at higher rates compared to a control population, those nearing the end of life require increased pharmacological support to manage depression and anxiety. Depression is a widely recognised problem in palliative care.[18] Previous research has shown that breast cancer patients at the end of life were more likely to receive prescribed antidepressants than other palliative patients, which corresponds to our research.[19,20] Depression and anxiety at the end of life are treatable, and primary care is well placed to offer pharmacological interventions to this population.

### 4.3. *Strengths and weaknesses of this study*

The results from this research should be considered within the context of several limitations. Firstly, the GPRD is a collection of primary care records used primarily for clinical use rather than for research. Although the pharmacological data in the GPRD is highly accurate as all prescriptions issued are automatically entered onto the computer system, GPs and nurses may not record all symptoms or diagnoses. However, the analyses in this study have all been conducted as comparisons between matched cases and controls, and it is unlikely that clinicians would record depression or anxiety differently in either group.

It is difficult to judge the severity of psychological disease amongst patients in this cohort. The Read/OXMIS coding system does not always distinguish whether patients who consulted for depression had clinically significant depression, which is either defined as an elevated DSM-IV or HAD score. Nonetheless, it is important that these patients have consulted with their GP for these issues, regardless of clinical definitions of depression or anxiety.

Lastly, although the GPRD provides high quality clinical and prescribing data from primary care, use of secondary or tertiary care is not consistently recorded. Cancer survivors, but not their controls, may have access to other services outside of primary care for psychological health issues, however, this analysis does not include these services.

### 4.4. *Unanswered questions and future research*

As part of this project, we received data from the National Cancer Intelligence Network, which provided data on the stage of cancer at diagnosis and treatment. However, the additional data from the GPRD-NCIN linkage wereas limited in this cohort; only half of all primary care practices in the GPRD participate in the linkage scheme and not all cancer registries collect data on treatment and stage. Our original hypothesis was that stage and treatment at the time of diagnosis may influence depression and anxiety outcomes in long-term cancer survivors. The limited data meant that we could not determine whether certain subgroups of patients with later stage disease or intensive treatment access psychological services differently in primary care.

## 5. Conclusions

Consulting behaviour for depression and anxiety was not increased in this cohort of long-term cancer survivors. Although we could not explore the effects of stage or treatment, our analysis shows that cancer survivors nearing the end of life access a higher volume of pharmaceutical interventions for anxiety and depression. While most long-term cancer survivors likely do not require screening for depression and anxiety, a subset of patients will continue to access pharmacological interventions in the long-term.

## Conflict of interest statement

None declared.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2010.07.035.

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# Appendix 7: Interview schedule - qualitative study

**Opening question**

"I'm interested in how having cancer impacts on your life nowadays. For example, how has it changed your life, and has it had any physical or emotional long-lasting effects. I realize that in order to make me make sense of that you may need to tell me a bit about your diagnosis and treatment. Can you tell me about your experience of living beyond cancer with reference where necessary to aspects of your diagnosis and treatment?

**Discharge from secondary care**

1. Can you tell me what happened at your last follow-up appointment with your hospital consultant?
    a. (When) are you expecting to be seen again?
    b. [Where appropriate] How did you feel when your hospital follow-up appointments stopped?
    c. Were you expecting to be discharged, were you expecting contact with GP
    d. [Where appropriate] Was there anything about your discharge from hospital follow-up that you would have liked done differently?
    e. (For patients who haven't been discharged) How do you feel about your follow-up appointments? Was it your decision to continue to have follow-up?

2. Were you given any information or advice? at the time of hospital discharge?
    a. Can you tell me what kind of information/advice? would have been helpful to you?
    b. How should it be delivered

3. Do you have any cancer related needs right now?
    a. Are those needs being met?
    b. If not, why not?
    c. Do you have any suggestions on how those needs could be met?

**Interactions with primary care**

1. Can you tell me about any times since hospital discharge when you have seen your GP or with a nurse at your GP surgery about something related to your past cancer?
    a. What do you think about the cancer-related care your GP provides?
    b. How could it be improved?

2. Do you think that your relationship with your GP has changed as a result of having had cancer?

3. Is there anything that you would like to improve about the kind of health care you receive from your GP as someone who has recovered from cancer?

4. Do you have any advice for GPs or nurses who deal with people who have had a diagnosis of cancer in the past?

5. Right now, who would you want to contact if you had a question or were worried about your previous cancer?
    a. Do you feel that there is someone right now you can ask if you have any questions about cancer?
    b. If you wanted to contact the hospital clinic again would you know how to do it?

6. Have you been invited for breast cancer screening (mammography)/PSA testing/colon screening (delete as appropriate) after you were discharged from your hospital follow-up?
    a. Do you attend screening?
    b. How do you feel about having cancer screening tests?

**Additional health needs**

1. Can you tell me about the treatments you had for your cancer?

2. Do you think that your cancer or cancer treatment left you with any ongoing health needs?
    a. How do these affect your life today?
    b. Is there anything that your GP could do to help you with any of these?

3. Do you ever still think about having had cancer?
    a. Do you ever think about the possibility of your cancer coming back?

4. Have you at any point received or looked for information on how to recognize if your cancer came back?

5. Has anyone ever suggested ways in which you could prevent it from coming back?
    (Prompts: lifestyle changes, complementary therapies, dietary changes, keeping fit and healthy)

6. Have you made any changes to your lifestyle as a result of having had cancer? Do you take better care of yourself, or are you more aware of your own health now?
    (Prompts: work patterns, changed occupation, diet, exercise, quit smoking, more time for self or family/friends)

7. Compared with your general health, how big of a health issue is having had cancer to you now?

8. Has having had cancer affected any of your family or personal relationships?
    a. Some people say their sex life/intimacy is affected by having had cancer. Has this happened to you?

**Current psychological health**

1. How have you felt emotionally and psychologically? Do you feel that you have had the support you need throughout?

2. Nowadays do you ever feel the need for psychological or emotional support to do with having had cancer in the past?

a. Who/where do you get this support from? (Prompts: friend, relative, professional, counsellor, no one)
b. Do you know how to find this kind of support if you need it?
c. Where would you like to get this kind of support if you needed it?

3. Are you aware of any support organisations, internet groups or local groups in your area?
    a. Have you ever thought of contacting them?
    b. Is this the first support group you've been in contact with?
    c. In what ways have they provided support to you?
    d. Or did you join in order to give support to others?

4. Has having had cancer changed your views on life?

5. Some people say their personal identity, or who they are as a person, is bound up with being a cancer survivor, to what extent do you feel this way and has it changed over time?
    a. How do you think other people view you?

6. Do you think anything positive has come out of your experience of having had cancer? (prompt: some people say they now appreciate life more, or have reassessed their relationships, does any of this ring true for you?)

**Practical issues: Finance, work, insurance**

1. Were you employed at the time of your cancer diagnosis?
    a. Can you tell me whether having had cancer in the past has affected your job or work?

2. Are your finances currently affected by the fact that you have had cancer in the past? (Prompts: inability to work/loss of income/claiming state benefits, obtaining travel/life/health insurance, increased insurance premiums)

3. Are there any other practical issues that have arisen recently as a result of having had cancer in the past?

**Final questions**

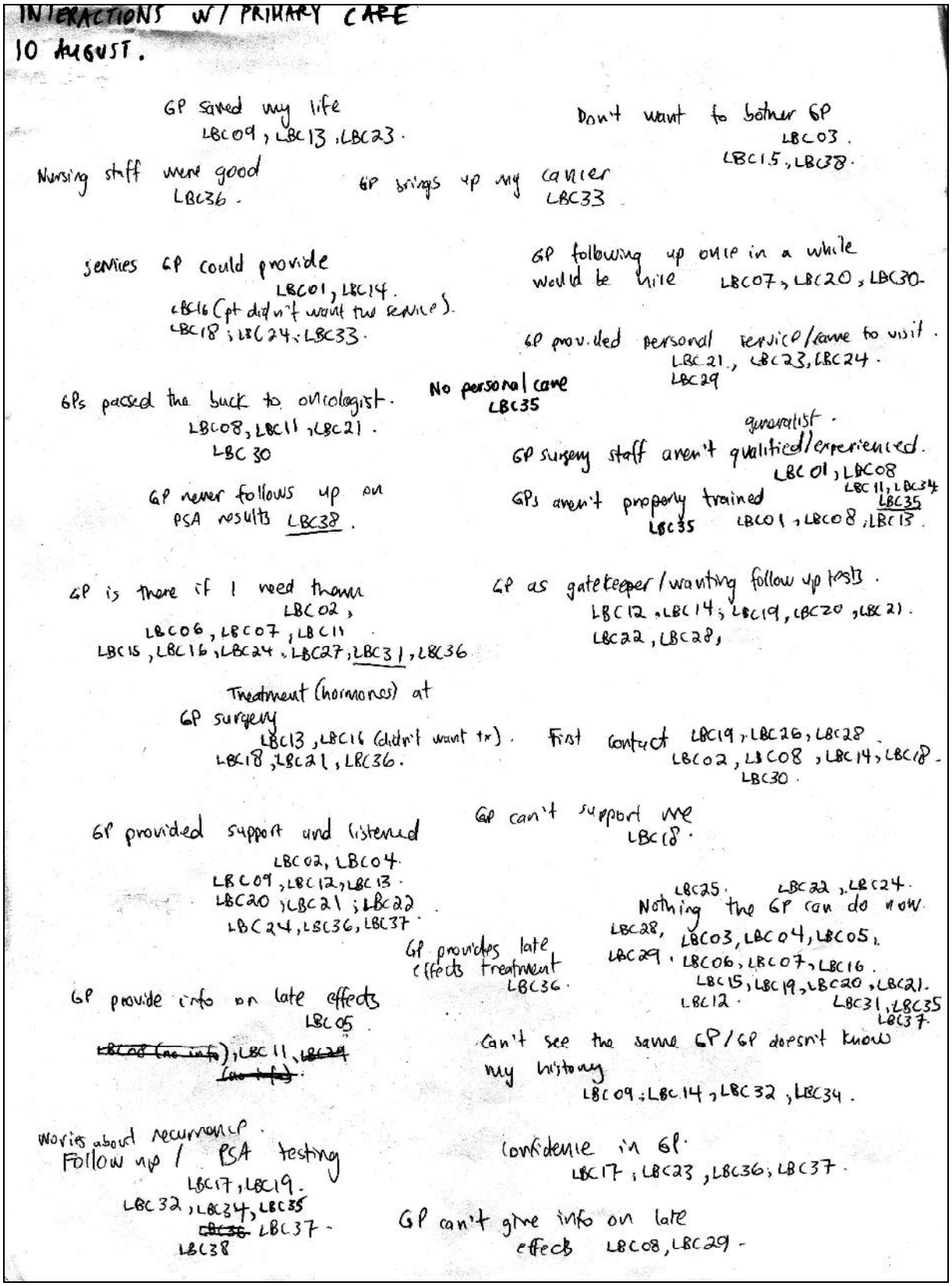
1. Are there things you would like to know about other peoples' experiences of living beyond cancer?

2. Do you have any message to other people who are living beyond cancer?

3. Is there anything else at all you would like to tell me?

## Appendix 8: One Sheet of Paper (OSOP) summarizing the 'Interactions with primary care'

**theme**


INTERACTIONS W/ PRIMARY CARE
10 AUGUST.
GP saved my life
LBC09, LBC13, LBC23.
Don't want to bother GP
LBC03.
LBC15, LBC38.
Nursing staff were good
LBC36.
GP brings up my cancer
LBC33
GP following up once in a while would be nice LBC07, LBC20, LBC30.
GP provided personal service/came to visit.
LBC21, LBC23, LBC24.
LBC29
No personal care
LBC35
GPs passed the buck to oncologist.
LBC08, LBC11, LBC21.
LBC30
GP never follows up on PSA results LBC38.
GP surgery staff aren't qualified/experienced.
LBC01, LBC08
LBC11, LBC34
LBC35
GPs aren't properly trained
LBC35
LBC01, LBC08, LBC13.
GP is there if I need them
LBC02,
LBC06, LBC07, LBC11
LBC15, LBC16, LBC24, LBC27, LBC31, LBC36
GP as gatekeeper/wanting follow up tests.
LBC12, LBC14, LBC19, LBC20, LBC21.
LBC22, LBC28,
Treatment (hormones) at GP surgery
LBC13, LBC16 (didn't want tx).
LBC18, LBC21, LBC36.
First contact LBC19, LBC26, LBC28.
LBC02, LBC08, LBC14, LBC18.
LBC30.
GP provided support and listened
LBC02, LBC04.
LBC09, LBC12, LBC13.
LBC20, LBC21, LBC22.
LBC24, LBC36, LBC37.
GP can't support me
LBC18.
LBC25. LBC22, LBC24.
Nothing the GP can do now
LBC28, LBC03, LBC04, LBC05,
LBC29. LBC06, LBC07, LBC16.
LBC15, LBC19, LBC20, LBC21.
LBC12. LBC31, LBC35
LBC37.
GP provides late effects treatment
LBC36.
GP provide info on late effects
LBC05.
~~LBC08 (no info)~~, LBC11, ~~LBC29 (no info)~~.
Can't see the same GP/GP doesn't know my history
LBC09, LBC14, LBC32, LBC34.
Worries about recurrence.
Follow up / PSA testing
LBC17, LBC19.
LBC32, LBC34, LBC35
~~LBC36~~ LBC37.
LBC38
Confidence in GP.
LBC17, LBC23, LBC36, LBC37.
GP can't give info on late effects LBC08, LBC29.