Time trends in childhood cancer: Britain 1966-2005

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Abstract

Increasing time trends in the recorded incidence of childhood cancer have been reported in many different settings. The extent to which these trends reflect real changes in incidence, rather than improvements in methods for diagnosis and registration, is controversial. Using data from the National Registry of Childhood Tumours (NRCT), this thesis investigates time trends in cancer diagnosed under age 15 in residents of Britain during 1966-2005 (54650 cases), and considers potential sources of artefact in detail.

Several different methods are used to estimate completeness of NRCT registration. The history of methods for diagnosis and registration of childhood cancers in Britain is described, and predictions are made for effects on recorded incidence.

For each of the 12 main diagnostic groups, Poisson regression is used to fit continuous time trends and 'step' models to the annual age-sex-standardised rates by year of birth and year of diagnosis. Age-specific rates by period, and quinquennial standardised rates for diagnostic subgroups, are shown graphically. For three broad groups (leukaemia, CNS tumours and other cancer), geographical variation is compared by period of diagnosis. The results of these analyses are discussed in relation to the predicted artefacts.

The evidence for a positive association between affluence and recorded incidence of childhood leukaemia is briefly reviewed. A special form of diagnostic artefact, the 'fatal infection' hypothesis, is proposed as an explanation of both this association and the leukaemia time trend. This hypothesis is examined in a novel test based on clinical data.

The recorded incidence of childhood cancer in Britain increased in each of 12 diagnostic groups during 1966-2005 (from 0.5% per year for bone cancer to 2.5% for hepatic cancer, with 0.7% for leukaemia). Evidence presented here suggests that these increases are probably artefacts of diagnosis and registration. The potential implications for epidemiological studies of childhood cancer should be considered.

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Abbreviations

ACCIS	Automated Childhood Cancer Information System
AFP	Alpha-fetoprotein
ALL	Acute lymphoblastic (i.e. lymphoid) leukaemia
AML	Acute myeloid leukaemia
ASR	Age-standardised rate
ASSR	Age-sex-standardised rate
BHCG	Beta human chorionic gonadotrophic hormone
CCLG	Children's Cancer and Leukaemia Group
CCRG	Childhood Cancer Research Group
CLWP	Childhood Leukaemia Working Party
CNS	Central nervous system (i.e. intracranial/intraspinal)
CR	Regional general cancer registry
CT	Computed tomography
DC	Death certificate
DCI	Death-certificate-initiated (cancer registration)
DCO	Death-certificate-only (cancer registration)
FAB	French-American-British leukaemia classification
FPC	Family Practitioner Committee
GP	General practitioner
HPA	Health Protection Agency
ICCC3	International Classification of Childhood Cancer, third edition
ICD-O	International Classification of Diseases for Oncology
IHC	Immunohistochemistry
ISD-Scotland	Information Services Division of the NHS in Scotland
MIBG	Meta-iodobenzylguanidine (scan for neuroblastoma)
MRC	Medical Research Council
MRI	Magnetic resonance imaging
NHL	Non-Hodgkin lymphoma
NHS	National Health Service
NHSCR	National Health Service Central Register
NICR	Northern Ireland Cancer Registry
NRCT	National Registry of Childhood Tumours
NRPB	National Radiological Protection Board
ONS	Office for National Statistics
OPCS	Office of Population Censuses and Surveys
OSCC	Oxford Survey of Childhood Cancers
PAS	Patient Administration Systems
PNET	Peripheral neuroectodermal tumour
SD	Standard deviation
SIOP	International Society of Paediatric Oncology
SNOMED	Systemised Nomenclature of Medicine
UKACR	United Kingdom Association of Cancer Registries
UKCCS	United Kingdom Childhood Cancer Study
UKCCSG	United Kingdom Children’s Cancer Study Group
US	Ultrasound

Chapter 1
Introduction

1.1 Childhood cancer in Britain

One in about 500 children in Britain is diagnosed with cancer before the age of 15. Effective treatments are available, and about 75% of patients are still alive at five years from diagnosis [1]. Nevertheless, cancer is one of the commonest groups of medical causes of death in childhood after infancy [2].

About a third of cases of childhood cancer are leukaemia, and about a quarter are intracranial or intraspinal tumours. The rest are solid cancers of other primary sites, including the lymphatic system (lymphoma), peripheral nervous system (mainly neuroblastoma), connective tissue, kidney, retina and bone, in decreasing order of frequency [1].

Childhood cancer is different from adult cancer. Most of the types of cancer that occur in children are rare or non-existent after adolescence. Tumour cells typically resemble the primitive cells found in embryonal development, and carcinoma (cancer of the epithelial cells) is relatively rare. The cancers that are common in old age (carcinomas of the lung, female breast, bowel, prostate etc.) hardly ever occur in childhood [3].

Childhood cancer is occasionally diagnosed at birth, and the typical distribution of age at diagnosis has a peak within the first few years of life, suggesting that the process leading to cancer may often start before birth. In a small proportion of cases, perhaps 5-10%, there is an inherited high-penetrance genetic abnormality [4]. In most cases, however, there is no known genetic predisposition, and at least one cell mutation is probably required. Mutation might occur either before or after birth, or both before and after birth. For the most common type of childhood leukaemia (B-precursor lymphoid leukaemia), it has been shown that one typical genetic mutation is present in blood samples taken at birth, and that at least one further mutation is needed to initiate disease [5]. Cell mutation during

childhood is most likely to occur at a stage of rapid cell division, either in response to particular changes in the environment, or as part of normal growth. This may explain some of the variation in age at diagnosis between diagnostic groups: for example, B-precursor leukaemia is most often diagnosed in early childhood, when the immune system is likely to be under stress, whereas bone cancer peaks in adolescence, when bone growth is fastest.

In Britain, a few rare types of childhood cancer have known environmental causes: Epstein-Barr and hepatitis B virus infection for nasopharyngeal and hepatic carcinoma respectively, and exposure to sunlight for skin carcinoma and melanoma [3]. Epstein-Barr virus is also implicated in both the Burkitt and Hodgkin subtypes of lymphoma, but its exact role in developed countries has not been established (although it is a known cause of childhood Burkitt lymphoma in sub-Saharan Africa, in conjunction with malaria [6]). There was a dramatic increase in childhood thyroid carcinoma in Belarus after the Chernobyl accident [7;8], but few children in Britain have ever been exposed to radiation at this level. Much less convincing evidence supports other proposed environmental risk factors, such as natural radiation, electromagnetic fields, and various kinds of parental occupational exposure [3].

Some intriguing but inconclusive evidence relates childhood leukaemia to infection [9]. It seems plausible that exposure to new infection might trigger childhood leukaemia in susceptible individuals, if only through promoting cell division by stimulating the immune system. It has been suggested that the 'second hit' in B-precursor leukaemia may consist of an abnormal immune response to common infection in childhood, and that this response may be more likely to occur in children who have received less stimulation of the immune system in infancy (the 'delayed infection' hypothesis) [10]. The observation that the reported incidence of childhood leukaemia tends to be higher in more affluent communities is consistent with this hypothesis, on the assumption that a better standard of living entails less contact with infection in infancy. Another suggestion (the 'population mixing' hypothesis) is that new contact between people from separate geographical areas increases the risk of childhood leukaemia by increasing the risk of exposure to new infection(s); this hypothesis is supported by a series of epidemiological studies in various different settings [11].

1.2 Time trends in recorded incidence of childhood cancer

Long-term good-quality childhood cancer registration data from many countries show increasing recorded incidence rates for many types of childhood cancer during the second half of the twentieth century [12-18]. The extent to which these increases are due to real changes in incidence, rather than to improvements in methods for diagnosis and registration, is not clear. Interpretation has ranged from definite acceptance that the changes are real [12] to total rejection [19]. Most authors argue that both real and artefactual changes might be involved. Some conclude that the changes are at least mainly real [13-18 20], whereas others are more sceptical [21;22]. For example, it has been shown that an increase in registration rates for malignant brain tumours in children in the United States followed the introduction of CT and MRI scanning during the mid-1980s [22].

The work described in this thesis uses data from the National Registry of Childhood Tumours (NRCT), a high-quality specialist registry that records cancer diagnosed since 1962 in children under the age of 15 years who were resident in England, Wales or Scotland (Britain) at diagnosis. The NRCT has been maintained continuously by a single organization, the Childhood Cancer Research Group (CCRG) in Oxford, since 1975. The registration process was described in 1995 [23] and 2007 [1].

There have been several previous reports of time trends in Britain based on NRCT data. In 1994, an analysis for selected diagnostic groups during 1962-1991 (1953-91 for leukaemia only) was published by the CCRG as a book chapter [24]. In 2006, NRCT data were included in a combined analysis of time trends from a consortium of European registries, the Automated Childhood Cancer Information System [25] (ACCIS). Registrations for England and Wales during the period 1971-95 were provided by the NRCT, while data for Scotland during 1975-97 were provided by the Scottish Cancer Registry. The results included trend estimates and quinquennial age-standardised rates (ASRs), by diagnostic group, for Britain during 1978-1997 (i.e. just Scotland during 1996-97) [26]. Quinquennial ASRs for selected diagnostic groups and subgroups in Britain were included in other ACCIS reports [27-31]. A further analysis of NRCT data covering Britain in the period 1966-2000 has been published as a book chapter [1 pages 107-130, Kroll and Stiller]. For childhood leukaemia only, national time trends up to 2000 have also been

reported by Kroll *et al.* [32], using NRCT data for Britain, and by Shah and Coleman [20], using ONS incidence and mortality data for England and Wales.

None of these publications considered variation in annual rates (except for leukaemia [24 32]), none of them extended beyond the diagnosis year 2000, and only the 1994 publication included an analysis by birth cohort. No previous time trend investigation using NRCT data has considered in detail the possibility of artefact.

1.3 Importance of time trends in childhood cancer

Whether real or artefactual, an increase in reported incidence of childhood cancer is important. If the increase is real, research should focus on potential explanations, in the hope of finding reversible causes. If some or all of the increase represents improvements in ascertainment, due to more complete diagnosis and/or registration of cases, there will be incompleteness and perhaps systematic bias in registry data from the past, which will affect the interpretation of epidemiological studies that use these data. If the increase is partly explained by improvements in methods of diagnosis, then lives might be saved by trying to ensure that all children with cancer are correctly diagnosed in future.

1.4 Aims of this study

In this thesis I aim to assess whether the variation over time in the recorded incidence of cancer under age 15 in Britain during 1966-2005 could be caused entirely by changes in methods for diagnosis and registration, or whether some, or all, of it is likely to represent real changes in incidence.

Results are discussed in each chapter. Chapters 2 and 3 outline the development of methods for diagnosis and registration of childhood cancer in Britain during the study period. Chapter 4 reports empirical evidence assessing completeness of registration in the NRCT. In Chapter 5, variation over time is described and discussed in detail, with particular attention to possible sources of artefact. Chapter 6 suggests a further explanation for the increase in recorded incidence of childhood leukaemia, and tests this hypothesis using clinical data. Chapter 7 contains a summary and the overall conclusions.

Chapter 2
Diagnostic methods

2.1 Introduction

Effective new treatments for childhood cancer became available during the second half of the 20th century. New diagnostic techniques were developed to support these treatments, with the aid of remarkable advances in science and technology [33].

This chapter aims to identify the approximate timing of the most important changes in diagnostic methods, and to predict effects on registration rates. The focus is on techniques that are relevant to the initial diagnosis of the primary cancer, not methods that are mainly used to assess prognosis or the extent of metastases. Exact timing is impossible, because most of these techniques developed and improved after introduction, and some may have been introduced at different times in different parts of Britain.

Sources of information are briefly reviewed in Section 2.2. Current methods for the diagnosis of childhood cancer are outlined in Section 2.3. Methods used in the first decade of the study period (before the mid-1970s) are described in Section 2.4. Developments over time are described in Section 2.5. Possible effects on the recorded incidence of childhood cancer are discussed in Section 2.6.

2.2 Sources of information

The main source of information for this chapter is a series of textbooks from successive decades of the study period, which were edited by Marsden and Steward [34] (1968), Bloom *et al.* [35] (1975), Voûte *et al.* [36] (1986), Plowman and Pinkerton [37] (1992), and Pinkerton *et al.* [38] (2004).

Marsden and Steward [34] (1968), and most of their contributors, worked in Manchester, England. They aimed to ‘describe the clinical and pathological manifestations of tumours

in children and to discuss the methods which are available for their treatment'. They commented that 'to call this a textbook would be to imply a greater certainty about many facets of the subject than we possess', since paediatric oncology was still in its infancy.

The International Society of Paediatric Oncology (SIOP) was established in the late 1960s, aiming to standardise treatment within Europe and elsewhere. Bloom *et al.*, the editors of the first SIOP textbook [35] (1975), worked in Britain, France, Germany and the Netherlands. Their many contributors were 'drawn mainly from Europe' but included 'experts from the USA, Canada, Japan and Cameroun'. The second edition of this text [36] (1986) had the same group of editors, with one British addition, and a similar international balance of contributors.

The remaining two source books are the first [37] (1992) and third [38] (2004) editions of a standard textbook published in Britain. The editors worked in Britain and the Netherlands, and the choice of authors was 'intended to give the book a European flavour'.

This series should give a reasonably accurate indication of the timing of the application of new diagnostic methods in Britain. Further detail is supplied by three editions [39-41] of a textbook from the USA (where the timing of innovations may have been rather different), and by various specialised books and reports.

2.3 Current procedure for diagnosis of childhood cancer in Britain

A typical patient is referred by a general practitioner to hospital for investigation. The referral may not happen immediately, because childhood cancer is rare and there may be a range of much more likely explanations for the patient's signs and symptoms. The likelihood of delay will vary with the type of cancer, the site of disease, and the accessibility of a suitable cancer service. Once the patient reaches a specialist paediatric oncology unit, the definitive diagnosis is normally made within a few days.

If the patient has a tumour, this may be visualised by conventional X-rays, ultrasound, computed tomography or magnetic resonance imaging. If appropriate, a tissue sample is

taken, by biopsy or surgery (for solid tumours), or by bone marrow aspiration (for suspected leukaemia). A histopathologist, or haematologist for leukaemia, assesses the sample to decide what the precise diagnosis is. For malignant neoplasms, this is done mainly by morphology (studying the shape of abnormal cells using a light- or electron-microscope, aided by staining), and immunohistochemistry (identifying cell constituents by a panel of antigen-antibody reactions). Specific biochemical abnormalities act as diagnostic markers for some types of cancer: alpha-fetoprotein and beta human chorionic gonadotrophin for hepatic malignancies and germ-cell tumours, and catecholamine metabolites for neuroblastoma. Chromosomal and molecular analyses [42] may be used to confirm the diagnosis and refine the prognosis.

Childhood cancer is usually not suspected until the signs are noticed in ordinary life. Slowly-progressing tumours may not be detected for a long time, particularly in sites where the tumour cannot be seen or felt. To give an extreme example, one possible interpretation of a report that unusually large head circumference at birth is a risk factor for some childhood brain tumours [43] is that these tumours originated in foetal development and were already present at birth, but were not diagnosed until much later in childhood. On the very rare occasions when neoplasia is diagnosed at autopsy following sudden unexplained death in infancy or childhood (0.14% in one series of autopsies under the age of 19 [44]), the immediate cause of death is usually that the tumour impaired the function of a vital organ, such as the heart or brain stem, or led to haemorrhage.

Asymptomatic tumours are sometimes discovered incidentally during clinical examinations for other purposes. Teratoma [45], neuroblastoma [46] [47] and other types of malignant tumour are sometimes found during routine prenatal ultrasound examinations. In the West Midlands and Northern regions of England, 6 of 78 neuroblastomas (8%) diagnosed in 1987-91 were found during a routine health check or investigation of an unrelated medical condition [48]. Mass screening for childhood cancer has been attempted only briefly and locally in Britain: in the Newcastle area (1986-90) and Birmingham (1992-94), using urinary catecholamine measurements to test for neuroblastoma in infants [49]. This was abandoned because many of the cases detected did not need treatment.

It is rarely possible to direct screening to a high-risk group, because the great majority of childhood cancer cases are apparently sporadic. The only important exception is retinoblastoma, which has a strong inherited component: about 10% of retinoblastoma cases are found by targeted screening of babies in known retinoblastoma families. In other diagnostic groups, known cancer syndromes account for only a very small proportion of cases. For example, although children with aniridia, hemihypertrophy and Beckwith-Wiedemann syndrome are routinely monitored for Wilms tumour in the UK [50], these syndromes were recorded in only 41/1622 (2.5%) of Wilms tumour cases diagnosed during 1971-91, and detected by screening in only 8 of these cases (0.5%) [51]. Children with Down's syndrome have an increased risk of leukaemia, but only 2-2.5% of children with leukaemia have Down's syndrome [38]. Overall, fewer than 5% of childhood cancer cases can be directly attributed to genetic conditions, and there are no known environmental risk factors that could be used to predict disease, apart from very high levels of ionising radiation [38].

If a tumour regresses, or matures to stable well-differentiated cells and ceases to be malignant, the patient goes into remission. This happens spontaneously in some cases of neuroblastoma. From 1973 mass screening programs in Japan, North America and Europe (now discontinued) detected early neuroblastoma by applying routine urine tests in babies under one year old. The associated increase in reported incidence has been attributed to the detection of cases that would otherwise have regressed without treatment [52-55]. International comparisons of neuroblastoma rates are consistent with this idea. During 1988-97 the recorded incidence of neuroblastoma was lower in Britain than in any of the other European countries in the ACCIS group. This was due to a deficit of cases diagnosed under two years of age, a group that consists mainly of low-stage good-prognosis cases. As predicted, overall survival rates were lower in Britain [56]. During 1987-91 the proportion of neuroblastoma cases found at a routine health check or unrelated investigation was significantly higher in Germany and Austria than in two regions of Britain [48]. These observations have been attributed to less active community health surveillance of babies in Britain, and less generous provision of ultrasound scanners.

2.4 Diagnostic methods before the mid-1970s

The classification of childhood cancer derives from the shape ('morphology') of abnormal cells ('blasts') found in the tumour, bone marrow or blood. For example, tumours containing bone-like cells are called 'osteosarcoma', and tumours containing primitive cells typical of the liver and retina are called 'hepatoblastoma' and 'retinoblastoma'. The tissue type is usually appropriate to the primary site, although tumours of the kidney called 'nephroblastoma' often include well-differentiated cells that do not resemble normal kidney tissue, and some tumours within bone ('Ewing sarcoma') do not contain bony cells. Soft-tissue tumours are called 'rhabdomyosarcoma' if they contain striped muscle cells and 'chondrosarcoma' if they contain cartilaginous cells. Hodgkin lymphoma is defined as a lymphoma producing tumours containing a particular type of abnormal (Reed-Sternberg) cell. Leukaemias are classified as lymphoid or myeloid by the lineage of abnormal cells in the marrow, which can usually be identified from their shape.

Morphology alone cannot always provide a definitive diagnosis, and few ancillary methods were available in the early part of the study period. For example, according to a report published in 1971 on the survival of children with acute leukaemia diagnosed in England and Wales during 1963-67:

> 'There is clearly a considerable subjective element in the morphological classification of acute leukaemia when it is based on a single conventionally stained bone marrow or peripheral blood slide; this is reflected in the widely differing proportion of the two main cell types in the different hospital regions' [57].

The blasts found in acute leukaemia can be so primitive that they are hard to classify by shape as myeloid or lymphoid [35]. Similarly, many types of solid cancer, including lymphoma, neuroblastoma, soft-tissue sarcoma, Ewing sarcoma, osteosarcoma, hepatoblastoma and retinoblastoma, can produce rapidly-growing tumours that consist mainly of undifferentiated immature 'small round cells', which cannot be reliably identified by conventional light microscopy [33]. Even the distinction between lymphoma and leukaemia can be uncertain, since both precursor-cell non-Hodgkin lymphoma and precursor-cell lymphoid leukaemia derive from immature lymphoid cells. Bloom *et al.* concluded, in 1975:

> 'Unfortunately, we have no good method of distinguishing between acute lymphocytic leukaemia and non-Hodgkin's lymphoma, and must rely on the appearance of the bone

> marrow and peripheral blood, so that considerable diagnostic overlap occurs'...'The histological border lines between undifferentiated lymphomas, undifferentiated soft tissue or bone sarcomas and acute lymphocytic leukaemia are not precise, and the final decision may in some measure be a matter of local custom' [35].

Delay in diagnosis was a greater problem in the early part of the study period than it is nowadays. Without effective methods of treatment, there was less incentive to consider the possibility of malignancy. Without modern imaging methods, internal solid tumours were difficult to detect and delineate until relatively large. There was no satisfactory way of identifying small tumours in the brain and spinal cord, and specialised X-ray imaging such as ventriculography and myelography could only show gross anatomical effects of large tumours:

> 'Before the advent of computerised tomography scanning in the late 1970s and magnetic resonance imaging in the mid-1980s, investigation of a child suspected of harbouring a brain or spinal tumour was a truly frightening experience for all concerned. Investigations were invasive, painful and even dangerous. The most frequently used modalities of imaging were ventriculography, for suspected intracranial mass lesions, and myelography, for suspected intraspinal tumours. Text books often painted pictures of late stages in disease processes, emphasizing the importance of rather gross physical signs. Paediatricians were reluctant to refer children until clinical features were relatively far advanced, with the consequence that the neurosurgeon was faced all too often with the prospect of a child in poor condition and with advanced neurological disease.' [58].

Even when a tumour or other clinical signs had been detected, there could be further delay in distinguishing cancer from non-malignant disease. In patients with disseminated cancer, many organs can be involved, including blood, bone marrow, bones, mediastinum, lymph nodes, liver and CNS. Clinical effects can therefore mimic a very wide range of non-cancer diseases. Sutow *et al.* [39] (1973) give the following non-cancer differential diagnoses for various signs of neuroblastoma (shown in brackets): hydronephrotic kidney or mesenteric cysts (abdominal mass); benign thymoma (mediastinal mass); malabsorption states (diarrhoea); intrinsic renal pathology (hypertension); rheumatic fever, rheumatoid arthritis or osteomyelitis (bone and joint pain); nutritional deficiencies or aplastic anaemia (blood abnormalities); allergic diseases, storage diseases, acute infections, granulomatous diseases or haematological disorders (metastases through the reticuloendothelial system).

In cases without conclusive morphology, the primary site of disease might be the only available way of refining the diagnosis of cancer. Due to delay in diagnosis, disease tended to be further advanced in the earlier part of the study period than it is nowadays,

and it is clear that there was often considerable difficulty in distinguishing primary from metastatic sites. For example, Sutow *et al.* [39] (1973) give a long list of cancers that might be confused with metastatic neuroblastoma, including leukaemia, lymphoma, CNS tumours, retinoblastoma, Wilms' tumour, liver tumours, and sarcomas of bone and soft tissue. When in doubt, age was sometimes used as evidence in making a diagnosis, for example to support metastatic neuroblastoma rather than Ewing sarcoma as the diagnosis for a non-osteogenic bone tumour in a young child. Since metastases often occur in lymph nodes, liver and bones, and very rarely in the kidney or retina, a diagnosis based on the site of disease is more reliable for Wilms' tumour (nephroblastoma) or retinoblastoma than for lymphoma, primary liver cancer or bone sarcoma.

This uncertainty of diagnosis is illustrated by a retrospective pathology review of tissue samples from 2104 solid tumours of childhood diagnosed in the West Midlands [59] (Table 2(a)). The review included 482 CNS tumours and 243 tumours diagnosed as soft-tissue sarcoma (the sizes of other subgroups are not reported). The period of original diagnosis was 1957-92, i.e. centred on the mid-1970s. Between 1984 and 1997 diagnoses were reviewed concurrently by three pathologists, using conventional morphology with special stains if required. The first level of the International Classification of Childhood Cancer (see Appendix 1) was subdivided into categories chosen to represent major differences in treatment (so that the distinction between categories would have clinical relevance); the sizes and specifications of the categories are not reported. Agreement among the review panel (defined as two out of three choosing the same category) was fairly good, ranging from 78% for samples originally diagnosed as lymphoma to 100% for retinoblastoma. For tumours that were originally diagnosed at the Birmingham Children's Hospital, a specialist centre, there was a similar level of agreement between the original diagnosis and the majority choice of the review panel. However, for tumours that were originally diagnosed at other hospitals the agreement with the review panel was less good: only 46% for hepatic tumours, 56% for soft tissue sarcomas, and 63% for lymphomas. These results confirm that diagnosis based on morphology is not always reliable, and suggest that in the past there may have been particular problems with childhood hepatic tumours, lymphomas and soft-tissue sarcomas in non-specialist hospitals.

Without effective methods of treatment, spontaneous remission was more likely to be observed. Marsden and Steward [34] (1968), citing references from the 1950s, describe the progression of untreated leukaemia, and mention that spontaneous remission sometimes occurred immediately after an acute infection or blood transfusion, and sometimes occurred without any apparent related event. According to Willis [60;61] (1962) spontaneous remission was well known in neuroblastoma and retinoblastoma, and might also occur in nephroblastoma, hepatoblastoma and even medulloblastoma. Willis suggested that the reason that spontaneous maturation of medulloblastoma was not often observed might be that the skull restricts expansion so that the tumour kills the patient before it regresses, whereas tumours in other sites may have time to regress because they have more space to grow into.

2.5 Changes in diagnostic methods during the study period

2.5.1 Introduction

Voûte *et al.* [36] (1986, preface) describe the advances that had occurred in paediatric oncology in the ten years since the first edition of the same text (Bloom *et al.* [35] (1975)) as 'really staggering'. The 'extraordinary progress' included the introduction of specialised centres, multidisciplinary care and collaborative clinical studies; greatly improved understanding of the biology of childhood cancer; and 'astounding advances' in imaging methods.

The history of some important diagnostic techniques is outlined in this Section. An approximate indication of timing is given in Table 2(b).

2.5.2 Urinary catecholamine measurement for neuroblastoma

Neuroblastoma cells derive from precursor cells of the sympathetic nervous system, and therefore produce and attract catecholamines, which are chemicals that normally transmit messages between nerve cells. It was suggested in 1959 that catecholamine metabolites could act as a specific marker for neuroblastoma [37]. Marsden and Steward [34] (1968) discuss the benefits of this approach:

> ‘Every pathologist encounters anaplastic tumours whose site of origin is uncertain, and if these occur in children he may be tempted to diagnose neuroblastoma on very little evidence. This tendency is to be deplored; a tumour of the sympathetic system can be diagnosed only if there is evidence that some at least of the cells show definite neural differentiation. In the past, this evidence has had to be purely histological and was sometimes difficult to obtain since there was no reliable staining method by means of which an immature neurite could be distinguished from an immature connective tissue fibre. However, the demonstration that almost all neuroblastomas can be diagnosed by the level of excretion of catecholamines and related compounds has greatly simplified the position and in most cases the biochemist can provide the answer’.

Sutow *et al.* [39] (1973) describe a catecholamine test based on a proposal published in 1971. Bloom *et al.* [35] (1975) list elevated urinary catecholamine excretion as a standard diagnostic test for neuroblastoma.

Bloom *et al*. report that the proportion of patients with positive excretion varied greatly between series, ranging from 77% to (in their own series) 96% [35]. By 1988, using sensitive techniques, elevated urinary catecholamines could be detected in more than 95% of neuroblastoma cases [62].

In the long run, catecholamine measurement would have greatly improved the ability to distinguish neuroblastoma both from other cancers and from non-cancer diseases. However, if Marsden *et al.* [34] are correct in suggesting that neuroblastoma was previously over-diagnosed, this test may have had the initial effect of reducing the proportion of childhood cancer diagnosed as neuroblastoma; for a while, it may even have led to some under-diagnosis, judging by the false-negative rate of 23% implied by Bloom *et al.* [35] (1975).

2.5.3 AFP/BHCG assay for hepatic and germ-cell tumours

Germ-cell tumours secrete alpha-fetoprotein (AFP) if they have yolk-sac elements, and beta-human-chorionic-gonadotrophic hormone (BHCG) if they have trophoblastic elements. Most childhood germ-cell tumours contain at least some component of yolk sac or trophoblastic tumour, and may therefore secrete AFP or BHCG, or both. Both AFP and BHCG can be measured in serum or (for CNS tumours) cerebrospinal fluid [37].

Bloom *et al.* [35] (1975) rather tentatively suggest that ‘it may be helpful to look for AFP in the patient’s blood to aid the diagnosis of malignancy of a teratoma’. In the UKCCSG’s

first malignant germ cell tumour study, which ran from 1979 to 1987, serum AFP and BHCG measurement before and after treatment were recommended. AFP was elevated at diagnosis in 115 of 123 patients and BHCG in 19 of 77, and measurement of these markers was shown to be helpful in monitoring response to therapy [63]. Hence, Voûte *et al.* [36] (1986) recommend assay of both AFP and BHCG as an aid to diagnosing germ-cell tumours. Plowman and Pinkerton (1992) comment that for diagnosing germ cell tumours 'in the case of a morphologically undifferentiated tumour, where diagnostic difficulty arises, an elevated AFP or BHCG may be the only clue' [37 page 395].

Bloom *et al.* [35] (1975) note that research published in 1970 had shown that AFP is present in serum in about 80% of cases of childhood 'liver cell carcinoma' (hepatoblastoma and hepatocarcinoma), and recommend that this assay should be used routinely in the diagnosis of childhood liver tumours. The sensitivity of the assay improved over time [37 page 109]. Voûte *et al.* [36] (1986) report that AFP assay is positive in about 90% of cases of 'liver cell carcinoma', and almost specific for 'liver cell carcinoma' and yolk-sac germ-cell tumours among malignancies, although AFP is physiologically raised below the age of 6 months.

AFP measurement would help in distinguishing yolk-sac tumours from other germ-cell cancers, and primary liver cancers from liver metastases of other malignancies. Both AFP and BHCG measurements would aid the distinction of germ-cell tumours from non-germ-cell cancers, and cancer from non-cancer at an earlier stage of disease.

2.5.4 Ultrasound imaging for solid tumours

Ultrasound imaging (US) is a refinement of sonar, which was developed during the Second World War for detecting submarines. Very high frequency sound is transmitted through the human body. The returning echoes are detected and converted into electrical signals. Variation in the quality of the tissue that reflects the sound produces variation in the electrical signal, which can be displayed as a two-dimensional picture on a screen. US can be used more freely than other forms of imaging, because it is convenient, non-alarming, fast and cheap, and does not involve ionising radiation.

For cancer diagnosis, US is generally more useful in children than in adults, because the resolution of the image is inversely related to the depth of tissue being examined. It is particularly good for examining the organs of the upper abdomen, including the liver, spleen and kidneys. It can also visualise the pelvic organs, eye, thyroid, testis and soft tissue of the limbs. Since it cannot penetrate bone or show tissue behind gas, US cannot detect intracranial, intraspinal or bone tumours, except for intracranial tumours in babies with an open anterior fontanelle, and it is not very useful for examining the chest. It may assist in diagnosing almost any other solid tumour of childhood. It is particularly useful in retinoblastoma, Wilms' tumour, liver tumours and neuroblastoma.

US was first used experimentally for diagnosis in the 1950s. It became potentially useful for clinical purposes when grey-scale 'B-mode' scanning was introduced in 1972, producing images that could be photographed and preserved from a monitor screen. 'Real-time' scanners, which display the pictures while the scanning is still taking place, were available from the mid-1970s. By 1975, US was a promising new method for diagnosing retinoblastoma and other solid cancers [35].

A book published in 1978 [64] describes the role of US in tumour diagnosis at that time. US was being used at Moorfields Eye Hospital to visualise retinoblastoma tumours following detection of abnormalities by ophthalmology. There had been a rapid increase in the use of liver imaging by US: it had been found to be very effective in detecting quite small lesions (over 1cm in diameter), and directing biopsy needles. US was now the primary imaging mode for evaluating kidney tumours: it was used to investigate renal masses seen on urography, to monitor patients known to be at risk of renal tumours (including Wilms' tumour in patients with aniridia, hemihypertrophy and Beckwith-Wiedemann syndrome), and to aid biopsy. US was also being used to visualise adrenal disease, with the hope that it might be possible to demonstrate adrenal neuroblastoma in children.

By 1986 real-time equipment was sufficiently portable to be used in outpatient clinics or at the bedside, and US was widely used for diagnosis of paediatric tumours [36]. Image quality and resolution continued to improve through the 1980s and 1990s, and examination techniques were gradually standardised.

Improvements in US technology would be expected to result in more sensitive diagnosis of many types of cancer, particularly retinoblastoma, neuroblastoma and primary tumours of the liver and kidney.

2.5.5 Immunohistochemistry for leukaemia

The 'French-American-British' (FAB) system, first devised in 1975 [65], is a set of standard morphological criteria for classifying leukaemias. FAB is effective for sub-classifying acute myeloid leukaemia (AML), but cannot reliably distinguish myeloid from lymphoid in 10-20% of cases of acute leukaemia, and does not define clinically useful subgroups of lymphoid leukaemia (ALL[*]) [66]. For most purposes the FAB system was superseded by the development of immunohistochemistry (IHC).

IHC is helpful for classifying apparently undifferentiated cancers, particularly acute leukaemias and 'small round cell' solid tumours (see Section 2.5.7); when used correctly, it is much less subjective than conventional morphology. Tissue cells are exposed to a series of substances that are known to react with antigens ('cell-surface markers') found on the cell surface of specific tumour types. If there is an antigen-antibody response to a particular substance, the cells are likely to belong to the corresponding tumour type. In leukaemia and lymphoma, the subgroups identified by IHC represent the cell type of origin (B-precursor, T-precursor, mature B-cell etc.).

IHC was initially developed for research purposes. In the UK, the Medical Research Council Working Party on Childhood Leukaemia organised a series of clinical trials of treatment protocols for ALL from 1970 onwards. A reference laboratory was established in London in 1975 to provide a IHC service for these trials [67]. During 1980-97, 80-90% of ALL patients diagnosed at ages 0-15 in the UK were enrolled. Although IHC techniques were still developing, a standard panel of tests was recommended throughout, and centralised diagnostic review was designed to ensure consistency over time [68].

[*] In childhood almost all lymphoid leukaemia is acute lymphoblastic leukaemia (ALL), and 'ALL' is used here as an abbreviation for 'lymphoid leukaemia'.

Sutow *et al.* [41] (1984) report that IHC could distinguish lymphoid from non-lymphoid (i.e. myeloid) leukaemia in virtually every case, and Voûte *et al.* [36] (1986) describe its use in identifying subtypes of ALL and NHL.

The introduction of IHC would make the allocation of leukaemia cases to lymphoid or myeloid lineage more reliable and complete, and define the cell type for the first time.

2.5.6 Computed tomography for solid tumours

Computed tomography (CT) visualises three-dimensional anatomy by combining digitised information from a large number of X-ray scans to produce a series of parallel cross-sectional images. The images are not obscured by overlying structures, and can distinguish fat, soft tissue and bone.

CT was the first effective non-invasive way of investigating intra-cranial disease. It revolutionised the diagnosis of brain tumours, and made several other specialised forms of X-ray scanning redundant. CT supplements ultrasound for assessing renal, adrenal and paraspinal tumours in the abdomen, and, unlike ultrasound, can evaluate bone lesions and chest disease, and calcification in retinoblastoma. However, compared to MRI (Section 2.5.8) it is poor at visualising structures in the posterior fossa; it is not very good at distinguishing between different types of soft tissue, or visualising very small abdominal or pelvic masses; and it involves fairly high doses of radiation.

Experimental CT scans of the brain were produced in 1971 at the Atkinson Morley Hospital in Wimbledon. In 1973 three commercial CT brain scanners were installed at hospitals in London, Manchester and Glasgow. Whole-body scanners were available from 1976, following the first clinical application in 1975 at Northwick Park Hospital. There were improvements in speed (particularly important for children) and precision. CT-guided stereotactic biopsy of brain tumours was introduced in 1980. According to Voûte *et al.*, CT was well-established in clinical paediatric oncology by 1986:

> 'Since the introduction of CT scanning into clinical practise in 1973, rapid technical advances have occurred leading to shorter scanning times which now make it possible to obtain high-quality images in the majority of children' [36].

The National Radiological Protection Board (NRPB), which is now part of the Health Protection Agency (HPA), monitors the use in Britain of medical X-ray examinations, including CT scanning. The 1977 NRPB survey found that:

> 'Twenty-one head scanners … and two body scanners … had been installed and were fully operational in Great Britain by the beginning of 1977, and a further eight head scanners and five body scanners were installed during the year' [69].

Most of the scanned patients were adults rather than children: the estimated annual number of CT examinations in NHS hospitals in Britain for patients aged 0-14 was 3100 in boys and 1200 in girls, compared with 33900 and 35600 for males and females of all ages. The 1983 survey reported that:

> 'At the beginning of 1983, 36 head scanners and 45 general purpose scanners were installed and in operation and a further nine general purpose scanners became operational during the year' [70].

There were approximately 200000 CT brain examinations and 25000 body scans in 1983, implying roughly a three-fold increase in activity from the level of 1977. Between 1983 and 1997/98 CT scans of the head and body increased by factors of more than 2 and 25 respectively, as proportions of all X-ray examinations in NHS hospitals, while the total rate of X-ray examinations was approximately constant [71]. Provision of scanners continued to increase after 1997: HPA data show that there were about 200 CT scanners installed in NHS hospitals in England in 1997, and about 370 in 2006 (Kim Stonell, personal communication).

Together, the NRPB surveys and HPA data suggest that a) up to 1977 only a very small number of hospitals used CT for head scanning, and hardly any used CT for body scanning; b) the use of CT scanning in general increased roughly threefold from 1977 to 1983; c) between 1983 and 1997/98, there was a very large increase in the use of CT for body imaging and a continued relatively slow increase (roughly twofold) in the use of CT for head scanning; d) provision of CT scanners approximately doubled between 1997 and 2006.

The most likely results of the availability of CT scanning are diagnosis at an earlier stage of disease, particularly for tumours of the CNS, bone and abdomen, and an increase in the proportion of brain tumours that could be biopsied and hence classified by histology. Effects on childhood cancer registration might start slightly earlier for brain tumours than

for tumours of other sites. If the overall use of CT is representative of its use in paediatric oncology, particularly big effects might be expected from about 1977.

2.5.7 Immunohistochemistry for solid tumours

As discussed in Section 2.4, morphology alone cannot always produce a definitive diagnosis for solid tumours. Various techniques that attempted to improve the objectivity of the process [66] were superseded by the development of immunohistochemistry (IHC), as described in Section 2.5.5.

The hybridoma method for mass-producing monoclonal antibodies, described by Köhler and Milstein [72] in 1975, eventually enabled laboratories all over the world to use identical standard cell-surface markers in diagnosing solid tumours. IHC is mentioned by Sutow *et al.* [40] (1977) as a promising new diagnostic technique for acute leukaemia and non-Hodgkin lymphoma (NHL). Sutow *et al.* [41] (1984) describe the use of cell-marker studies and monoclonal antibodies for identifying leukaemia subtypes and classifying lymphoreticular neoplasms, and mention the existence of tumour-associated antigens on sarcoma cells. For rhabdomyosarcoma, Voûte *et al.* [36] (1986) include a statement that 'the new immunohistochemical techniques with antibodies, which detect embryonic tissue with high specificity, make it possible to arrive at a firm diagnosis'. By 1992, according to Plowman and Pinkerton [37], IHC was 'the single most useful adjunct to straightforward tissue diagnosis currently in use', and had 'within the past decade virtually revolutionized tumour and tissue diagnosis'.

The benefits and problems of IHC as used in the USA for diagnosing solid tumours during the early 1990s are clearly described by Pizzo *et al.* (1993):

> 'The most visible development in diagnostic pathology of the past decade has been the introduction of light microscopic IHC as a routine diagnostic technique… Before 1980 the technique was purely a research tool. Since then, it has grown enormously; in our lab, the number of requests for diagnostic IHC for all specimens doubled each year for 5 consecutive years. Recent improvements in sensitivity and quality of antibodies have further enhanced the value of the technique… It is extremely useful to augment conventional IHC with a panel of monoclonal antibodies of known specificity… We have beneficially used a relatively limited panel of such antibodies in connection with the small round cell tumours of childhood… we have successfully distinguished between neuroblastoma, Ewing's sarcoma, peripheral neural tumours (peripheral neuroepithelioma, Askin tumour, PNET of bone and soft tissue), and lymphoma of bone.'

However:

> 'The panel discussed here represents the pragmatic application of a few monoclonal antibodies to a limited spectrum of tumour diagnoses… caution is in order when using a new or uncharacterized monoclonal antibody… extensive evaluation is mandatory before relying on such antibodies for tumour diagnosis.' [73]

By 2004, although some caution was still needed in the interpretation of results, IHC was well established for distinguishing neuroblastoma, Ewing-family tumours, rhabdomyosarcoma, and NHL, among undifferentiated small round-cell tumours.

> 'The development of IHC has resulted in refinements to diagnosis and prognosis over the past few decades, and it is now the most widely available ancillary technique.' [38]

The development of IHC for solid cancer made diagnosis more accurate and specific, particularly for undifferentiated tumours of indeterminate sites.

2.5.8 Magnetic resonance imaging for solid tumours

Like CT, magnetic resonance imaging (MRI) uses digital information to construct a series of cross-sectional images. Unlike CT, MRI does not entail exposure to ionising radiation: the picture derives from the differing amounts of energy that are absorbed by the hydrogen nuclei of different types of human tissue when bombarded with radiofrequency waves in a strong uniform magnetic field. MRI is more sensitive and accurate than CT for evaluating intracranial tumours; particularly in the posterior fossa, because CT scans of this region tend to be obscured by neighbouring bony structures [58].

The first commercial MRI scanner in Europe was installed in Manchester in 1983. Voûte *et al.* [36] (1986) mention MRI as a valuable new technique that was still being evaluated for cancer diagnosis in children. By 1992, MRI was in use for diagnosis of neuroblastoma and CNS tumours [37]. In 1993 (in the USA) MRI was described as at least equal to CT for most applications (except the detection of calcification, early cortical bone erosion and periosteal reaction), and 'as revolutionary in the 1980s as CT was in the 1970s' [73]. In 1997 MRI was described as having advantages over CT in diagnosing CNS tumours including brain stem glioma, astrocytoma and medulloblastoma [66]. Unpublished HPA data show that there were about 110 MRI scanners installed in NHS hospitals in England in 1997, and about 280 in 2006 (Kim Stonell, personal communication).

The availability of MRI scanning would be expected to lead to earlier diagnosis of spinal cord tumours and tumours of the posterior fossa such as glioma, ependymoma and PNET of the brain stem and cerebellum (see above) [58]. By facilitating biopsy, it might improve the precision of diagnosis of CNS tumours.

2.5.9 MIBG scanning for neuroblastoma

Meta-iodobenzylguanidine (MIBG) is a compound that concentrates in neuroblastoma cells because it has a structural similarity to catecholamines (see Section 2.5.2). It can be labelled with a radio-active isotope of iodine and injected into the patient, and then detected by X-ray body scanning. This is a very effective way of identifying primary and metastatic sites all over the body, including bone, bone marrow and lymph nodes [74].

MIBG was first developed as an imaging agent for pheochromocytoma in 1985. Its potential use in the diagnosis of neuroblastoma was mentioned by Voûte *et al.* in 1986 [36]. By 1992 [37] MIBG scanning was a well-recognised, although not entirely standardised, technique, and by 1997 [66] it was part of the internationally-agreed recommendations for the assessment of neuroblastoma. In 2004 it was said to have nearly 100% sensitivity for detecting primary and secondary neuroblastoma [58].

The availability of MIBG scanning would be expected to make the diagnosis of neuroblastoma more sensitive, and perhaps more accurate. It might also tend to increase the recorded stage of disease at diagnosis, because the extent of metastasis would be more completely detected.

2.5.10 Leukaemia/lymphoma boundary

Childhood lymphoid leukaemia (ALL) and non-Hodgkin lymphoma (NHL), of the same cell type, are the same disease [75]. The distinction between the two diagnoses is arbitrary, and is usually defined by the proportion of blasts in the bone marrow. The overlap occurs mainly in the T-precursor cell type, because mature-cell leukaemia and B-precursor lymphoma are rare in children.

Marsden and Steward [34] (1968) require more than 20% blasts in the bone marrow to confirm a diagnosis of leukaemia, and suggest more than 5% blasts in the peripheral blood as strong presumptive evidence. Bloom *et al.* [35] (1975) do not give a boundary, and stress that untreated NHL patients can subsequently develop symptoms that are indistinguishable from ALL. For T-cell disease specifically, Voûte *et al.* [36] (1986) say that 'current practice often assigns "leukaemia" or "lymphoma" therapy on the basis of percentage of marrow infiltration at 5%, 10% or 25%, or of the presence of circulating malignant cells' – there is a 'lack of uniform criteria among different institutions about the definitions'. In Britain, a series of clinical trials run by the UKCCSG for NHL treatment between 1977 and 1990 consistently used 25% as the boundary [76-79]. By 1992 the boundary had apparently been standardised: 'for the purposes of therapy, ALL and non-Hodgkin's lymphoma are considered and treated as the same entity if blast cell infiltration in the bone marrow exceeds 25% of cells' [37].

Nowadays, the diagnosis is arbitrarily defined as ALL if there is at least 25% marrow infiltration, or if any leukaemic blasts are present in the peripheral blood or cerebrospinal fluid; and as NHL otherwise [38]. In the early years of the study period, however, the chosen threshold for ALL was often lower than 25%, as described above. The disease probably tended to be further advanced at diagnosis, and leukaemia is more likely to be diagnosed in more advanced disease, because the bone marrow is more likely to be involved. These factors would tend to create a decreasing time trend for ALL and an increasing trend for NHL.

An upper limit to the potential diagnostic transfer can be very roughly estimated. In Britain during 1991-2000, according to NRCT data [1 Table 3.2, page 29], the age-standardised rates for leukaemia, ALL, lymphoma, and NHL (including Burkitt lymphoma) were respectively 45.5, 36.1, 12.5, and 7.3 per million. For NHL not known to be of B and/or mature cell type, the age-standardised rate was 2.3 per million [1 Table 3.8, page 53]. On the extreme assumptions that all these cases were of the T-precursor type and that they would all have been diagnosed as 'ALL' at the beginning of the study period, the transfer from ALL to NHL would have caused a decrease in ALL of about 6% (2.3/(36.1+2.3)) and an increase in NHL of about 46% (2.3/(7.3-2.3)). Overall, this transfer could produce at most a decrease in total leukaemia of 5% (2.3/(45.5+2.3)) and an increase in total

lymphoma of 23% (2.3/(12.5-2.3)). The transfer might start with the UKCCSG trials in 1977 (see above), and would probably have been completed by 1992.

2.6 Conclusions

There was a revolution in methods for diagnosis of childhood cancer between 1966 and 2005. The timing of these changes is summarised in Table 2(b).

Imaging techniques were probably the most important innovations, because a scan is often the first indication of a tumour. There was no satisfactory method for investigating suspected intra-cranial and intra-spinal tumours until CT was introduced, and MRI was a further major advance. US and CT were much more effective for imaging non-CNS non-bone solid tumours than the various forms of X-ray that had existed previously. MIBG scanning and various biochemical assays (urinary catecholamines for neuroblastoma, and AFP/BHCG for hepatic and germ-cell cancer) helped to distinguish malignant from non-malignant tumours. With these new techniques, the diagnosis would be less likely to be delayed until after the age of 14, or to be missed completely, and so the recorded incidence of childhood cancer would be expected to increase. Immunohistochemistry for leukaemia and solid tumours is less likely to have had this effect, because it is not used in the initial diagnosis of cancer. All these techniques, however, would improve the accuracy and precision of the diagnosis, and so might lead to some transfer between diagnostic groups.

None of the known changes in diagnostic methods is likely to have had a direct effect on the initial diagnosis of leukaemia, which has always relied on bone marrow examination. Indirectly, however, reduced delay in diagnosis of lymphoma and a consistent definition of the boundary between lymphoma and leukaemia might have improved the accuracy of the diagnosis of leukaemia.

For solid tumours, improvements in precision, accuracy or completeness of registration would be predicted around 1975 (catecholamine assay), 1986 (US, CT and AFP/BHCG) and 1992 (MRI, IHC and MIBG).

Table 2(a). Mean percentage agreement from pathology review for 2104 solid tumours of childhood diagnosed in the West Midlands during 1957-92. [59]

Tumour type	Within panel	Original (BCH) v. panel	Original (non-BCH) v. panel	Original (all) v. panel	N
Retinoblastoma	100	100	100	100	-
Renal tumours	98	95	97	96	-
Sympathetic chain	95	97	74	92	-
Bone tumours	94	100	89	91	-
Germ cell tumours	93	97	96	93	-
Hepatic tumours	90	78	46	65	-
Epithelial tumours	89	73	80	87	-
CNS tumours	85	85	82	86	482
Soft tissue sarcoma	81	85	56	72	243
Lymphoma	78	76	63	68	-
Overall mean	90	89	78	85	2104

Within panel = Mean percentage agreement within pathology review panel.
Original v. panel = Mean percentage agreement between review panel and:
(BCH) original diagnosis made at Birmingham Children's Hospital
(non-BCH) original diagnosis not made at Birmingham Children's Hospital
(all) original diagnosis made anywhere.
N = number of tumours, where reported.

Table 2(b). Approximate timing of introduction of important diagnostic techniques.

Technique	Diagnosis	Experimental	Pioneering	Routine
Catecholamine assay	Neuroblastoma	1959	1968	1975
AFP / BHCG assay	Hepatic/germ-cell tumours	1970	1975	1986
Ultrasound imaging	Solid tumours	1972	1975	1986
Immunohistochemistry	Leukaemia	1970s	1975	1986
Computed tomography	Solid tumours	1973	1977*	1986
Immunohistochemistry	Solid tumours	1970s	1986	1992
MRI	Solid tumours	1983	1986	1992
MIBG scanning	Neuroblastoma	1985	1986	1992

'Pioneering' and 'Routine' use are based on appearance in selected text books, by year of publication, except for pioneering use of computed tomography, which is based on NRPB data *.
AFP = alpha-fetoprotein; BHCG = beta-human-chorionic-gonadotrophic hormone;
MIBG = meta-iodobenzylguanidine; MRI = magnetic resonance imaging.

Chapter 3
Registration methods

3.1 Introduction

Records of the occurrence of cancer are essential for monitoring the burden of disease, planning the organisation of care, assessing the effects of treatment, and supporting research that may lead to better understanding of the biology and causes of cancer.

Britain has a long-established system for registering cases of cancer at diagnosis, which has been population-based since 1962, in the sense that it covers the whole geographical area of Britain. The system relies mainly on medical and administrative records from the NHS hospitals where cancer is diagnosed and treated. Data collection is managed by a network of regional cancer registries, which supply notifications to the central registries maintained by the national statistical services of England/Wales and Scotland. Several specialised regional registries and a national registry, the National Registry of Childhood Tumours (NRCT), give special attention to the small minority of cases that occur in childhood.

This chapter assesses the timing of changes in the procedures of the NRCT and its sources that might have affected the quality of the registration data used in this thesis. Using previously unpublished information, the procedures and their history are described in Sections 3.2 and 3.3. The history of the sources is outlined in Section 3.4. Possible effects of changes in registration methods on accuracy, specificity and completeness of registration are discussed in Section 3.5.

3.2 Recent procedures of the National Registry of Childhood Tumours

The NRCT hold records of children diagnosed with cancer from 1 January 1962 while resident in England, Wales and Scotland. Children from Northern Ireland who were

diagnosed after 1992 are also registered by the NRCT, but are not included in this study. The registration procedure is described here as it was in 2005, the last year of the study period (Figure 3(a)).

Notifications of cases diagnosed under the age of 15 are received from the regional and national general cancer registries of the UK, and from the specialist childhood cancer registries that exist in some regions. Further information is obtained from the register of patients seen by clinicians affiliated to the UK Children's Cancer Study Group (UKCCSG, the organisation that co-ordinates clinical paediatric oncology in the UK and Eire), and, for leukaemia patients only, from registers of participants in national clinical trials supported by the Medical Research Council (MRC).

The eligibility criteria are as follows.

- Malignant neoplasm of any site; or any neoplasm within the skull or spinal column ('CNS tumour').
- Age at diagnosis under 15 years; or death under the age of 16 years with an eligible neoplasm given as the underlying cause.
- Residence within UK at the time of diagnosis; or at the time of death if the date of diagnosis is not known, as above.

All CNS tumours are eligible whether known to be malignant or not, because biopsy is not always possible for intracranial and intraspinal sites. Ineligible notifications (e.g. over-age or foreign at diagnosis) are excluded from the NRCT but kept on file for reference. Implausible notifications (e.g. cancer types that do not occur in children) are investigated by questioning the source registry.

Each eligible notification is compared with the existing NRCT. Duplicates are identified and amalgamated. Identification details are recorded, including sex, date of birth, address at diagnosis, and all known names. A copy of the child's birth certificate is requested from the relevant national statistical office (Office of National Statistics (ONS) for England and Wales, or General Register Office (GRO) for Scotland); if obtained, this confirms the name and birth date, and supplies the address at birth. Two versions of the date of diagnosis are recorded, from the general cancer registration system and from the

UKCCSG register, if both are available. Where they differ, analyses of NRCT data normally use the earlier of the two.

As a check on completeness of registration, copies of death certificates are received for all deaths under the age of 20 with 'neoplasm' given as the underlying cause. Deaths under the age of 16 are held on the NRCT computer database. In the very rare event that a valid notification from a death certificate is not ascertained through another source, the case is registered and the date of death is used to represent the date of diagnosis. Unlike the general cancer registries, the NRCT does not receive death certificates showing cancer only as an associated cause.

About three years from diagnosis, any patient for whom a death certificate has not been received is, if possible, traced and recorded ('flagged') on the NHS Central Register, a database that includes all UK certificated births since 1939 and all persons registered with an NHS general practitioner. This acts as a further check for duplicate registrations and inaccurate identifying information. Discrepancies are resolved by questioning the individual patient's consultant or GP if necessary. For UKCCSG patients, the accuracy of the information held by the NRCT is confirmed by a series of routine follow-up enquiries to the notifying clinical paediatric oncologists

The diagnosis coding system is periodically updated. All cases held by the NRCT are currently coded to the site and type codes of the third edition of the International Classification of Diseases for Oncology (ICD-O), and hence to the third edition of the International Classification of Childhood Cancer (ICCC3) (see Appendix 1). Most UKCCSG notifications include a copy of the pathology report; for these cases, the accuracy of the diagnostic coding is checked at the CCRG by a medically-qualified member of staff. The coding of the diagnosis given on each death certificate is also checked.

The NRCT does not find cases actively, but aims to include all the cases known to a variety of routine sources. The process of careful cross-checking and validation should ensure that the registrations take the best from all the sources, and are as accurate and complete as possible.

3.3 History of the National Registry of Childhood Tumours

3.3.1 The Oxford Survey of Childhood Cancers

The NRCT incorporates case records collected for the Oxford Survey of Childhood Cancers (OSCC). This was a very large national case-control study of childhood cancer, which was directed by Dr Alice Stewart at the Social Medicine unit in Oxford University during 1953-74, and subsequently at the Department of Social Medicine in Birmingham University. In the 1950s, most cases of childhood cancer could be identified from death certificates, because patients usually died soon after diagnosis.

OSCC cases were initially ascertained from death certificates that gave 'malignant neoplasm' as the underlying cause for children who died under the age of 10 in England, Wales and Scotland from 1953 onwards. These cases were known as the *Dead* series (Table 3(a)). The upper age limit was extended to 15 for leukaemia deaths in England and Wales from 1955, and to 16 for deaths from any childhood cancer from 1956 (in Scotland) or 1961 (in England and Wales). For deaths from 1966 onwards, the case definition was extended to include death certificates giving any neoplasm as the underlying cause of death before age 16, whether specified as malignant or not.

The OSCC included several other series of cases (Table 3(a)). Deaths during 1959-65 from 'neoplasm not specified as malignant' up to age 15 formed the *Q* series, consisting almost entirely of deaths from CNS tumours in England and Wales. Death certificates giving 'neoplasm' as the underlying cause for deaths at ages 16-19 were collected, but were never used as a source of ascertainment, and did not contribute information to the database unless relating to a case that was diagnosed at age under 15 and also ascertained from another source; they were filed as paper records, by year of death from 1963 onwards (the *E* series). Unlike most childhood cancers, retinoblastoma could usually be cured; accordingly, some living retinoblastoma patients diagnosed during 1951-61 were identified by contacting certain hospitals directly (the *R* series). This was intended to be a representative sample of retinoblastoma cases, not a population-based register, and subsequent follow-up studies excluded cases from sources that were no longer felt to have unbiased ascertainment.

Epidemiological data for each case were sought from the child's parents, through an interview conducted by the child's GP, by staff from the office of the local Medical Officer of Health, or, later, by a peripatetic interviewer.

As survival improved, the OSCC was extended to include a survey of living cancer patients. From the regional general registries, cancer registrations were obtained for all patients who had been diagnosed under the age of 15 in Britain from 1962 to 1971 and who were thought to have survived at least three years from diagnosis. These cases were almost entirely non-leukaemias. Those that were not already in the Dead, Q or E series when notified to the OSCC were allocated to the *Live* series. The few cases that were already in the E series were re-allocated to the *F* series. The Live series included some patients who had already died at notification but were not included in the Dead/Q series because a death certificate had not been received (for example, if neoplasm was not given as the underlying cause, or the patient had died abroad). Patients were not transferred from the Live series to the Dead series if they died after notification to the OSCC.

As far as possible, the diagnostic information was validated from clinical sources. For live patients this was done through enquiries to the treating hospitals; for dead patients, GP records were obtained in batches from Family Practitioner Committees (FPC). At that time GP records were normally destroyed three years after death, and confidentiality of patient information was enforced less formally than it is now. In the Dead series, the proportion of cases that were validated increased over time, from 54% of deaths in 1953 to 82% in 1957, 94% in 1961 and 97% in 1973; of deaths during 1962-73, 95% were validated. In the Live series 91% of cases diagnosed during 1962-70 were validated.

3.3.2 The Childhood Cancer Research Group

When Dr Stewart moved to Birmingham in 1974, the Department of Health accepted a proposal that systematic registration should continue in Oxford. The Childhood Cancer Research Group (CCRG) was established in April 1975, and Dr Gerald Draper (who had worked on the OSCC since 1966 as the University Lecturer in Medical Statistics) became its first Director. The CCRG was originally part of the Department of the Regius

Professor of Medicine, but transferred to the Department of Paediatrics when Professor Richard Doll retired in 1979.

A copy of the OSCC identification data from the Live, Dead, Q and F series for cases diagnosed from 1962 to 1971 formed the basis of the NRCT. For cases from the Dead and Q series, and any relevant cases that were missing from the OSCC, this was supplemented by information from a retrospective search of the cancer registration files held by the Office of Population Censuses and Surveys for England and Wales (OPCS) and the Information Services Division of the NHS in Scotland (ISD-Scotland).

Ascertainment and validation continued in much the same way as before. Notifications were received from the regional general cancer registries for cases diagnosed under the age of 15 in Britain from 1972 onwards (as for the OSCC Live and F series, except that there was no restriction on survival time), and from the national statistical offices for death certificates giving neoplasm as the underlying cause of death before age 16 (as for the Dead and Q series). Death certificates giving neoplasm as the underlying cause of death at ages 16-19 continued to be collected but not used for registration. As before, diagnostic information obtained from death certificates was validated from GP records, and other diagnostic information was validated through routine enquiries to clinicians at the treating hospitals.

The MRC Leukaemia Trials Office, and subsequently the Clinical Trials Service Unit, supplied further detail for the children who were entered in the leukaemia trials run by the Childhood Leukaemia Working Party in increasing numbers from 1970 onwards.

3.3.3 Changes since the establishment of the Childhood Cancer Research Group

In 1977 UK Children's Cancer Study Group began to register patients in collaboration with the CCRG, providing an invaluable source of reliable supplementary information for a large and increasing proportion of NRCT cases, and an additional source of ascertainment (see Section 3.2).

Up to 1980, the OSCC continued to accrue cases from death certificates, and validation from GP records was done by Dr LM Kinnier Wilson jointly for the NRCT and the OSCC. Subsequently Dr Bridget Caplan continued this process for the NRCT. Validation ceased when Dr Caplan retired in 2001: the proportion of patients who died had become much smaller, the quality of data from other sources had improved, and there were increasing problems (destruction or loss of records, and requirements for permission or payment) in obtaining data from the FPCs and their successors, the Family Health Services Authorities. Validation from GP records had probably been attempted for all under-16 cancer deaths to the end of 1996, irrespective of whether a notification had also been received by the NRCT from the general cancer registration system.

For cases with more than death certificate notification, some diagnostic information is still validated by the CCRG through routine enquiries to clinicians at the treating hospitals. These enquiries originally included all cases as far as possible, but became more selective over time as better information became available through other channels, and they are now very limited: for example, a special enquiry form was introduced a few years ago to cope with an artefact of diagnostic coding which had produced a spate of spurious melanoma notifications.

3.4 History of the routine sources of ascertainment

Except for the inclusion of the UKCCSG register from 1977 onwards, the NRCT registration procedure did not essentially change from 1966 to 2005. However, the proportions of cases notified by the various different sources varied considerably (Figure 3(b)). Moreover, the quality and completeness of the data supplied by the various sources probably changed over time. The history of these sources is outlined in this Section.

3.4.1 General cancer registration in England and Wales

The introduction of a form of radiotherapy was the original incentive for cancer registration. The Ministry of Health proposed in 1923 that cancers should be registered to enable the outcome of treatments using radium to be monitored [80]. In 1929 the National Radium Commission began to distribute radium to selected hospitals in England and

Wales, and in 1932 a Registrar was appointed to direct the compilation of annual statistics monitoring the use and effectiveness of radium for the treatment of disease, especially cancer, in these centres.

The Cancer Act of 1939 gave local authorities the duty of making arrangements for the diagnosis and treatment of cancer within their areas, and required that 'clinical records relating to each patient should be kept so as to show clearly and accurately the history of the case'. From 1944 the local authorities who were operating treatment schemes under the Cancer Act were encouraged by the Ministry of Health to participate in a voluntary system of cancer registration. In 1945 it was agreed that the Radium Commission would produce a report combining information from all the registries, and in 1947 this responsibility was transferred to the General Register Office [81].

Voluntary cancer registration continued when the NHS took over the delivery of treatment in 1948. In 1950 cancers were being registered in 74 separate local centres [81]. During the following decade centres were combined and geographical coverage was extended so that, by 1962, there was a network of registries covering the whole of England and Wales [82]. By the early 1960s all the regional registries were routinely receiving copies of death certificates mentioning cancer [81]. Other notifications were, as before, obtained mainly from the administrative and clinical records of the treating (or diagnosing) hospitals.

The boundaries of the registries changed over time. In 1971 there were 14 registries in England and Wales, each covering a single hospital region. At the start of 1973, Wessex separated from South Thames [81]. In April 1974, when the Regional Health Authorities were formed [81], registration for North Wales was transferred from the Mersey region to the Welsh registry, which previously had only covered South Wales [83]. In 1978 the responsibility for registration transferred from the region of treatment (or diagnosis) to the region of residence, and it was agreed that the registries would exchange data so that each included any patients who were normally resident in that region but had been treated or diagnosed elsewhere [81]. At the start of 1985, with the aim of coping with the recognized special difficulties of cancer registration in the London area, the Thames registry was formed by amalgamating three previously separate registries covering NE

Thames, NW Thames and S Thames [81]. The South Western and Wessex registries amalgamated in 1995, and the Northern and Yorkshire registries amalgamated in 1996 [82].

By 2005 there were nine regional cancer registries in England, and a registry for Wales (Table 3(b)). Each registry covered the territory of one or more of the former Regional Health Authorities that had replaced the hospital regions in 1974. The registry regions corresponded only very loosely with the nine Government Office Regions, and the only region that was exactly the same in both systems was the West Midlands.

A review in 1963 stressed the importance of achieving a high level of completeness of ascertainment, and the need for a standard simple accurate minimum dataset [82]. However, reviews in 1970 [84], 1980 [80], 1990 [85] and 2000 [82] all concluded that the methods, content, accuracy and completeness of registration varied between regions.

In 1970, an Advisory Committee reported that the national cancer registration scheme was essential for planning services and facilitating research, but that methods and quality of registration varied considerably between regions. The committee proposed various revisions designed to make the system more consistent and efficient [84]. It also recommended that the central registry should be transferred to the Office of Population Censuses and Surveys (OPCS), and cancer registrations flagged in the NHS Central Register in the same way as deaths [82]. The revised scheme was introduced in 1971, to cover cases with diagnosis dates from 1 January 1971. This scheme forms the basis of the present cancer registration system in England and Wales.

In 1980, using statistics from 1976, an Advisory Committee reported considerable variation between regions in the ratio of cancer registrations to deaths, and tentatively suggested that ascertainment might be as low as 60-70% in regions with decentralised systems and little involvement from clinicians, on the assumption of 90% ascertainment in the best regions [80]. No attempt was made to compare regional variation by age or cancer type.

In 1986 the quality of cancer registry data for England and Wales was discussed in detail by Swerdlow [81]. In the best regional registries, completeness was reported to be high (93-

96% in the North West, over 98% in the West Midlands, and close to 100% in Trent). However completeness was unlikely to be uniformly good, because the regions differed considerably in their sources and methods of ascertainment (see Table 3(c)). In particular, there were differences in the treatment of cases ascertained only from death certificates. The registries in Wales, and also in NE and NW Thames to some extent, simply recorded the diagnosis shown on the death certificate, and used the date of death to represent the date of diagnosis. All the other regions checked the validity of the diagnosis from clinical and other local sources and registered the true date of diagnosis if available. If the case was not traced they used the date of death, except in Oxford region where the case was not recorded, and in Yorkshire, where the case was not recorded unless supported by a post mortem.

Subsequent publications supported the conclusions of Swerdlow [81]. A report published in 1988 by the Welsh cancer registry [83] confirms the methods used in Wales during the period 1974-84. Validation of death-certificate notifications is reported to have been very incomplete in the area previously covered by the S Thames registry during the late 1980s and early 1990s [86]. A comparison of the sources of ascertainment reported in 1994 for the Cancer Registry Handbook [87] with those reported by Swerdlow [81] suggests that there had been some changes since 1986, but that there was still considerable variation between regions (Table 3(c)). In both 1986 and 1994 the number of different sources was noticeably lower in Wales than in the English regions.

Efforts to improve the system continued. Between 1969 and 1986 nearly all the regional registries became computerised, in the sense that they moved from manual to machine-readable media for submitting data to OPCS [81]. In 1992 the UK Association of Cancer Registries was founded, with the aim of co-ordinating the work of the regional registries. From 1 January 1993 registration ceased to be voluntary: it became mandatory for NHS hospitals to supply a standard data set for each cancer patient to the regional cancer registry, and for regional registries to supply data to OPCS. Current procedures in two regional registries appear to date from the early 1990s (see Appendix 2), perhaps reflecting re-organisation in response to these initiatives. Between 1990 and 1995 the central computer system was completely redeveloped, and the validation system was overhauled. When OPCS merged with the Central Statistical Office in 1996 [82], the newly-

created Office for National Statistics (ONS) undertook the responsibility for central cancer registration.

Nevertheless, when the ambitious NHS Cancer Plan* was published in September 2000, the cancer registration system was still thought to be inadequate. An 'Action Programme for Cancer Registration' in England† was adopted, based on the recommendations of the Advisory Committee review of April 2000. Extra funding for three financial years from April 2001 was provided. A National Co-ordinator for Cancer Registration was appointed, and a National Cancer Registry Advisory Group was set up. The intention was to increase the accountability of the regional registries in England, and to 'drive up the quality, timeliness and completeness of cancer registration'.

3.4.2 General cancer registration in Scotland

Like England and Wales, Scotland has a long-established cancer registration scheme [88] [89]. The system was initiated by the National Radium Commission in 1936, and had been extended to cover the whole of Scotland by 1947. Regional registries in Edinburgh (SE), Glasgow (W), Dundee (E), Aberdeen (NE) and Inverness (N) were established in 1958. The work of the regional registries was co-ordinated initially by the Scottish Office Home and Health Department, and subsequently, from 1974, by ISD-Scotland. In January 1997 the responsibility for registration was transferred from the regions to ISD-Scotland, although diagnostic information was still verified locally.

Various procedural changes may have affected completeness and accuracy of registration over time. From 1971, as in England and Wales, cases were routinely traced and flagged at the national NHSCR. During the 1970s, death certificates mentioning cancer were apparently not used as a source of notification without clinical validation [90]; the extent to which validation was attempted varied between regions [91], and until 1975 death certificates (with validation) were a systematic source of ascertainment only in SE Scotland [88]. After 1981 validation was more widely attempted [89] and, in some regions at least, cases that could not be validated were included as death-certificate-only (DCO)

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* See [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4009609].

† See [http://www.ociu.nhs.uk/data/National_Cancer_Reg_Action_Prog.pdf].

registrations, making 4% of the total in the central Scottish register during 1981-90 [92]. Computerised collection systems, with automated data checking routines, were introduced in all the regions during the early 1990s [88]. Centralisation at ISD in 1997 involved a change to computerised linkage of records from multiple sources by probability matching, with local verification from medical records [92 93]. Re-abstraction studies of cases attributed to 1990 [94 95] and 1997 [93] concluded that accuracy was good in both years, but possibly improved a little between 1990 and 1997; the proportion of DCO registrations decreased from 3.2% to 0.4%.

During the 1970s [91] and 1980s [89] the five regional registries in Scotland probably differed in completeness. A report published in 1979 comments that the quality of registration varied between regions, and notes that ascertainment was particularly low in Western Scotland, partly because of difficulty in co-ordinating the large number of hospitals in that region [96]. The 1992 edition of 'Cancer Incidence in Five Continents' [97], a standard international compilation of cancer statistics, draws attention to regional differences within Scotland in registration methods for cases diagnosed during 1983-87. For example, whereas most regions used a range of sources, in East Scotland registration was based almost entirely on notification by the treating hospital clinician, with cancer deaths used as a source only if occurring in hospital or found at autopsy; and in North Scotland, unlike other regions, non-validated death-certificate notifications were not registered. Regional differences in sources of ascertainment persisted into the 1990s, as shown in Table 3(d) [87].

3.4.3 Regional specialist childhood cancer registries

There are currently four population-based regional specialist childhood cancer registries in Britain. The Manchester Children's Tumour Registry has covered the under-15 population of a large area in North West England since 1953 [98]; this was the first specialist childhood cancer registry in the world. Other British regional specialist registries followed: the West Midlands Regional Children's Tumour Registry [99 59] (established in 1984 with retrospective data from 1957 onwards), the Northern Region Children's Malignant Disease Registry [100] (data from 1968 onwards) and the Yorkshire Children's Cancer Registry [101] (data from 1974 onwards). A further population-based

register of childhood cancer patients operated in South West England during the decade 1976-85 [102]. These registries aim to achieve high standards of accuracy and completeness of registration within certain individual regions. They work closely with local clinicians, and obtain detailed pathological review of most cases. They routinely exchange data with the appropriate regional general cancer registries and the NRCT.

3.4.4 MRC leukaemia trials and the UK Children's Cancer Study Group

Since 1970, the Medical Research Council has sponsored a near-continuous series of clinical trials for treatment of childhood lymphoid leukaemia (ALL) in the UK. The trial protocols were originally designed to be used not only in specialist centres but also by general paediatricians. The registers of these trials are one of the NRCT's routine sources, providing detailed and reliable diagnostic information for many ALL patients, and ascertainment of a few cases not notified by any other source.

During the early 1970s, several British paediatricians received training in combination chemotherapy for childhood cancer at specialist centres in the USA, and returned to set up regional treatment centres in the UK. As the specialism expanded, it became clear that the centres needed to combine forces. Accordingly, in January 1977 the United Kingdom Children's Cancer Study Group (UKCCSG) [103] was founded, with the following aims:

- to establish co-operative clinical trials for childhood cancer in the UK
- to establish a central register of all patients seen by UKCCSG clinicians
- to collect epidemiological and other data for these patients
- to exchange ideas and discuss research
- to encourage individual clinicians to specialise in particular tumours.

The founder members were a group of paediatric oncologists from seven regional treatment centres: Birmingham, Bristol, Liverpool, St Bartholomew's and Great Ormond Street Hospitals (London), Manchester and Newcastle. During the first year, they were joined by clinicians from eight more centres: Cardiff, Edinburgh, Glasgow, Leeds, Nottingham, Royal Marsden Hospital (Sutton), Sheffield, and Southampton. Clinicians from other centres followed rapidly, and from 1980 all specialist paediatric oncology consultants in the UK were UKCCSG members. The last centres to be established were

Leicester (1981), Middlesex Hospital (London) (1991), and Oxford (1992). See Table 3(e).

In collaboration with the CCRG, the UKCCSG [*] started to register patients on 1 July 1977. This procedure has remained essentially the same for more than thirty years [†]. UKCCSG clinicians at the regional treatment centres are responsible for completing a registration form for each patient, to record identification and diagnostic data, and some epidemiological information. A copy of the completed form is sent to the CCRG, and the data become part of the NRCT registration for the patient; in return, the CCRG provides the UKCCSG with an annual statistical report. Notification usually reaches the NRCT more quickly from the UKCSSG than from the regional cancer registries. The CCRG also receives patient registers from clinical trials organised by the UKCCSG; this information has been used in analyses comparing outcome between trial and non-trial patients, and may occasionally clarify a patient's diagnosis.

The proportion of NRCT cases registered by UKCCSG clinicians has increased over time: overall, it was about 60% in 1980, 80% in 1990, and 90% in 2000. The proportion also varied by diagnostic group: during most of the study period, it was higher for leukaemia than for non-CNS solid tumours, and lowest for CNS tumours (Figure 3(b)).

During various time periods within 1991-96, newly-diagnosed childhood cancer patients resident in Britain were recruited to a case-control study, the United Kingdom Childhood Cancer Study (UKCCS) [104]. In England and Wales the accrual of cases ran from April or September 1992 to the end of 1996 for leukaemia, to the end of 1995 for NHL, and to the end of 1994 for all other diagnoses. In Scotland accrual ran from the beginning of 1991 to the end of 1994 for all diagnoses. Cases were notified primarily by paediatric oncologists working in regional treatment centres. Some further cases were provided by other hospital departments including specialist cancer units treating mainly adults, by the regional general cancer registries, and by the NRCT. Despite the similarity of name, the UKCCS was not organised by the United Kingdom Children's Cancer Study Group

[*] Except the Newcastle centre, which started to register patients on 1 January 1978.

[†] On 1st August 2006 the UKCCSG merged with the UK Childhood Leukaemia Working Party - the group that had organised clinical trials for childhood leukaemia - to form the Children's Cancer and Leukaemia Group. Here, for simplicity, the combined group is referred to as the UKCCSG.

(UKCCSG), and it was not a source for the NRCT. However, the participating paediatric oncologists were inevitably members of the UKCCSG, and the cases they notified should nearly match the relevant subsets of the UKCCSG register. It is not clear whether the UKCCS had access to any source of ascertainment not available to the NRCT.

3.4.5 Death certificates

A death certificate gives, in words, a list of conditions that jointly caused the death. The causes are coded at the office of the Registrar General, and the 'underlying' cause is identified. For example, if intracranial tumour and meningitis are shown as contributory causes of death, the underlying cause is likely to be the tumour, not the meningitis.

Conventions for selecting the underlying cause have varied over time. In England and Wales from 1940 to 1992 the choice of underlying cause depended only to some extent on the order in which the causes were listed on the certificate [105]. The certificate was sometimes sent back to the certifying doctor for clarification if the implied underlying cause was thought to be improbable (except during 1967 and 1981-82), and the rules were changed in 1984 to allow the order of causes on the death certificate to be disregarded. These practices tended to increase the proportion of deaths coded to cancer and decrease the proportions in the relatively unspecified categories. The tendency was reversed when automatic coding was introduced with computerisation in 1993, ensuring that the order on the certificate completely determined the choice of underlying cause, except that since 1986 no underlying cause has been attributed for deaths occurring under the age of 29 days.

Since the NRCT directly receives only death certificates that give neoplasm as the underlying cause of death, it might be thought that these changes could have affected completeness of registration. However the NRCT indirectly receives information from death certificates with cancer mentioned anywhere on the certificate, through notifications from the general cancer registries (sections 3.4.1 and 3.4.2). The proportion of cases notified to the NRCT only by death certificate has been very small since the mid-1970s, and there was certainly no sign of a decrease around 1993 (Figure 3(b)).

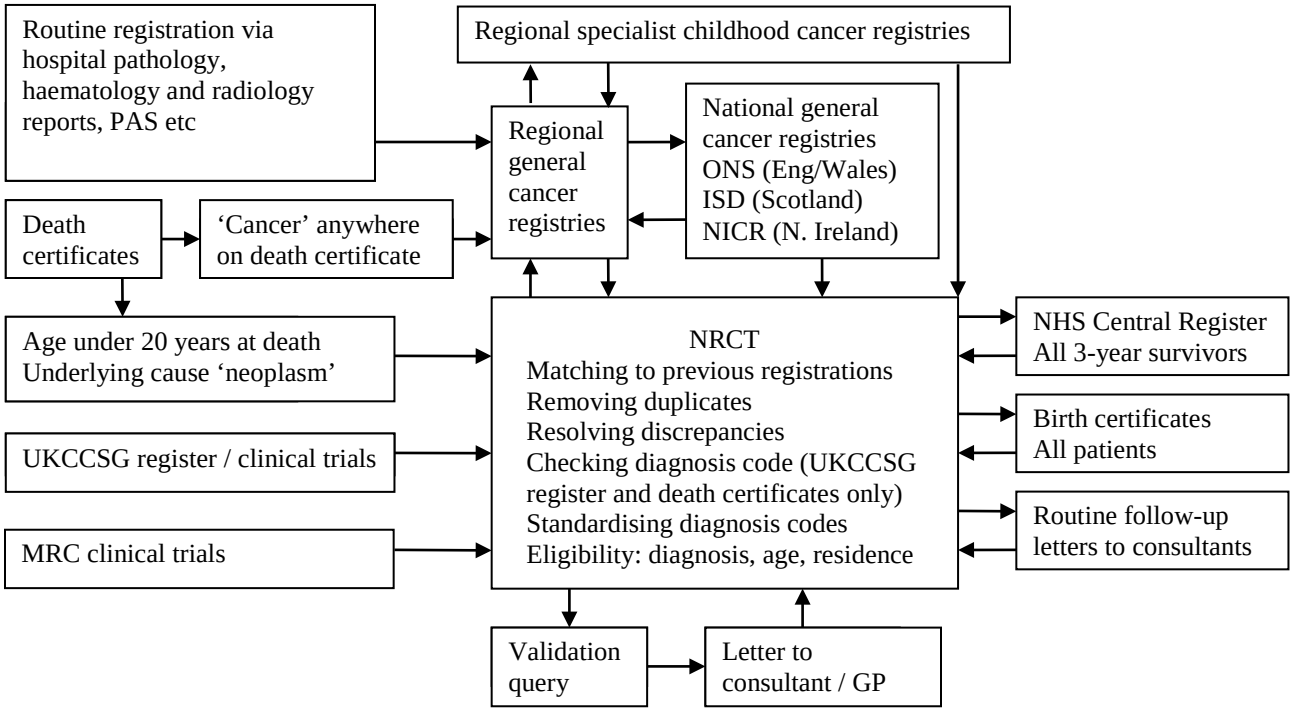
3.5 Conclusions

Although the procedure for NRCT registration did not essentially change during the study period, there were changes in the sources of ascertainment, which are summarised in Table 3(f).

The quality of the source data improved over time. There may have been considerable variation between the regional general cancer registries in the early years of the study period, with particular inaccuracy and incompleteness in the Thames region, Wales and Scotland. Differences probably persisted into the 1990s at least. At various times during the study period, regional childhood cancer registries provided more precise and accurate (but not necessarily more complete) information for cases from the Manchester area, the West Midlands, the Northern Region, Yorkshire or the South West. From mid-1977 the inclusion of the UKCCSG register improved timeliness, accuracy and precision for an increasing proportion of NRCT records.

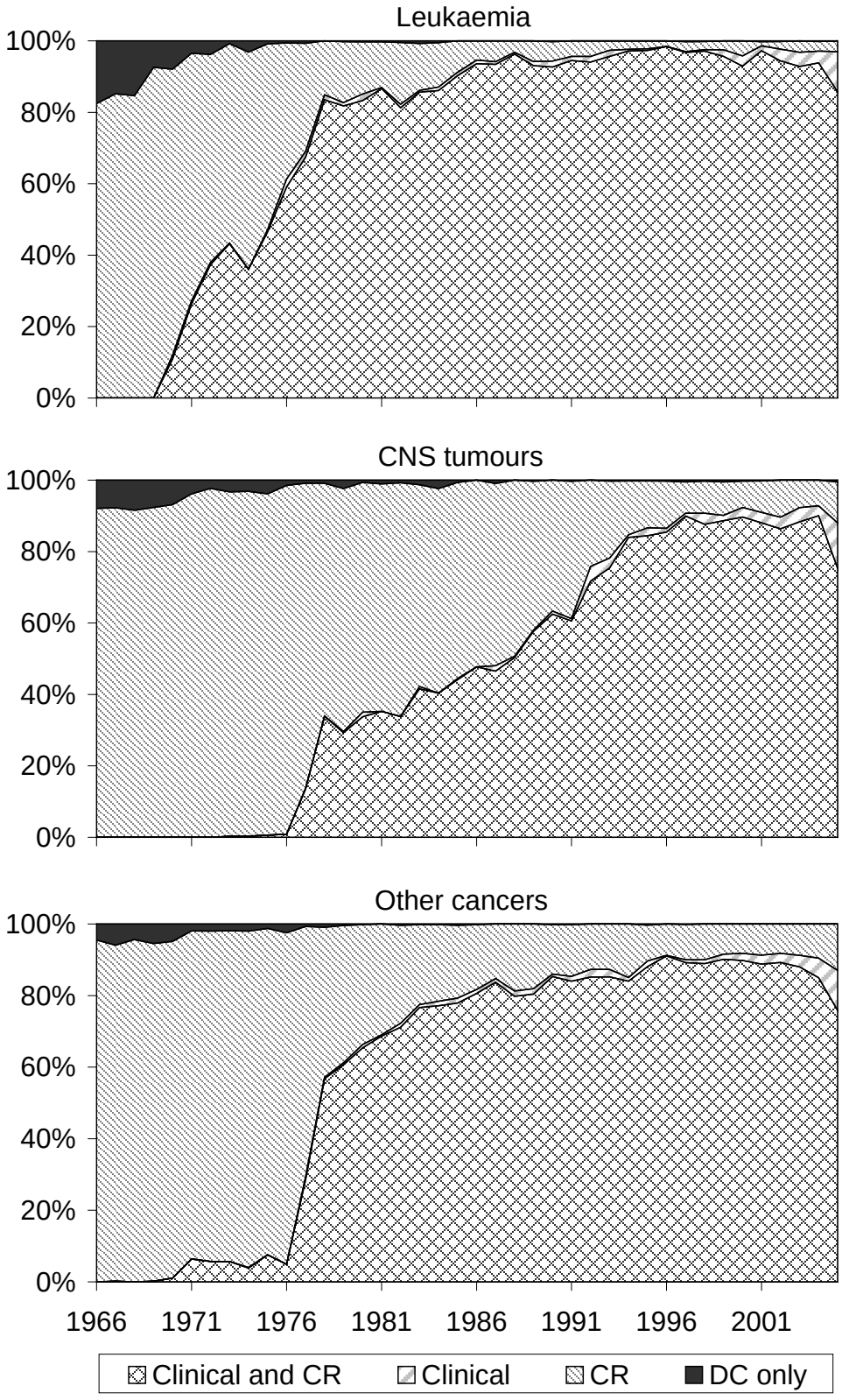
Some changes in registration methods probably happened gradually, but others might have been more abrupt. Noticeable effects on recorded incidence at the national level might be expected in 1971 (the revised scheme for cancer registration), in 1978 (the first full year of the UKCCSG register), in 1993 (mandatory registration and greater use of computers), and in 2001 (the Action Programme with specific funding for improvements to the registration system).

Figure 3(a) NRCT registration procedure in 2005.



See list of Abbreviations at start of thesis.

Figure 3(b). NRCT sources of notification (%) by year of diagnosis 1966-2005, Britain.



Clinical = UKCCSG register and/or UKCCSG/MRC clinical trial
CR = regional general cancer registry and/or regional specialist childhood cancer registry
DC only = death certificate only.

Table 3(a). Summary of the OSCC case series.

Series	Source	Diagnosis / underlying cause of death	Event	Period	Age
Dead	DC DC	Malignant neoplasm Neoplasm	Death Death	1953-65 1966-80	Various 0-15
Q	DC	Neoplasm not specified as malignant	Death	1959-65	0-14
E	DC	Neoplasm	Death	1963-	16-19
R	Selected hospitals	Retinoblastoma	Diagnosis	1951-61	Any
Live/F	CR 3-year survivors	Malignant neoplasm / CNS neoplasm	Diagnosis	1962-71	0-14

CR = regional general cancer registries; DC = death certificates.

Table 3(b). Regional general cancer registries in England and Wales, in 2005.

Regional Cancer Registry (2005)	Parts of Government Office Regions
Northern and Yorkshire Cancer Registry	Yorks/Humber, NorthEast, NorthWest
North West Cancer Intelligence Service	NorthWest
Trent Cancer Registry	EastMidlands, Yorks/Humber
Welsh Cancer Intelligence and Surveillance Unit	Wales
West Midlands Cancer Intelligence Unit	WestMidlands
Oxford Cancer Intelligence Unit	SouthEast, EastMidlands
Eastern Cancer Registration and Information Centre	East
Thames Cancer Registry	London, SouthEast, East
South West Public Health Observatory and South West Cancer Intelligence Service	SouthWest, SouthEast

Table 3(c). Regional general cancer registries in England and Wales, during 1985-94: sources of ascertainment.

Registry region	Sources of ascertainment										
1985-94	Hospital records							Other			
	In-patient	Out-patient	Discharge records	Radiotherapy	Pathology	Cytology	Chest clinic	GP / FHSA	Coroner	Hospice / private	Specialist registry
Northern	XO	XO		XO	O	O		O			
Yorkshire	XO	XO	X	XO	XO	O	X	X		XO	O
N Western	XO	O			O	O		O		O	O
Mersey	XO	XO	O	XO	XO	XO		XO	O	XO	
Trent	X	X	O	X						O	
Wales		X	XO	O							
W Midlands	XO	XO	O	XO	XO	XO	X	XO	X	XO	O
Oxford	X		XO	XO	XO	XO	X	O	X	O	
E Anglia	XO	XO	X	XO	XO	XO			XO	O	
S Western	X	X	XO	XO	XO	O					
Wessex		X	XO		O	O			X	O	O
Thames	XO	XO	XO	XO	XO	X	X	XO	X	XO	O

X = source of ascertainment in 1985 (Swerdlow [81] 1986).
O = source of ascertainment in 1994 (Cancer Registry Handbook [87] 1994).
FHSA = Family Health Service Authority, the predecessor of the Primary Care Trust.
The meaning of 'specialist registry' is not clear in the original, but may include regional specialist childhood cancer registries and/or the NRCT.
Screening units for breast or cervical cancer were sources for some registries, but are omitted here because they are irrelevant for childhood cancer.
All registries also received death certificates mentioning cancer and exchanged data with other regions.

Table 3(d). Sources of ascertainment for regional cancer registries in Scotland.

Regional registry	Sources of ascertainment										
1958-96	Hospital records							Other			
	In-patient	Out-patient	Discharge records	Radiotherapy	Pathology	Haematology	Cytology	GP/FHSA	Coroner	Hospice/private	Specialist registry
Edinburgh (SE)				O	O		O			O	O
Glasgow (W)	O	O	O	O	O	O	O	O		O	O
Dundee (E)	-	-	-	-	-	-	-	-	-	-	-
Aberdeen (NE)	O	O	O	O	O					O	O
Inverness (N)	O	O		O	O		O				

O = source of ascertainment in 1994 (Cancer Registry Handbook [87] 1994).
No information is given for Dundee (E) in the original.
All these registries also received lists of deaths with cancer mentioned on the certificate, and exchanged data with other regions. The meaning of 'specialist registry' is not clear in the original, but may include the NRCT.

Table 3(e). UKCCSG paediatric oncology centres in 2005, with year of affiliation.

UKCCSG centre	Year of affiliation
Birmingham	1977 ⌗
Bristol	1977 ⌗
Liverpool	1977 ⌗
Great Ormond Street Hospital (London)	1977 ⌗
St Bartholomew's and (later) the London Hospitals (London)	1977 ⌗
Manchester	1977 ⌗
Newcastle	1977 ⌗
Cardiff	1977
Edinburgh	1977
Glasgow	1977
Leeds	1977
Nottingham	1977
Sheffield	1977
Southampton	1977
Royal Marsden Hospital (Sutton)	1977
Belfast	1979
Cambridge	1979
Dublin	1979
Aberdeen	1980
Leicester	1981
Middlesex and University College Hospitals (London)	1991
Oxford	1992

⌗ = founder member.

Table 3(f). Events in the history of sources of ascertainment to the NRCT (shaded area), by year of diagnosis 1966-2005.

Diag Year	UKCCSG	MRC	Regional specialist childhood cancer registries					General registries	DC
	Paediatric oncologists	Clinical trials (leukaemia)	Manchester	West Midlands	Northern	Yorkshire	South West	Regions England+Wales (GRO/OPCS/ONS) Scotland (ISD)	Cancer deaths
1966									
1967									
1968									
1969									
1970									
1971								Revised scheme	
1972									
1973								Wessex Cancer Registry	
1974								Boundary changes	
1975									
1976									
1977	14 centres								
1978	+ Newcastle							Region of residence	
1979	+ 3 centres								
1980	+ Aberdeen								
1981	+ Leicester								
1982									
1983									
1984									
1985								Thames Cancer Registry	
1986									
1987									
1988									
1989									
1990									
1991	+ Middlesx								
1992	+ Oxford								
1993								Mandatory registration	
1994									
1995								South and West CR	
1996								North and Yorkshire CR	
1997								ISD Scotland	
1998									
1999									
2000									
2001								Action Programme	
2002									
2003									
2004									
2005									

See list of Abbreviations at start of thesis.

Chapter 4
Completeness of registration

4.1 Introduction

Completeness of cancer registration cannot be estimated without a suitable independent set of notifications for comparison.

For patients who die of cancer, clinical records and death certificates are independent sources of notification. The proportion of cases notified only by death certificate is sometimes used as a rough measure of relative completeness; for example, in the comparisons between regional general cancer registries that are included in the internal reports of the UK Association of Cancer Registries (UKACR). However, this may not be an accurate measure of absolute completeness, particularly for children. The implicit assumption is that the registration process for those who died is typical of cancer patients in general. This may be not even approximately true, since patients who died may be more likely than others to have had extended contact with the clinical services, and therefore to have been ascertained from clinical sources. Moreover, among children, those who die may be in the minority: at 10 years from diagnosis, only about 30% of all recently-diagnosed childhood cancer patients in Britain will have died [1], compared with 50-60% of adult cancer patients [*].

The regional general cancer registries have recently begun to use a more sophisticated approach, the *flow* method, for estimating completeness [106]. This takes death certificates as the comparison set, but fits a statistical model to the flow of data through the registration system, and includes an estimate of the survival time for each diagnostic group. Section 4.2 describes a (new) application of the flow method to the NRCT.

In 1991, completeness of NRCT ascertainment of leukaemia and NHL cases diagnosed during 1966-83 was estimated to be 99% [107] by the two-sample *capture-recapture*

[*] Source: http://info.cancerresearchuk.org/cancerstats/survival/latestrates/index.htm

method [108]. The calculation assumed that notification by the regional general and specialist childhood cancer registries was independent of notification from all other sources combined (death certificates, the UKCCSG register and the MRC leukaemia trial registers). This assumption cannot have been strictly valid, because death certificates have been a source of ascertainment to the regional registries since the early 1960s (see Chapter 3). For the recent past, however, the UKCCSG and the regional cancer registries can probably be treated as independent sources of notification, provided that the comparison is restricted to the records as they were before the current system of formal data exchange began. The results of applying the capture-recapture method in this way are presented and discussed in Section 4.3, and differences between the characteristics of cases notified by the different sources are described.

In recent years, anonymised records of in-patient admissions to NHS hospitals in England, and (for residents of England only) to NHS hospitals in Wales, have been made available for research purposes, in electronic format. These data are known as Hospital Episode Statistics (HES). Since almost every child treated for cancer in Britain is seen in a NHS hospital, HES data provide a new opportunity for a cross-check with the NRCT. This cross-check is reported in Section 4.4.

As mentioned in Chapter 1, a positive association between recorded childhood leukaemia incidence and higher SES is consistently found in cancer registry data in many different settings. Previous investigations using NRCT data suggest that the association may be specific to lymphoid leukaemia (the commonest subtype of childhood leukaemia) [109], particularly in the age group 1-4 [110], which includes the peak age for B-precursor lymphoid leukaemia. Registration artefact might be an explanation of this association, if the availability of sources of ascertainment, or the efficiency of cancer registration, varied with SES. The analysis described here includes some attempts to investigate this possibility. In Section 4.3, capture-recapture completeness estimates are compared between geographical areas with different levels of SES, for a range of age-diagnosis groups, including leukaemia in the age group 1-4. In Section 4.4, the cross-check with HES data focuses on leukaemia patients who were born in 1998 and diagnosed before the end of 2004, thus including the whole of the age group 0-5 completed years, i.e. age group 1-4 with a margin of one year on each side.

4.2 Flow method

4.2.1 Introduction

The UK Association of Cancer Registries (UKACR) offers its affiliated registries a standard computer program that produces estimates of completeness of registration by the flow method [106]. The calculations described here were performed by a slightly adapted version of this program. The method had not previously been applied to the NRCT.

The aims were to investigate the validity of the flow method for the NRCT, and to assess any evidence for variation in completeness over time, between age groups, or between broad diagnostic groups.

4.2.2 Background

Regional general cancer registries (CRs) receive notifications at diagnosis from clinical sources, and at death from death certificates (DCs) that mention cancer as either an underlying or a contributory cause. The structure of the CR system is shown in Figure 4.2(a).

The flow method models the flow of cases through the system. At a specified time from diagnosis an unregistered case is defined as 'missing' if the patient is still alive, or 'lost' if the patient has died and the death certificate did not mention cancer. A file consisting of all deaths that occurred within an arbitrary time period is used to estimate the probability that a case has been notified from clinical sources at a specified time from diagnosis. A file consisting of all cases registered within an arbitrary time period is used to estimate the probability of death and the probability of cancer being mentioned on the death certificate.

Unlike the CRs, the NRCT is restricted to cases diagnosed under the age of 15. The structure of the NRCT system is shown in Figure 4.2(b). As described in Chapter 2, there are two main sources of clinical notifications: the UK Children's Cancer Study Group

(UKCCSG)* and the CRs. The NRCT also routinely receives a copy of every DC that gives 'neoplasm' as the underlying cause for death under the age of 20 in a resident of Britain. The existence of the DC is recorded on the database for cases that have already been notified, but only those DCs that record deaths under the age of 15 are used as a source of notification. Notification only from a DC is very rare in the NRCT, because ascertainment from DCs mentioning cancer is received indirectly, through CR notification, for cancer deaths in which either the death occurred under the age of 15, or the CR succeeded in obtaining a date for diagnosis under the age of 15.

Since the NRCT receives information on death at any age for registered cases, there is no difficulty in estimating the probability of death from a set of cases diagnosed within a given period. Death certificates giving 'neoplasm' as the underlying cause (for deaths under the age of 20) can be used to represent death certificates mentioning cancer. However, the NRCT does not hold the data needed to estimate the probability that a date of diagnosis will be obtained by the CRs for DC-initiated cases who died at or over 15 years of age. The proportion of lost cases will be under-estimated if this probability is over-estimated, and vice versa, particularly in age group 10-14. The method was tested under different assumptions to assess the importance of this uncertainty.

The method amalgamates observations over a long time period (potentially back to the start of the registry), on the assumption that registration is in a steady state; for the NRCT this assumption is not likely to be valid, because the UKCCSG provided a faster source of ascertainment for an increasing proportion of cases between the late 1970s and the mid-1990s (see Chapter 3). To reduce the effect of this inaccuracy on the comparison of completeness between different diagnosis years, the estimate of the probability of notification was made more specific to a particular time period by restricting the range of diagnosis years covered by the deaths file.

The method requires a registration date for each case. Although the NRCT database stores a 'creation date' for almost all cases registered since 1981, there are no creation dates before 1981, and there was a hiatus during 2000 when a new computer system was introduced. For consistency, a registration date was imputed for each case, using the

* Since 2006, the Children's Cancer and Leukaemia Group.

consecutive serial number that has been allocated to each NRCT case diagnosed since the start of the current system in 1974. On the assumption that a case cannot be registered before it is diagnosed, the earliest serial number for each year of diagnosis marks the beginning of registrations for that diagnosis year. All the following serial numbers, until the earliest serial number for the next year of diagnosis, were allocated to the same registration year. Assuming that the time to registration is roughly six months on average, and that the average diagnosis date is half-way through the year, the registration date for all cases in the group was imputed as 1 January in the year following the diagnosis year of the first serial number. For example, since the lowest serial numbers for diagnosis years 1974 and 1975 are 800576 and 801764 respectively, all the index numbers from 800576 to 801763 were given the imputed registration date 1 January 1975. This is not very accurate, but it is probably adequate for 10-year completeness estimates: the mean imputed registration date is within a year of the mean recorded creation date for cases diagnosed in each year 1980-2004 (Table 4.2(a)).

4.2.3 Method

The UKACR provided a Stata program to implement the flow method, with detailed instructions for its use. Following these instructions (with the minor adaptations discussed in section 4.2.2), six sets of records were extracted from the NRCT on 3 July 2008, consisting of cases that were diagnosed during 1981, 1986 and 1991, and deaths that occurred during 1982-91, 1987-96 and 1992-2001 (see Table 4.2(b)). Skin carcinomas were excluded. The cases were broadly grouped by diagnosis (leukaemias, CNS tumours, and other cancers[*]) using the International Classification of Childhood Cancer [111], and by age at diagnosis (0-4, 5-9 and 10-14).

The program was used to estimate completeness of registration at 10 years from diagnosis for leukaemias, CNS tumours, other cancers and total cancers diagnosed in 1981, 1986 and 1991 at ages 0-4, 5-9, 10-14 and 0-14. 10 years was chosen as a time by which essentially all notifications would have been received. Two different versions of the program were tested, on the two different assumptions that the probability that a date

[*] Intra-cranial and intra-spinal germ-cell tumours were allocated to the CNS tumour category.

of diagnosis is obtained for DC-initiated cases who die at age>=15 is one (version 1) and zero (version 2).

To avoid a systematic difference between the estimates for 1981, 1986 and 1991, imputed dates of registration were used for all cases, and, since the deaths file for diagnosis year 1981 was unavoidably truncated at the earliest available diagnosis year (1974), the deaths files for 1986 and 1991 were truncated at the equivalent years (1979 and 1984). The average dates of diagnosis in the resulting deaths files were 1984, 1989 and 1994 respectively, i.e. reasonably close to the specified diagnosis years (Table 4.2(b)).

To test the sensitivity of the method, the analysis for 1991 (version 1) was repeated with variations. Imputed registration dates for diagnosis years 1974-79 and recorded creation dates for 1980-2004 gave almost the same results as imputed dates for 1974-2004. Truncating the deaths file for 1991 at 1974 instead of 1984 gave very slightly (within 1%) lower estimates of completeness, perhaps because the average date of diagnosis in the deaths file was slightly earlier (1993). To verify that there was no important increase in completeness of registration after 10 years from diagnosis, 20-year completeness was estimated for cases diagnosed in 1981; the estimates were almost the same as at 10 years.

4.2.4 Results

Table 4.2(c) gives estimates of completeness of ascertainment by the NRCT ten years after diagnosis, for cases diagnosed in 1981, 1986 and 1991, on the assumption that the true diagnosis date is obtained for all death-certificate-initiated registrations for childhood cancer deaths at any age (version 1). Table 4.2(d) gives the same estimates on the assumption of no direct or indirect notification from death certificates for deaths at age>=15 (version 2). For cases diagnosed in 1981, there was some evidence of incompleteness in both versions.

In version 1 for 1981, the all-ages overall completeness estimate was 0.96 (95% confidence interval 0.95 to 0.97). The completeness estimate was 0.97 (0.96 to 0.99) for leukaemias, 0.94 (0.91 to 0.97) for CNS tumours, and 0.98 (0.95 to 0.99) for other cancers. By age group, the lowest estimates were 0.93 (0.86 or 0.87 to 0.97) for CNS

tumours at ages 0-4 and 5-9, and 0.95 (0.90 to 0.98) for other cancers at ages 10-14 (Table 4.2(c)).

In version 2 for 1981, the all-ages completeness estimate was 0.93 (0.91 to 0.95). The completeness estimates for age group 10-14 were noticeably lower in version 2 than in version 1, i.e. 0.83 (0.76 to 0.88) compared with 0.98 (0.96 to 1.00) for leukaemias, 0.89 (0.82 to 0.95) compared with 0.96 (0.90 to 0.99) for CNS tumours, and 0.87 (0.81 to 0.92) compared with 0.98 (0.95 to 0.99) for other cancers (Tables 4.2(c) and 4.2(d)). The estimates in the two versions were similar for the other age groups.

For cases diagnosed in 1991, there was very little evidence of incompleteness. In version 1, the completeness estimate was at least 0.99 in every group of cases (Table 4.2(c)). As expected, in version 2, for the age group 10-14 only, the estimates were slightly lower: 0.95 (95% confidence interval 0.88 to 0.99) for leukaemia, and 0.98 for CNS tumours, other cancers and total cancers (Table 4.2(d)). For cases diagnosed in 1986, the completeness estimates generally fell between the corresponding estimates for 1981 and 1991, as expected.

4.2.5 Discussion

The overall estimates of 10-year completeness (depending on assumptions) were 93-96% for cases diagnosed in 1981, 97-99% for cases diagnosed in 1986, and 100% for cases diagnosed in 1991. These results appear to be consistent with contemporary reports of completeness for general cancer registration the mid-1980s [81] (93-100% in the best regional registries of England and Wales, but lower elsewhere - see Chapter 3), bearing in mind that the NRCT had an additional source of notification (the UKCCSG). The results are internally consistent, and appear to be reasonably robust, judging from the sensitivity analyses described in section 4.2.3.

The apparent improvement in completeness over time, seen in almost all age-diagnosis groups, is consistent with the increasing contribution of the UKCCSG register during the 1980s, and changes in the methods of the general cancer registries (see Chapter 3). The relatively low completeness estimates for CNS tumours in 1981, and (to a lesser extent)

1986, are consistent with the relatively low proportion of CNS cases referred to the UKCCSG in the 1980s: 36% compared with 64% of total cancers in 1981-84, and 56% compared with 76% of total cancers in 1989-92 [112].

In view of the various uncertainties outlined in section 4.2.2, these results must be interpreted with caution. A particular problem is death-certificate-initiated registrations for children who died after their 15th birthday. Since the effectiveness of the CRs' trace-back procedures cannot be estimated from the NRCT data, the completeness estimates are uncertain, particularly for older children. Tables 4.2(c) and 4.2(d) show that completeness of registration by the NRCT for age group 10-14 in 1981 might have been as low as 83% or as high as 98% for leukaemia, as low as 89% or as high as 96% for CNS tumours, and as low as 87% or as high as 98% for other cancers. Similar, but smaller, variation between Tables 4.2(c) and 4.2(d) is seen for 1986. Assuming that trace-back was not perfect, it seems likely that registration by the NRCT during the 1980s may have been rather less complete for older children than for younger children; if some CRs were more thorough than others, this kind of incompleteness would have varied between the regions.

In estimating the probability of notification at a given time from diagnosis, dead cancer patients are assumed to be representative of all cancer patients. This is less likely to be valid for the NRCT than for the CRs, because deaths are rarer (see Section 4.1). Patients who died may have had more contact with clinical services than the average childhood cancer patient, and therefore a higher chance of registration. If so, the flow method will under-estimate the time to registration, and over-estimate completeness, particularly for types of childhood cancer with high survival rates.

Patients who were successfully treated entirely in non-cancer specialist units (some patients with retinoblastoma, or tumours of bone or CNS, for example) would not be ascertained from death certificates, and might be missed by the CRs if notifications came only from cancer units. The flow method cannot make any assessment of this possibility.

Figure 4.2(a). Regional Cancer Registries (CR): registration status of a case at time T after diagnosis.

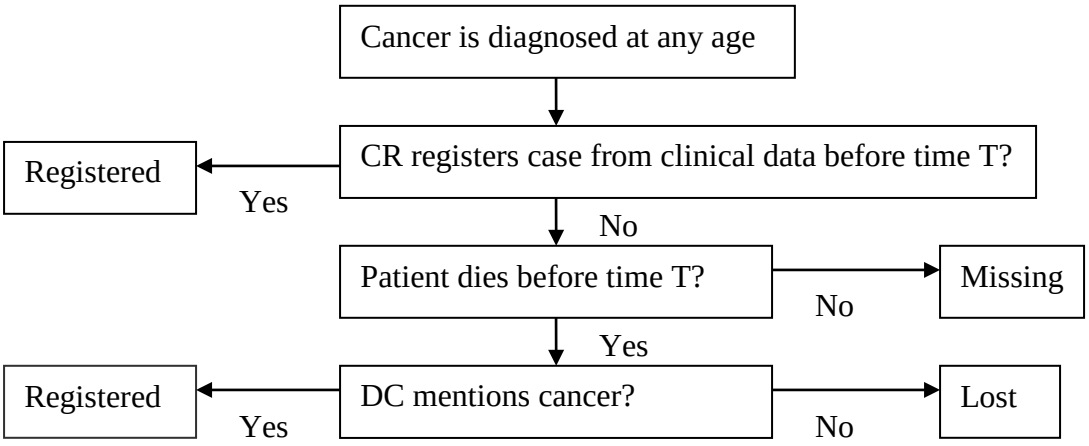
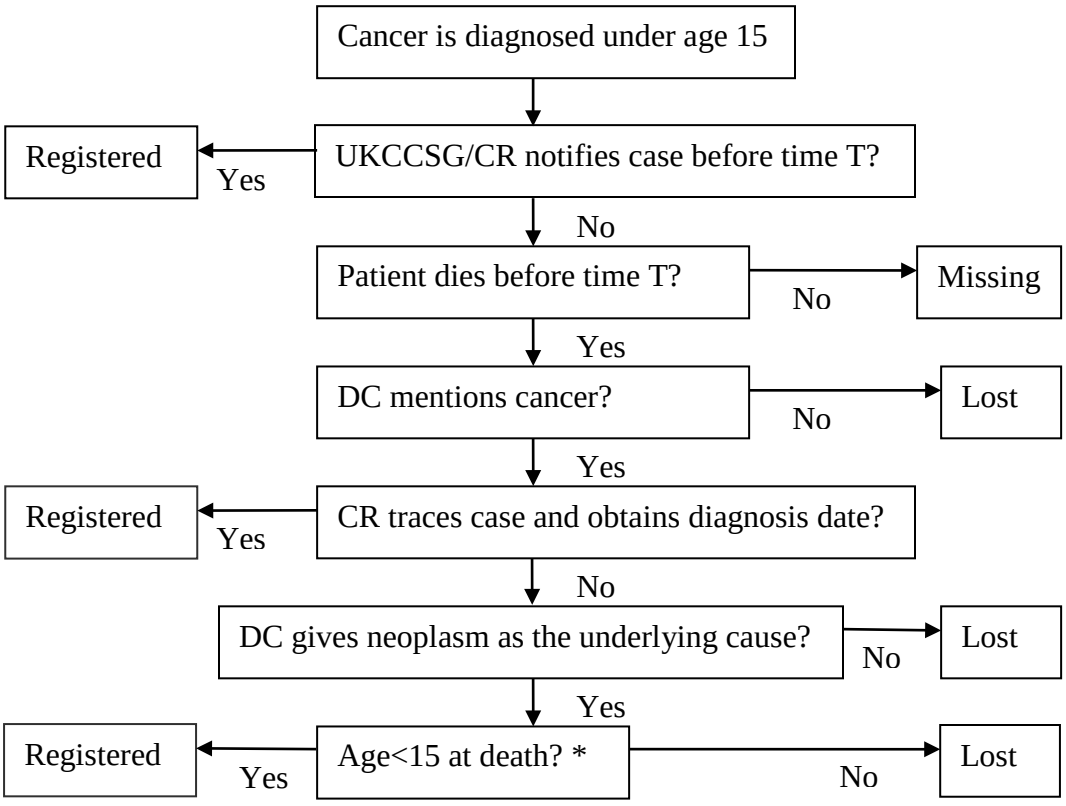


Figure 4.2(b). National Registry of Childhood Tumours (NRCT): registration status of a case at time T after diagnosis.



* The NRCT attempted to trace the date of diagnosis for directly-notified cancer deaths at age 15 up to the end of 1996.

Table 4.2(a). Comparison of mean imputed registration date with mean recorded creation date for NRCT cases by year of diagnosis 1974-2004.

Year of diagnosis	Mean creation date	Mean imputed date	Number of cases
1974	Not recorded	06-Dec-76	1320
1975	Not recorded	29-Mar-78	1353
1976	Not recorded	07-Mar-79	1386
1977	Not recorded	08-Nov-79	1353
1978	Not recorded	20-Sep-80	1294
1979	Not recorded	22-Sep-81	1208
1980	27-Mar-83	22-May-82	1214
1981	27-Mar-84	18-Oct-83	1164
1982	22-Nov-84	28-Jun-84	1218
1983	06-Jul-85	20-Jan-85	1189
1984	04-Apr-86	19-Dec-85	1225
1985	15-Jun-87	26-Mar-87	1222
1986	25-Apr-88	23-Nov-87	1210
1987	17-Jun-89	19-Jun-89	1315
1988	22-Mar-90	02-Feb-90	1300
1989	16-Feb-91	10-Apr-91	1235
1990	08-May-92	08-Jul-92	1395
1991	01-Sep-92	20-Nov-92	1329
1992	31-Aug-93	16-Dec-93	1398
1993	21-Jul-94	20-Sep-94	1434
1994	23-May-95	10-Jul-95	1464
1995	14-May-96	19-Aug-96	1485
1996	04-Jun-97	29-Jun-97	1425
1997	31-Jul-98	02-Jul-98	1482
1998	19-Jul-99	28-May-99	1442
1999	24-Jan-01	22-Aug-00	1499
2000	04-Mar-02	01-Aug-01	1417
2001	12-Aug-02	14-Jun-02	1492
2002	11-Sep-03	20-Jul-03	1632
2003	21-Nov-04	09-Aug-04	1469
2004	13-Sep-05	19-Apr-05	1516
Total			42085

Table 4.2(b). Specification of diagnosis and deaths files for flow program.

Diagnosis file		Deaths file			
Diagnosis year	Total cases	Death years	Earliest diagnosis year	Mean diagnosis year	Total cases
1981	1164	1982-1991	1974	1984	5072
1986	1210	1987-1996	1979	1989	4487
1991	1329	1992-2001	1984	1994	4106

Table 4.2(c). Estimated completeness of NRCT registration at 10 years from diagnosis, with 95% confidence limits (CI), by diagnostic group, age group and year of diagnosis. Version (1).

Year	1981		1986		1991	
Completeness	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Leukaemia						
0-4	0.97	0.94 to 0.99	0.99	0.97 to 1.00	1.00	1.00 to 1.00
5-9	0.99	0.97 to 1.00	0.98	0.96 to 1.00	1.00	0.98 to 1.00
10-14	0.98	0.96 to 1.00	0.98	0.95 to 1.00	0.99	0.95 to 1.00
Total	0.97	0.96 to 0.99	0.99	0.97 to 1.00	1.00	1.00 to 1.00
CNS tumours						
0-4	0.93	0.86 to 0.97	0.97	0.92 to 0.99	1.00	1.00 to 1.00
5-9	0.93	0.87 to 0.97	0.96	0.92 to 0.99	0.99	0.96 to 1.00
10-14	0.96	0.90 to 0.99	0.99	0.95 to 1.00	0.99	0.94 to 1.00
Total	0.94	0.91 to 0.97	0.98	0.95 to 0.99	1.00	0.98 to 1.00
Other cancers						
0-4	0.98	0.96 to 1.00	1.00	0.98 to 1.00	1.00	0.99 to 1.00
5-9	0.99	0.97 to 1.00	0.99	0.95 to 1.00	0.99	0.95 to 1.00
10-14	0.95	0.90 to 0.98	0.97	0.93 to 0.99	0.99	0.97 to 1.00
Total	0.98	0.95 to 0.99	0.99	0.98 to 1.00	1.00	0.99 to 1.00
Total cases						
0-4	0.96	0.94 to 0.97	0.99	0.97 to 1.00	1.00	1.00 to 1.00
5-9	0.97	0.95 to 0.99	0.98	0.96 to 0.99	0.99	0.98 to 1.00
10-14	0.97	0.95 to 0.99	0.98	0.95 to 0.99	0.99	0.98 to 1.00
Total	0.96	0.95 to 0.97	0.99	0.98 to 1.00	1.00	0.99 to 1.00

Assumption: the true diagnosis date is obtained for all death-certificate-initiated registrations for childhood cancer deaths at any age.

Table 4.2(d). Estimated completeness of NRCT registration at 10 years from diagnosis, with 95% confidence limits, by diagnostic group, age group and year of diagnosis. Version (2).

Year	1981		1986		1991	
Completeness	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Leukaemia						
0-4	0.98	0.96 to 1.00	1.00	1.00 to 1.00	1.00	1.00 to 1.00
5-9	0.99	0.98 to 1.00	1.00	0.98 to 1.00	1.00	1.00 to 1.00
10-14	0.83	0.76 to 0.88	0.91	0.84 to 0.96	0.95	0.88 to 0.99
Total	0.95	0.93 to 0.97	0.98	0.97 to 1.00	1.00	0.99 to 1.00
CNS tumours						
0-4	0.94	0.87 to 0.99	0.96	0.91 to 0.99	1.00	1.00 to 1.00
5-9	0.93	0.86 to 0.98	0.97	0.92 to 0.99	0.99	0.97 to 1.00
10-14	0.89	0.82 to 0.95	0.88	0.82 to 0.93	0.98	0.93 to 1.00
Total	0.92	0.88 to 0.95	0.94	0.91 to 0.96	0.99	0.98 to 1.00
Other cancers						
0-4	0.99	0.97 to 1.00	1.00	0.99 to 1.00	1.00	0.99 to 1.00
5-9	1.00	0.97 to 1.00	1.00	0.97 to 1.00	0.99	0.95 to 1.00
10-14	0.87	0.81 to 0.92	0.89	0.85 to 0.93	0.98	0.96 to 0.99
Total	0.95	0.92 to 0.97	0.97	0.95 to 0.98	1.00	0.99 to 1.00
Total cases						
0-4	0.98	0.96 to 0.99	0.99	0.98 to 1.00	1.00	1.00 to 1.00
5-9	0.98	0.95 to 0.99	0.99	0.97 to 1.00	0.99	0.98 to 1.00
10-14	0.85	0.82 to 0.88	0.88	0.84 to 0.91	0.98	0.96 to 0.99
Total	0.93	0.91 to 0.95	0.97	0.95 to 0.98	1.00	0.99 to 1.00

Assumption: no direct or indirect notification from death certificates for deaths at age>=15

4.3 Capture-recapture method and comparison between sources

4.3.1 Introduction

The analysis described in this section compares the numbers and characteristics of cases diagnosed during the two-year calendar period 2003-04, between the two main sources of ascertainment to the NRCT: the regional general cancer registries (CRs) and the UKCCSG. Estimates of completeness are made by the two-sample capture-recapture method [108], on the assumption that these sources were independent.

It is conceivable that referral patterns might vary with socio-economic status (SES). If children living in more deprived areas were less likely to be referred to a UKCCSG centre, they would be more likely to miss registration, because they would be more likely to have only one potential source of notification. To investigate this possibility, completeness estimates and the proportions of NRCT cases notified by the UKCCSG are compared between geographical areas of different levels of SES.

4.3.2 Background

Through the NRCT itself, there has always been a certain amount of informal or formal transfer of data between the UKCCSG register and the CRs. In the past, on request, the NRCT quite often supplied relevant data obtained from a CR to a local UKCCSG centre, or UKCCSG data to a CR. Since February 2007 there has been a system of regular quarterly data exchange between the NRCT and the CRs, which now routinely transfers data obtained from the CCLG (the UKCCSG's successor) to the CRs.

Data exchange handicaps the capture-recapture method. Any new notification from the NRCT to a source registry should be returned to the NRCT in a subsequent batch of data from that source. If this occurs, the NRCT will be unable to distinguish the case from cases supplied by that source which did not originate from the NRCT. Hence, the NRCT's sources are not independent, and the capture-recapture method is unlikely to be valid.

Fortunately, for this study, it was possible to construct an acceptable file for capture-recapture and the comparison of sources, by restricting coverage to a brief diagnosis period immediately before the start of the formal data exchange system.

4.3.3 Method

In February 2007, as the first stage of the new exchange system, registry staff at the CCRG supplied to each CR a copy of a file containing all existing NRCT registrations for cancers diagnosed during the three-year calendar period 2003-05 in residents of the CR's region. There had been no previous data transfer from the NRCT to any of the CRs, or to any UKCCSG centre, for this diagnosis period. The NRCT had received routine notifications from all its sources for diagnoses to the end of 2004. Routine notifications for 2005 were still incomplete.

For the present study, all these CR files were amalgamated, and cases diagnosed during 2005 were excluded. The resulting '2007' file was a nominally complete set of cases diagnosed during the two-year calendar period 2003-04, as notified to the NRCT by February 2007, before any transfer of data from the NRCT to its source registries.

To enable valid independent notifications received after February 2007 to be included, the 2007 file was compared with a file of the same specifications that was extracted from the NRCT in August 2008. During the intervening period there is thought to have been no transfer of data from the NRCT to any UKCCSG centre. The 2008 file contained 38 cases that were not in the 2007 file. These cases were appended to the 2007 file. In the combined file, each case was counted as a UKCCSG notification if it had been received from the UKCCSG by August 2008, and as a CR notification if either it was in the 2007 file as CR notification, or it was not in the 2007 file, but had been received by August 2008 as a CR notification. The potential for dependence between sources among the 38 extra cases seems slight. Only 9 of these cases were notified by both a CR and the UKCCSG, and therefore could possibly have been post-February-2007 UKCCSG notifications transferred to the CR through feedback from the NRCT. All the remaining 29 cases were notified by only one source and so could not have derived from NRCT feedback. 18 cases from the 2007 file were not in the 2008 file because they had been

found to be ineligible for the NRCT after the 2007 file was extracted; these were deleted. 3 cases were excluded because they were notified to the NRCT only by death certificate, and not by a CR or the UKCCSG. There were 3005 cases in the remaining analysis file.

The cases were grouped by CR region of residence at diagnosis, by age at diagnosis (0, 1-4, 5-9 and 10-14), and by the 12 main diagnostic groups defined by the first level of the ICCC3 classification [111]. For each of these categories, the proportions of cases notified by the two sources were compared, and maximum-likelihood estimates of completeness of registration were calculated by the conventional two-sample capture-recapture method [108].

Two approaches were used to investigate the possibility of an association between SES and the probability of registration. Firstly, the cases were grouped by quintile category (within 1981 census wards in Britain) of the 1981 Carstairs deprivation index for the census ward in which each child lived at the time of diagnosis [*]. Three broad diagnostic groups were defined: leukaemia, CNS tumours (including CNS germ-cell tumours) and other cancers. The sources were grouped as non-UKCCSG (CR only) and UKCCSG (both or UKCCSG only). In each age-diagnosis group, the proportions of cases notified by the UKCCSG in the various SES categories were compared by Fisher's exact test for multiple categories (Stata version 10). Secondly, cases from England and Wales (excluding skin carcinoma and previously non-malignant non-CNS diagnoses as defined in Chapter 5) were grouped by child-population-weighted quintile category (within 2001 census wards in England and Wales) of the 2001 Carstairs deprivation index, and separate capture-recapture completeness estimates were made for each SES category within each age-diagnosis group.

4.3.4 Results

Of the 3005 cases that were notified by the UKCCSG, a CR, or both, 85% (2552) were notified by both the UKCCSG and a CR, 8% (229) were notified by the UKCCSG and not by a CR, and 7% (224) were notified by a CR and not by the UKCCSG.

[*] For this analysis, the quintiles were not population-weighted, and the score could not be assigned for 15 cases. The 1981 Carstairs index was used because more recent available Carstairs indices did not include Scotland – see Section 5.2.5

The first section of Table 4.3(a) shows the distribution of sources of notification according to the CR region in which the child lived at the time of diagnosis, irrespective of whether the CR actually notified the case or not. The proportion of cases notified both by a CR and by the UKCCSG varied by region, from 95% in West Midlands to 73% in Thames. The proportion notified only by the UKCCSG was much higher for patients resident in the Thames region (18%) than elsewhere: the CR missed 22% of the 227 Thames patients notified from Great Ormond Street Hospital, and 44% of the 109 Thames patients from St Bartholomew's, the Middlesex and the Royal London Hospitals. 22% of registrations for Wales were not notified by the UKCCSG. On the assumption that the sources are independent, the estimated completeness of NRCT registration was 98% in Thames, 99% in Trent, Eastern region, and Scotland, and 100% elsewhere.

The second section of Table 4.3(a) shows the distribution of sources of notification by age group at diagnosis. The CRs tended to miss younger patients, particularly infants: 12% of cases diagnosed under age 1 were notified only by the UKCCSG, compared with 6% at ages 10-14. The UKCCSG tended to miss older patients: 13% of patients aged 10-14 at diagnosis were notified only by a CR, compared with 4% at ages 1-4 and 7% at age 0. On the assumption that the sources are independent, the estimated completeness of NRCT registration was 100% at age 1-4, and 99% in the other age groups.

The third section of Table 4.3(a) shows the distribution of sources of notification by diagnostic group. The CRs tended to miss retinoblastoma: 17% of cases were notified by the UKCCSG only. Both the UKCCSG and the CRs tended to miss 'germ-cell tumours and gonadal neoplasms': only 72% of cases were notified by both these sources. The UKCCSG notified nearly all (97-100%) cases of the typical early-childhood cancers (leukaemia, neuroblastoma, retinoblastoma, renal and hepatic tumours), but missed 6-8% of lymphomas, CNS tumours and sarcomas of soft tissue and bone, and more than half of 'other carcinomas and melanoma'. 'Other and unspecified malignant neoplasms' and various relatively unspecified diagnostic subgroups (not shown) were much more often notified by CRs than by the UKCCSG. On the assumption that the sources are independent, the estimated completeness of NRCT registration was 100% for leukaemias, neuroblastoma, renal and hepatic cancers and soft tissue sarcomas, and 99% for the other

specified groups, except ‘germ-cell tumours and gonadal neoplasms’ (97%) and ‘other carcinoma/melanoma’ (95%).

Table 4.3(b) shows the distribution of cases by source and SES category for each age group, separately for leukaemias, CNS tumours and other cancers. There was no statistically significant association between source and SES in any of the age-diagnosis groups ($p>0.05$). For leukaemias diagnosed at age 1-4, in particular, the proportions of UKCCSG-notified cases were very similar in all SES categories, and there was no apparent trend with SES.

Tables 4.3 (c) to (e) show completeness estimates by age-diagnosis group and SES category, on the assumption that the sources are independent. All estimates are at least 98%. For leukaemias, in every age group the completeness estimate is 100% in each of the two most deprived categories; in the age group 1-4 the estimate is 100% in all five SES categories. In the other diagnostic groups, the estimated level of completeness is consistently very high, and there is little or no suggestion of systematic variation with SES (with the possible exception of slightly lower completeness in the most deprived categories for non-CNS solid cancer diagnosed at age 0).

4.3.5 Discussion

The capture-recapture estimates of completeness of registration were very high in almost all groups of cases. Completeness was estimated as 100% in almost all regions; the exceptions were 99% in Trent, Eastern region and Scotland, and 98% in the Thames region. The completeness estimate was 100% at ages 1-4 and 99% in the other age groups; and 99-100% in almost all the other diagnostic groups. The slightly lower estimates for Scotland and the Thames region are consistent with the recognized difficulties of cancer registration in these areas (see Chapter 3).

The regional cancer registration system and the UKCCSG each notified 92-93% of the NRCT registrations for cases diagnosed in Britain during the two-year period 2003-04. Although these overall proportions were similar, the characteristics of the cases notified by the two sources were different.

As expected, the overall proportions notified by the UKCCSG were very high for the 'typical' cancers of childhood: 97-100% of leukaemia, neuroblastoma, retinoblastoma, and renal/hepatic tumours, and 96% of all cases diagnosed at ages 1-4. In contrast, the UKCCSG notified only 87% of cases diagnosed at age 10-14, probably because older children, and children with cancers that are usually seen in adults, are more likely to be treated in specialist centres that are not specifically paediatric.

The CRs notified 93-94% of cases in each of the over-0 age groups, but only 88% of cases in age group 0. The CRs notified almost all cases in Wales and the South West, and 90-95% of cases in most other regions. The Thames registry, on the other hand, appears to have had difficulty in obtaining registration data from some of the London teaching hospitals, and missed 18% of patients resident in its region. A similar problem probably explains the relatively high proportion (17%) of retinoblastoma cases that were missed by the CRs: locally, patients may be seen by ophthalmologists rather than cancer specialists, and one of the two national treatment centres for retinoblastoma is in London. Fortunately for the completeness of NRCT registration, cases from these hospitals should be reliably ascertained through the UKCCSG.

The CRs were much more likely than the UKCCSG to give vague or unusual diagnostic details, involving either the diagnostic group XII ('other/unspecified malignancies') (Table 4.3(a)), or various histologically-unspecified subgroups of the main diagnostic groups (not shown). Two-thirds of cases in group XII (14/22) were from Wales and notified only by the Welsh CR. Possible explanations might include a higher standard of diagnostic accuracy and specificity in the UKCCSG centres, or a tendency to refer only definite cancer cases to the centres. Only 72% of 'germ-cell tumours and gonadal neoplasms' were notified by both the UKCCSG and the CRs - probably because most cases in this group are diagnosed either in infancy or in adolescence, the ages at which, respectively, CR and UKCCSG registration is apparently less complete.

The analyses reported here found almost no evidence to suggest that children living in more affluent areas of Britain were more likely to be notified to the NRCT than children from more deprived areas, in any age-diagnosis group. In particular, variation in

completeness of registration is not likely to account for any association between higher SES and recorded incidence of childhood leukaemia in recent records from the NRCT.

The justification of this method relies on the assumption of independence of sources. Using a file extracted before transfer of data from the NRCT (see Section 4.3.2) ensures that the two sources are not linked through the NRCT. However, registration by both systems depends on the NHS clinical service, and there could well have been formal or informal exchange between the systems before the notifications were sent to the NRCT. (For example, there was some data exchange during the 1990s between the clinical database in the Oxford paediatric oncology unit, which was the source of notifications for the Oxford centre to the UKCCSG, and the Oxford regional CR.) In this analysis, the very low proportions of cases notified only by the UKCCSG in Wales and the South West suggest the possibility of data transfer from the UKCCSG centre to the regional CR. If this occurred, the capture-recapture method would over-estimate completeness for these regions.

Like the flow method, the capture-recapture method cannot assess the possibility that the CRs might have tended to miss patients who were successfully treated entirely in non-cancer units.

Table 4.3(a). Sources of notification and estimated completeness of NRCT registration, by CR region of residence at diagnosis, by age group at diagnosis, by diagnostic group (first level of ICCC3), and overall. Britain 2003-04.

	Total number of cases	% UKCCSG and CR	% UKCCSG only	% CR only	Estimated completeness of NRCT
CR region of residence					
at diagnosis:					
Northern & Yorkshire	328	89.6	6.4	4.0	1.00
Trent	266	86.1	6.4	7.5	0.99
Eastern	292	81.9	9.9	8.2	0.99
Thames	559	72.5	18.4	9.1	0.98
Oxford	160	91.3	2.5	6.3	1.00
Wales	147	78.2	0.0	21.8	1.00
West Midlands	295	94.9	2.4	2.7	1.00
North West	221	87.8	5.4	6.8	1.00
Mersey	126	87.3	8.7	4.0	1.00
South West	338	90.5	0.9	8.6	1.00
Scotland	273	85.7	6.2	8.1	0.99
Age at diagnosis:					
0	304	80.6	12.2	7.2	0.99
1-4	995	88.7	7.3	3.9	1.00
5-9	813	86.2	7.0	6.8	0.99
10-14	893	81.0	6.4	12.7	0.99
Diagnostic group:					
I Leukaemias	959	88.8	8.0	3.1	1.00
II Lymphomas	271	86.0	8.1	5.9	0.99
III CNS neoplasms	719	86.4	5.7	7.9	0.99
IV Neuroblastoma	188	87.2	9.6	3.2	1.00
V Retinoblastoma	83	80.7	16.9	2.4	0.99
VI Renal tumours	170	90.6	7.7	1.8	1.00
VII Hepatic tumours	34	100.0	0.0	0.0	1.00
VIII Mal. bone tumours	128	84.4	8.6	7.0	0.99
IX Soft-tissue sarcomas	232	86.6	5.2	8.2	1.00
X Germ-cell/gonadal	100	72.0	11.0	17.0	0.97
XI Other carc/melanoma	99	43.4	4.0	52.5	0.95
XII Other/unspec. mal.	22	13.6	4.6	81.8	0.79
Total	3005	84.9	7.5	7.6	0.99

Number of NRCT registrations; proportions notified by UKCCSG, by a CR, or both; estimated completeness of NRCT registration for cases diagnosed 2003-04, on the assumption of independence of notification by UKCCSG and by CRs.

Table 4.3(b). Variation across SES categories (1 = most affluent, …, 5 = most deprived) in the proportion of NRCT cases notified by the UKCCSG, by age group within diagnostic group. Britain 2003-04.

SES	1		2		3		4		5		Het.
UKCCSG / any source	%	N	%	N	%	N	%	N	%	N	P
Leukaemias											
0	92.3	13	88.9	9	92.9	14	95.0	20	94.4	18	0.96
1-4	98.5	66	97.3	73	97.5	80	98.8	86	97.5	121	0.96
5-9	97.7	43	95.0	40	98.4	62	98.4	62	100.0	62	0.45
10-14	92.5	40	89.3	28	93.5	31	97.4	38	100.0	50	0.11
Total	96.3	162	94.7	150	96.8	187	98.1	206	98.4	251	0.22
CNS											
0	100.0	3	100.0	4	83.3	6	100.0	14	100.0	7	0.38
1-4	94.1	34	87.5	40	94.3	35	89.8	49	96.3	54	0.51
5-9	92.3	39	85.7	35	88.0	50	93.9	49	96.9	64	0.24
10-14	94.4	36	91.7	36	92.2	51	89.8	49	96.6	58	0.67
Total	93.8	112	88.7	115	90.8	142	91.9	161	96.7	183	0.07
Other											
0	89.5	19	100.0	22	95.0	40	88.9	45	91.3	69	0.52
1-4	95.9	49	98.2	57	100.0	57	93.6	94	97.9	96	0.22
5-9	94.1	51	91.9	37	86.3	51	94.2	69	89.5	95	0.56
10-14	80.6	72	83.6	67	79.1	91	81.8	99	84.4	141	0.86
Total	89.0	191	91.8	183	88.3	239	89.3	307	90.0	401	0.81

Number (N) of NRCT registrations, by unweighted quintile category (SES) of 1981 Carstairs deprivation index for census ward of residence; proportion of cases (%) notified by UKCCSG; result (P) of Fisher's exact test for heterogeneity in proportions between SES categories.

Table 4.3(c). Leukaemia, England and Wales 2003-04.
Sources of notification and estimated completeness of NRCT registration by SES category (1 = most affluent, …, 5 = most deprived) and age at diagnosis.

Age at diagnosis	SES	Total number of cases	N UKCCSG and CR	N UKCCSG only	N CR only	Estimated completeness of NRCT
0	1	10	10	0	0	1.00
	2	13	10	1	2	0.98
	3	14	11	1	2	0.99
	4	17	14	3	0	1.00
	5	14	12	0	2	1.00
1-4	1	75	66	7	2	1.00
	2	91	84	6	1	1.00
	3	79	72	5	2	1.00
	4	70	62	7	1	1.00
	5	86	72	13	1	1.00
5-9	1	60	56	2	2	1.00
	2	48	44	4	0	1.00
	3	45	42	3	0	1.00
	4	43	40	1	2	1.00
	5	37	31	6	0	1.00
10-14	1	37	27	4	6	0.98
	2	41	37	2	2	1.00
	3	30	27	3	0	1.00
	4	28	25	2	1	1.00
	5	29	22	7	0	1.00

Number of NRCT cases within each age group, by child-population-weighted quintile category (SES) of 2001 Carstairs index for census ward of residence; number (N) notified by UKCCSG, by a CR, or both; estimated completeness of NRCT registration for cases diagnosed 2003-4 on the assumption of independence of notification by UKCCSG and by CRs.

Table 4.3(d). CNS tumours, England and Wales 2003-04.
Sources of notification and estimated completeness of NRCT registration by SES category (1 = most affluent, …, 5 = most deprived) and age at diagnosis.

Age at diagnosis	SES	Total number of cases	N UKCCSG and CR	N UKCCSG only	N CR only	Estimated completeness of NRCT
0	1	6	6	0	0	1.00
	2	3	2	1	0	1.00
	3	9	9	0	0	1.00
	4	6	5	0	1	1.00
	5	6	6	0	0	1.00
1-4	1	33	27	3	3	0.99
	2	45	37	2	6	0.99
	3	42	38	0	4	1.00
	4	47	44	0	3	1.00
	5	26	26	0	0	1.00
5-9	1	53	47	1	5	1.00
	2	43	38	1	4	1.00
	3	35	31	1	3	1.00
	4	41	37	1	3	1.00
	5	44	35	8	1	0.99
10-14	1	38	33	2	3	1.00
	2	55	49	2	4	1.00
	3	52	49	2	1	1.00
	4	34	26	4	4	0.98
	5	38	35	2	1	1.00

Number of NRCT cases within each age group, by child-population-weighted quintile category (SES) of 2001 Carstairs index for census ward of residence; number (N) notified by UKCCSG, by a CR, or both; estimated completeness of NRCT registration for cases diagnosed 2003-4 on the assumption of independence of notification by UKCCSG and by CRs.

Table 4.3(e). Non-CNS solid cancer, England and Wales 2003-04.
Sources of notification and estimated completeness of NRCT registration by SES category (1 = most affluent, …, 5 = most deprived) and age at diagnosis.

Age at diagnosis	SES	Total number of cases	N UKCCSG and CR	N UKCCSG only	N CR only	Estimated completeness of NRCT
0	1	29	23	4	2	0.99
	2	37	34	1	2	1.00
	3	25	16	9	0	1.00
	4	41	29	9	3	0.98
	5	49	38	6	5	0.98
1-4	1	75	67	6	2	1.00
	2	49	44	3	2	1.00
	3	58	52	5	1	1.00
	4	77	65	5	7	0.99
	5	61	52	9	0	1.00
5-9	1	56	48	5	3	0.99
	2	48	38	5	5	0.99
	3	55	48	1	6	1.00
	4	58	50	3	5	0.99
	5	52	45	6	1	1.00
10-14	1	84	69	4	11	0.99
	2	80	60	3	17	0.99
	3	83	67	6	10	0.99
	4	78	59	1	18	1.00
	5	86	68	9	9	0.99

Number of NRCT cases within each age group, by child-population-weighted quintile category (SES) of 2001 Carstairs index for census ward of residence; number (N) notified by UKCCSG, by a CR, or both; estimated completeness of NRCT registration for cases diagnosed 2003-4 on the assumption of independence of notification by UKCCSG and by CRs.

4.4 Cross-check with Hospital Episode Statistics

4.4.1 Introduction

This section describes a cross-check between the NRCT and the national Hospital Episode Statistics (HES) database, for leukaemia patients who were born in 1998 and diagnosed before the end of 2004.

If there is any serious defect in the registration process for leukaemia recently diagnosed in early childhood, it should appear in this cross-check, because treatment of acute leukaemia almost always involves admission to hospital. If registration of childhood leukaemia is incomplete, there should be some patients in the HES data who are not known to the NRCT; if registration is biased, there might be evidence that these children were treated in non-specialist centres, or lived in relatively deprived areas.

4.4.2 Background

The HES system provides an electronic record of each in-patient episode since April 1997 at any NHS-funded treatment centre in England (for patients resident anywhere), or in Wales (for residents of England only). The level of completeness should be high, as the system uses data kept for management purposes. Every episode includes one or more diagnosis code(s) as contributing cause(s) of the episode, up to a maximum of 14.

No names are supplied, but each episode is marked with a HES identification number (ID), which is allocated automatically by the central HES database, from an algorithm based on the NHS number (given for most but not all episodes), date of birth, sex, post code, etc. Episodes with the same ID can be assumed to refer to the same patient. However, episodes with different IDs do not necessarily refer to different patients, because the differences may reflect change, error or incompleteness in the identifying data.

The date of diagnosis is essential for identifying and selecting patients. It is not explicitly recorded in HES, but should be approximately the date of the patient's first episode with the relevant diagnosis code, provided that the HES file contains a complete record of all

episodes in each patient's life. To ensure that the HES records covered each child's whole life, allowing for a possibly incomplete start-up period during 1997, children born before 1998 were excluded from this cross-check.

Leukaemia should be a relatively easy diagnosis to trace in the HES data, because its treatment often involves many hospital admissions. As discussed in Section 4.1, leukaemia diagnosed at ages 1-4 is of particular interest, because of the possibility that registration bias might explain the association of childhood leukaemia with SES. At the time the cross-check was done, NRCT data were available for diagnoses up to the end of 2004. For the birth cohort of 1998, this provides complete follow-up from age 0 to age 5 completed years, i.e. the age group 1-4, as required, with a margin of a year on each side. This comparison was therefore restricted to children born in 1998.

The cross-check was carried out in November 2008. At that time, the CCRG held HES data for the time period 1 April 1997 to 30 June 2007, and the NRCT had received all routine notifications for cases diagnosed up to the end of 2004. The HES IDs had been linked to the NRCT cases at the CCRG by means of the NHS number, or if that failed, through the combination of date of birth, sex, and post code (of the home address at the time of the episode (for HES), or at birth, diagnosis or death, as available (for the NRCT)).

4.4.3 Method

All episodes with the following specifications were extracted from the HES data:

Year of birth of patient: 1998

Diagnosis: Leukaemia (ICD-10 code C91 to C95) in any of the 14 diagnosis codes

Residence: England.

The episodes were grouped by HES identification number (ID), and sorted by episode date within ID. Any ID with first episode after the end of 2004 was excluded. The episodes and identifying data for the remaining IDs, including the index numbers of their matched NRCT cases, constituted the 'HES' file.

An equivalent 'NRCT' file was extracted from the NRCT in October 2008, consisting of children resident in England at diagnosis, born in 1998, and diagnosed with leukaemia before the end of 2004.

The HES and NRCT files were compared. Episodes for unmatched HES IDs, unmatched NRCT cases, and HES IDs matched to ineligible NRCT cases, were listed and checked manually.

4.4.4 Results

There were 432 different IDs in the HES file, of which 390 (90%) had been matched to a case in the NRCT.

42 IDs were not matched to any NRCT case. None was recorded as having died, and 31 had five or fewer episodes; 21 had only one episode. Identifying information was often incomplete. The episodes were grouped by birthdate, sex, postcode and NHS number, as available. This reduced the 42 IDs to 26 probably distinct patients. They were compared with the main NRCT database (for birthdate, sex, diagnosis, and episode dates), and with the NRCT's records of excluded cases. Of these 26, nine appeared to be possible matches for NRCT cases that had already been linked to other IDs in the HES file, and four were definite matches for excluded cases. Checking the full HES database, four patients (representing eight 'leukaemia' episodes altogether) appeared to have a non-leukaemia diagnosis - beta thalassaemia (2), autoimmune haemolytic anaemia (1), idiopathic thrombocytopenic purpura (1). Only nine patients could not be at least tentatively accounted for. Of these, seven may have been unidentified treatment fragments or errors, since they represented only 11 'leukaemia' episodes altogether. The remaining two patients, who had 37 and 44 episodes respectively, were traced by enquiry at the relevant treatment centres, and were both found to be genuine but ineligible for the NRCT because not resident in Britain at diagnosis.

There were 273 cases in the NRCT file, of which 269 were matched to at least one HES ID. Of the four not matched to patients in the HES file, one had congenital acute leukaemia of unspecified type and died at 4-5 months old. The other three had acute

myeloid leukaemia: one died at 3 days old; one was diagnosed and treated at a private hospital, was referred to Great Ormond Street Hospital at relapse for a second opinion (which may not have involved an in-patient stay), and died 3 days later; and one was resident in England when diagnosed at 2-3 months old, but resident in Wales when registered by the CR at 10 months old. If, as seems quite possible, none of these patients was seen as a NHS in-patient while resident in England, then it is correct that none of them appears in the HES file. All but 9 of the NRCT patients were seen in a UKCCSG centre.

Of the 390 matched IDs, 362 were linked to 269 distinct eligible NRCT cases. Where more than one HES ID was linked to the same NRCT case, the central HES system had presumably failed to identify the IDs as referring to the same child. The remaining 28 matched HES IDs should not have been eligible for the HES file, according to the information held by the NRCT: two had birth year 1997, not 1998; three were not English residents at diagnosis; and 23 were non-leukaemias, comprising non-cancer (7), lymphoma (4), CNS tumour (3), neuroblastoma (5), retinoblastoma (1), renal tumour (2) and hepatic tumour (1). The five birth year and residence discrepancies can be explained respectively as minor inaccuracy and incompleteness in the HES data. The non-leukaemia cases are probably explained by diagnostic uncertainty in the HES data. It is possible that some might represent secondary leukaemia following treatment for solid cancer: according to the NRCT most of the relevant patients were diagnosed at least six months before the first HES leukaemia episode, and several died soon afterwards.

4.4.5 Discussion

After careful examination, the agreement between the NRCT and HES for this set of records appears to be good. On the assumption that 42 unmatched and 28 apparently ineligible IDs in HES are correctly explained by duplication and inaccuracies, as described above, the number of leukaemia patients who were born in 1998 and diagnosed before 2005, while resident in England, was 273 in the NRCT and 269 in HES. 269 cases occurred in both HES and the NRCT. The other four cases were apparently not seen as NHS in-patients while resident in England, and hence were probably not eligible for the HES file.

A previous study based on NRCT data for 1986-95 found that the reported incidence of lymphoid leukaemia at ages 1-4 (but not at ages 0 or 5-14) was higher in more affluent areas of England and Wales [110]. From the HES comparison described here, it seems unlikely that registration bias could explain a similar association in more recent years. Successfully-treated acute leukaemia cases should appear in the HES data, because the treatment almost always involves NHS in-patient episodes; any other cases should be notified to the NRCT through death certification. There was no convincing evidence that any leukaemia patient resident in England, diagnosed at ages 0-5, and known to HES, was unknown to the NRCT, and almost all these patients were seen at a UKCCSG centre.

From the available HES data it was not possible to investigate whether there was a deficit in NRCT registration among children older than 5-6. The comparison would ideally be extended to a longer time period, and other age-diagnosis groups.

4.5 Conclusions

Three different approaches to estimating completeness of registration of diagnosed cases by the NRCT are investigated in this chapter; each has its strengths and limitations. The flow method produces estimates for the past, so that changes over time can be investigated, but involves a complicated modelling process. The capture-recapture method is relatively simple, but (here) is limited to a brief recent time period. The HES comparison is in principle the most straightforward method, but is limited to a recent time period, and (here) to a single diagnostic group.

The flow method suggests that overall completeness of registration by the NRCT improved slightly over time, from 93-96% for cases diagnosed in 1981 (depending on assumptions), to 97-99% in 1986, and to very nearly 100% in 1991. For cases diagnosed in 1981 completeness was probably a few percentage points lower for CNS tumours than for leukaemias or other cancers, and may have been as much as 15% less complete for the age group 10-14 than for the younger age groups.

The capture-recapture method suggests that completeness of NRCT registration for cases diagnosed during 2003-04 was very high (99-100%) in all regions and age groups, and in almost all diagnostic groups, including leukaemia. The CRs and the UKCCSG each notified 92-93% of cases. The CRs tended to miss younger children, particularly infants, and retinoblastoma. The UKCCSG tended to miss older children and ‘adult’ cancers. CR notifications were low from the Thames region, and UKCCSG notifications were low from Wales. There was no indication that completeness of registration varied systematically with the SES category of the patient’s address at diagnosis, either for leukaemia cases diagnosed at age 1-4, or (with the possible exception of non-CNS solid cancer at age 0) in any other age/diagnosis group.

The HES comparison found no convincing evidence that the NRCT failed to register eligible patients recorded by HES who were born in 1998 and diagnosed with leukaemia before 2005 while resident in England. There was no evidence of a deficit of these cases from relatively deprived areas.

Although the three sets of results seem reasonable, and are consistent with each other, each method involves some uncertainty. The HES comparison required some rather subjective assessment of imperfect data. The flow and capture-recapture methods involved assumptions about the registration system that may not be entirely justified for the NRCT. Moreover, neither of these methods would be able to detect non-registration of patients who were successfully treated in non-cancer centres. The HES comparison suggests that this problem is unlikely to affect leukaemia registration, but it is a real possibility for some other diagnostic groups.

Both the HES comparison and the internal comparison of sources during 2003-04 suggest that it is unlikely that any recent association between SES and childhood leukaemia in the NRCT could be caused by biased ascertainment of diagnosed cases.

Chapter 5
Variation in recorded incidence over time

5.1 Introduction

5.1.1 Scope of this chapter

This chapter presents a detailed analysis of variation over time in reported incidence rates of childhood cancer in Britain during 1966-2005, by year of birth and by year of diagnosis. For three broad subtypes (leukaemia, CNS tumours and non-CNS solid cancers) the analysis includes an investigation of changes over time in the geographical variation of recorded incidence within England and Wales. Results are discussed in relation to the history of diagnostic and registration methods described in Chapters 2 and 3; first separately for each of 14 diagnostic groups, in section 5.3, and then jointly for the analysis as a whole, in section 5.4.

5.1.2 Predicted effects of changes in methods for diagnosis and registration

There are several possible ways in which changes in methods for diagnosis and registration of childhood cancer could have led to changes in recorded incidence.

The process of death certification is not infallible. Autopsy following death in childhood is not usual, except in cases of suspected non-accidental injury. Cancer can affect almost any bodily function. It is quite possible that a child could die from an underlying cancer without cancer ever being diagnosed, and that the death could be certified as due to non-malignant disease. As diagnostic techniques improved, non-diagnosis of cancer would become less likely, and cancer registration rates would increase.

Cases of neuroblastoma (and possibly some other types of childhood cancer) occasionally remit without treatment. As diagnostic techniques improved, these cases would be more

likely to be diagnosed before spontaneous remission, and registration rates would increase.

For most types of childhood cancer, improvements in diagnostic techniques would lead to diagnosis at an earlier stage of disease. Effects on registration rates would depend on the distribution of age at diagnosis. For cancers that can occur in adolescence, the age-standardised rate for ages 0-14 would be expected to increase, because registrations in the later period would include some patients who previously would not have been diagnosed until age 15 or older. For cancers that are relatively common in adolescence, such as lymphoma and melanoma/carcinoma, the increase in the age-standardised rate would be particularly noticeable, and the rates in later childhood would be expected to increase more than the rates in earlier childhood. For cancers that are rare after childhood, such as renal cancer and retinoblastoma, the age-standardised rate would not change, because there is no source of extra cases: the rates would be expected to increase in infancy and early childhood and decrease in later childhood.

In the past, regional general cancer registries may have tended to miss successfully-treated patients not seen in specialist cancer treatment centres - for example, retinoblastoma patients treated in local ophthalmology units. Mandatory cancer registration from 1993, and other initiatives to improve the completeness of the regional registries, might reduce the chance of these cases being missed. They would not be notified to the NRCT from any other source.

In the early part of the study period, the exact diagnosis was probably sometimes rather uncertain. Subsequent improvements in accuracy would be expected to create time trends in the various possible choices of diagnosis. With the intention of minimising this effect, the diagnostic groups in section 5.3 are defined mainly by primary site rather than histology, because site is likely to be more reliable than histology. However, even the site is not always easy to identify - particularly at a late stage, when disease is disseminated through the body – and some shift between diagnostic groups is to be expected.

Changes in registration methods over time should improve the accuracy and completeness of registration. The proportion of relatively unspecified diagnostic

subgroups is expected to decrease. Overall increases in rate are more likely to be visible in regions, age groups and diagnostic groups that were relatively incomplete towards the start of the study period. From the results of Chapters 3 and 4, it can be tentatively suggested that these might be the Thames region, Scotland and Wales, and the age and diagnostic groups that were likely to be treated outside specialist paediatric oncology units (particularly if non-fatal), i.e. ages 0 and 10-14; and retinoblastoma, melanoma/carcinoma, and less-aggressive tumours of CNS and bone.

Based on the results of Chapters 2 and 3, Table 5.1 lists the approximate timing of some important changes in methods for diagnosis and registration. Corresponding effects on recorded incidence would be expected to show more clearly by year of diagnosis than by year of birth. Artefacts of registration might be expected to produce variation in rates by region, because of the probable differences of completeness of registration by the various regional cancer registries, particularly in the earlier part of the study period. Artefacts of diagnosis might produce variation in the rates by region if new diagnostic methods were introduced at different times in different regions, and by SES if clinical provision was better in more affluent geographical areas.

The effects of any sudden changes in real risk factors would appear as sudden changes in the rates by year of diagnosis if the risk factors acted shortly before the time of diagnosis, or as sudden changes in the rates by year of birth if the factors acted around the time of birth, or during gestation.

Not all the differences discussed in Section 5.5 are tested formally, and some, although of interest, may not be statistically significant.

Table 5.1. Approximate timing of selected events in the history of diagnostic and registration methods for childhood cancer in Britain (see Chapters 2 and 3).

Short description	Longer explanation	Year
CR revised scheme	Revised scheme for general cancer registration	1971
Catecholamines	Assay of urinary catecholamines as test for neuroblastoma	1975
CR by residence	Cancer registration by region of residence, not diagnosis	1978
UKCCSG	First full year of registration by clinicians' organisation	1978
US	Ultrasound scanning for diagnosis of solid tumours	1986
CT	CT scanning for diagnosis of solid tumours	1986
AFP/BHCG	Serum hormone assays for hepatic and germ-cell tumours	1986
IHC (leukaemia)	Immunohistochemistry for sub-classification of leukaemia	1986
MRI	MRI scanning for diagnosis of solid tumours	1992
IHC	Immunohistochemistry for diagnosis of solid tumours	1992
MIBG	MIBG scanning for neuroblastoma	1992
CR mandatory	General cancer registration scheme becomes mandatory	1993
CR action plan	Additional funding to promote completeness of registration	2001

5.2 Materials and methods

5.2.1 Measurement of time

To comply with the available population data, and to eliminate any seasonal variation, the unit of time was defined to be one year.

For the analysis by year of birth, the children were grouped by date of birth. For reasons that are explained in section 5.2.2, 'year of birth' was defined not as the calendar year running from 1 January to 31 December, but as the 12 months from 1 July to 30 June. It was not necessary to use the conventional age-period method [113] to construct birth cohorts, because the date of birth was known for each individual case [*].

For the analysis by year of diagnosis, the children were grouped by date of diagnosis. The 'year of diagnosis' was defined as the calendar year running from 1 January to 31 December.

5.2.2 National population data

Annual national population estimates for 1 July (mid-year) 1966-2005, by sex and single year of age, were obtained from [http://www.statistics.gov.uk]. These figures are calculated by the Office of National Statistics for England and Wales, and by the General Register Office for Scotland, using census counts taken in 1971, 1981, 1991 and 2001, supplemented by inter-censal information on births, deaths and migration [†].

For the analysis by year of diagnosis, the mid-year population estimates were used to represent the number of children of the specified age and sex living in Britain during the calendar year running from 1 January to 31 December. The total at-risk population for a

[*] For registry data consisting of counts by age and period of diagnosis, the number of events by birth cohort has to be assessed from age-period groups, rather than from the exact year of birth. For example, children diagnosed at age 0 in 2000, 1 in 2001 and 2 in 2002 would all be assigned to the 'birth cohort of 2000'. The resulting cohort actually spans two years, not one: in this example, the range of possible birth dates is 1 January 1999 to 31 December 2000. The effect is to smooth out the year-on-year variation. This would be acceptable when assessing long-term time trends, but not when looking for discontinuities that might be associated with sudden changes in factors affecting the recorded incidence rates.

[†] See [www.statistics.gov.uk/downloads/theme_population/Short_Guide_revision_Nov_04] for details.

specified age-time group, in child-years, was defined as the sum of the mid-year population estimates over that age group and time period. For example, the total at-risk population in the age-time group specified as ‘aged 1-4 during diagnosis period 1 January 2000 to 31 December 2000’ is the sum of the mid-year populations aged 1 in 2000, 2 in 2000, 3 in 2000 and 4 in 2000.

For the analysis by year of birth, two different possible ways of assessing the population at risk were considered.

The first method is to take the total number of live births occurring during the chosen birth period, and multiply this by the number of years constituting the specified age group. This assumes that deaths and migration do not produce any net change in the size of the cohort as time passes, which is clearly inaccurate - although much less inaccurate than the equivalent assumption for adults would be.

The second method uses the mid-year population estimates to allow for deaths and migration. As in the analysis by year of diagnosis, the total at-risk population is the sum of the mid-year population estimates over the age group and time period. However, the time period is now defined by date of birth rather than date of diagnosis, and the years run from 1 July to 30 June, not 1 January to 31 December. For example, the mid-year population estimate for children aged under one year old (‘age 0’) in 2000 consists by definition of the number of births that occurred between 1 July 1999 and 30 June 2000, minus the number of these children who died or emigrated before 30 June 2000, plus the number of children of this age who entered the country in the same period. The mid-year population estimate for children aged 1 in 2000 consists of the number of children who were less than one year old on 1 July 1999, allowing for deaths and migration in children of this age between 1 July 1999 and 30 June 2000; and so on. The total at-risk population for children in the age-time group specified as ‘aged 1-4 and born between 1 July 1999 and 30 June 2000’ is the sum of the mid-year populations aged 1 in 2000, 2 in 2001, 3 in 2002 and 4 in 2003.

Neither method is perfect. The first does not allow for deaths in the birth cohort, and will slightly over-estimate the at-risk population if there is no net migration. The second does

not include part-years contributed by children who died before 30 June, and may slightly under-estimate the at-risk population. Whether these differences are important or not depends on childhood mortality and migration rates. In fact there was very little reduction in population between birth and age 14 among cohorts born in Britain after the mid-1970s. However, the reduction was slightly larger in earlier cohorts, and this might have tended to inflate any estimates of increasing long-term trends. So the second method, based on mid-year population estimates, was used in the following birth cohort analyses.

Tables 5.2 (a) and (b) show the population at risk, in thousands of child-years, by grouped time periods, age and sex, for the analyses by year of birth and year of diagnosis respectively.

5.2.3 Case data

A file containing 55439 cases was extracted from the NRCT on 6 April 2009. By this date, the NRCT had received and processed all routine notifications for cases diagnosed up to the end of 2005. The specification was: children diagnosed with ICCC3 disease under the age of 15 while resident in Britain, during the time period 1 January 1966 to 31 December 2005. Non-CNS cancer diagnoses classified as non-malignant in earlier standard coding systems (ICDO-3 histology codes 82403, 89313, 97183, 97313, 97543, 99313, 99503, 99603, 99613, 99623, 99803, 99823, 99833, 99843 and 99893) were excluded because they would not have been systematically registered during the eras of these coding systems. Cases coded as skin carcinoma[*] were excluded because they were very likely to have been incompletely registered. After these exclusions, there were 54650 cases.

To obtain complete coverage up to the 15th birthday within the diagnosis period, the analysis by year of birth was restricted to the 24 12-month birth cohorts consisting of children born between 1 July 1966 and 30 June 1967, 1 July 1967 to 30 June 1968 and so on, up to 1 July 1989 to 30 June 1990. With this restriction, there were 32004 cases for the analysis by year of birth.

[*] But 53 cases coded as skin malignancy of unspecified histology were retained as part of the other/unspecified group (XIIb in ICCC3 - see section 5.2.4).

5.2.4 Diagnostic classification of cases

The third edition of the International Classification of Childhood Cancer (ICCC3) is a three-level hierarchical code, published in 2005 [111]. Diagnostic data detailed enough for coding at the third level was not generally available until fairly recently (following the advances in diagnostic methods described in Chapter 2), and both the two earlier editions of ICCC included only two levels of code. Appendix 1 shows the first two levels of ICCC3, with the corresponding ICDO-3 histology and site codes.

Most of the twelve first-level ICCC3 groups are defined by the primary site or organ of disease, and most of the second-level groups are defined by histology. The main exception is germ-cell tumours, a relatively rare type of neoplasm that occurs most commonly in gonadal sites but is also found in the brain, pineal gland, spinal cord, and elsewhere: in the ICCC3 all germ-cell tumours are grouped with gonadal cancers. In childhood most renal and hepatic cancers are nephroblastoma and hepatoblastoma respectively, and most gonadal cancers are germ-cell tumours [1]. Nevertheless, carcinomas of the kidney, liver and gonads do occur in childhood: in the ICCC3 these cancers are included in the renal, hepatic and gonadal groups, while carcinomas of other sites are included with melanoma in a separate 'not otherwise specified' category. The ICCC3 category 'central nervous system (CNS) tumours' consists of intracranial and intraspinal tumours except germ-cell tumours. The 'peripheral nervous system' (PNS) category consists almost entirely of neuroblastoma.

A simplified version of ICCC3 was used for the analyses described in this chapter. 'Intracranial and intraspinal germ-cell tumours' (ICCC3 Xa) were grouped with CNS tumours, because their problems of diagnosis and registration were thought to be more like those of other CNS tumours than those of other germ-cell tumours. Some of the second-level ICCC3 codes were amalgamated, and the third-level codes were not considered. The resulting classification is shown in Table 5.2 (c).

For the time trend analyses, 14 diagnostic groups were defined. These consisted of the 12 categories listed in Table 5.2 (c), a sub-total group 'non-CNS solid cancer' containing all cases except those in the leukaemia and CNS tumour categories, and a total group

containing all cases. The geographical analyses were restricted to leukaemia, CNS tumours, and non-CNS solid cancer.

5.2.5 Definitions and explanatory factors for geographical analyses

The geographical analyses used data from the UK censuses taken in 1981, 1991 and 2001. The unit of observation was the child population of each census ward during each of the three decades centred on a census year, i.e. 1976-85, 1986-95 and 1996-2005. The population at risk in each census ward during each census decade was estimated as 10 times the population recorded at the census for that ward.

Census ward population counts, by age group and sex, were obtained from MIMAS (the national data centre based at the University of Manchester) for the 1981 and 1991 censuses, and from ONS for the 2001 census. Ward boundaries varied between censuses. Within the 1991 and 2001 censuses, a few wards with very small populations were amalgamated to comply with confidentiality rules, as explained below.

The explanatory factors for the geographical analyses were region and socio-economic status (SES). 'Region' was defined as either Wales or one of the nine Government Office Regions within England: North East, North West, Yorkshire and Humberside, East Midlands, West Midlands, Eastern, London, South East, and South West. The areas covered by these regions are loosely related, but not identical, to the areas covered by the regional cancer registries (see Table 3(b)). SES was measured by the Carstairs deprivation index [114], a widely-used community-based measure of socio-economic status that has been applied in previous analyses of NRCT data [109]. The Carstairs index assesses relative deprivation within a pre-defined set of small geographical areas, based on aggregated census information for these areas. It measures the SES of the geographical area, rather than the SES of any individual person or household within the area.

The Carstairs index for the 1981 census wards in Britain had been calculated at the CCRG for a previous study [109]. The Carstairs index for the 1991 census wards in England and Wales was downloaded from the MIMAS website ([http://cdu.mimas.ac.uk/], accessed on 2-09-08). The Carstairs index for the 2001 census wards in England and

Wales was downloaded from the ONS website ([www.statistics.gov.uk/statbase/], accessed on 2-09-08) [115]. Since neither MIMAS nor ONS could provide a Carstairs index for a set of census wards covering the whole of Britain, the geographical analysis was restricted to England and Wales.

Each case was allocated to the census decade that included its date at diagnosis. Within each census decade, using the appropriate set of census wards, each case was then allocated to the ward that included the post code of the address at diagnosis. For the 1981 census wards this information is a standard part of the NRCT dataset. The GeoConvert service provided by MIMAS was used to relate post codes to the 1991 and 2001 census wards ([http://geoconvert.mimas.ac.uk/]). 15 cases diagnosed during 1976-85, 39 cases diagnosed during 1986-95 and 7 cases diagnosed during 1996-2005 could not be allocated to a census ward because the post code was not known, or (in one case) not recognised by the GeoConvert system. After these exclusions, the files for the geographical analysis contained 11355, 12333, and 13569 cases from England and Wales diagnosed during 1976-85, 1986-95 and 1996-2005 respectively.

There were 10444 wards in Britain at the 1981 census, of which 9289 were in England and Wales. As supplied, both the 1991 and the 2001 Carstairs indices amalgamated a few census wards with small populations to comply with confidentiality rules. On request, MIMAS and ONS each provided a list of these wards, and the corresponding population and case counts were amalgamated to match. After these amalgamations, the 1991 and 2001 Carstairs indices were based on respectively 9363 and 8797 wards. For each census, within England and Wales, the wards were grouped into categories defined by child-population-weighted quintiles of the Carstairs index (i.e. each containing approximately the same number of children aged 0-14), and the quintile category number (1 to 5) was used as a measure of SES for each ward (1 = most affluent, 5 = most deprived) [*].

5.2.6 Standardisation of rates

The rates were directly standardised [116] for age and sex. The chosen common distribution for these confounders was the uniform distribution, i.e. with the numbers of children in

[*] This definition is used here for consistency with previous publications [109;110]. Confusingly, the higher quintile category numbers represent areas of lower SES.

each of the age groups being proportional to the number of years of age contributing to each age group, and equal numbers of males and females. (For the analysis by birth cohort, this is not very different from the actual overall distribution of age and sex in the childhood population of Britain in the study period, since childhood mortality rates were low and the sex ratio at birth was not very far from 1:1.) Similarly, sex-standardised rates within age groups were calculated assuming equal numbers of males and females.

Almost all the time trend analyses used the age groups that are conventional for childhood cancer registration data, i.e. 0, 1-4, 5-9 and 10-14 completed years at diagnosis. Neighbouring age groups were amalgamated to achieve sufficient numbers of cases in a few diagnostic groups (Section 5.2.7.3).

To illustrate the effects of time trends on age at diagnosis in more detail than is possible with the conventional age groups, sex-standardised rates were calculated by single year of age at diagnosis for successive periods of birth or diagnosis. The resulting age distributions are shown in Figures 5.3.1.1(a) and 5.3.1.2(a) etc.

5.2.7 Poisson regression analysis

5.2.7.1 General methods

Poisson regression methods were used to model variation in childhood cancer rates by year of birth and by year of diagnosis [117]. All models included terms representing the main effects of age group and sex, and their interactions. Where necessary, for time trend analysis in a few diagnostic groups, adjacent age groups were combined to ensure that the number of model parameters fitted was not greater than 10% of the number of cases observed, as recommended to justify the use of 'large sample' approximations [117]. The models were tested for goodness of fit using the deviance statistic, and compared by likelihood ratio tests. All significance tests were two-sided, and were at the 5% level unless stated otherwise. No correction was made for multiple testing, and some significant results were expected to occur by chance. All calculations were done in Stata version 10 [118].

5.2.7.2 Trend models for variation over time

For time trend estimation, a continuous time variable (measured in whole years) was included as an explanatory factor in the Poisson model. The trend was estimated as the incidence rate ratio (IRR) for an increase of one year in the time term, and the annual average percentage change was calculated as (IRR-1)x100. On the assumption of a constant rate of change over time, the Poisson model provided an estimate of the 95% confidence interval for the trend. Interaction terms were used to test for heterogeneity of the trend by age group and by sex.

For each diagnostic group, by year of birth and by year of diagnosis, the following models were fitted to the sex-standardised rates, separately for each age group:

Model 1. A separate time trend within each age group.

Model 2. Separate time trends for boys and girls within each age group.

For each diagnostic group, by year of birth and by year of diagnosis, the following models were fitted to the age-sex-standardised rates, over all age groups:

Model 3. Parallel time trends for all age groups.

Model 4. Separate time trends for boys and girls, parallel for all age groups.

Model 5. Separate time trends for different age groups, parallel for boys and girls.

Model comparisons were as follows.

Model 1 v Model 2: Heterogeneity of trend by sex within age group

Model 3 v Model 4: Heterogeneity of overall trend by sex

Model 3 v Model 5: Heterogeneity of overall trend between age groups.

The Stata commands used to fit these models are listed in Appendix 3.

Since most of the relevant model comparisons did not detect statistically significant differences in time trends between boys and girls, the tests for heterogeneity of trend by sex are not reported in the main tables of results (Section 5.3). The few exceptions are shown in Table 5.2(d). One is based on a very small number of cases, and may be due to chance. Others are for sub-total and total groups that are hard to interpret. For the remaining groups by year of diagnosis (lymphoma in age group 10-14, retinoblastoma in

age group 1-4, and gonadal/germ-cell cancer in age group 5-9), the rates for subtypes by 5-year of diagnosis are shown separately for boys and girls (Tables 5.3.2.2(f), 5.3.5.2(d), 5.3.10.2(e)).

To ensure at least 30 cases within each age group for model 2, which involves three parameter estimates (sex, year, and the interaction of sex and year), some adjacent age groups were amalgamated (see Section 5.2.7.1), as follows.

Analysis by birth cohort:

retinoblastoma: 0, 1-4, 5-14

bone cancer, melanoma/carcinoma, other/unspecified cancer: 0-4, 5-9, 10-14.

Analysis by year of diagnosis:

retinoblastoma: 0, 1-4, 5-14

bone cancer: 0-4, 5-9, 10-14.

5.2.7.4 Step models for variation over time

As an objective way of identifying possible discontinuities in the change in rate over time, 'step' models were fitted to the age-sex-adjusted rates by year of birth and by year of diagnosis. The simplest acceptable model was found by the iterative process defined in Figure 5.2(a). At the start of the process, the 'periods' are defined as single years of birth or single years of diagnosis, as appropriate. At the end of the process the periods indicate the positions of a series of steps in the annual rates, by year of birth or year of diagnosis.

Sensitivity to the choice of significance level for the test of equality was investigated by running the method with various different levels (0.100, 0.050, 0.010, 0.005). The sets of step models produced by the significance levels 0.005 and 0.010 were almost exactly the same. All the significance levels gave reasonable and internally consistent results, both by year of birth and by year of diagnosis. The significance level 0.010 was chosen because it produced a small number of (mainly increasing) steps for most diagnostic groups.

In general these models did not always accurately represent the observed variation in rate: the models were tested for goodness of fit in the usual way, and there was significant lack of fit for some diagnostic groups, in the interim or final models, or both.

Nevertheless, the method should be valid for identifying the likely timing of steps in rate, on the assumption that such steps exist.

For the analysis by year of diagnosis, the changes in rate predicted by the step models were graphically compared with the timing of some important changes in methods of diagnosis and registration that had been previously identified from the literature, as described in Chapters 2 and 3, discussed in Section 5.1.2, and listed in Table 5.1(a).

5.2.7.5 Models to investigate changes in geographical variation over time

Poisson regression models were used to analyse variation in recorded incidence between small geographical areas (census wards) of England and Wales. Changes in geographical variation over time were investigated by fitting separate models to the rates for three successive decades of diagnosis, centred on the three UK census years 1981, 1991 and 2001. It was appropriate to define time periods by year of diagnosis, not year of birth, because the aim of the analysis was to detect possible artefacts of diagnosis or registration. To ensure sufficient numbers of cases, the analyses were restricted to three broad diagnostic groups: leukaemia, CNS tumours, and non-CNS solid cancer (the rest).

Within each census decade, the appropriate set of census wards was categorised according to region (i.e. Wales and the nine English Government Office Regions), and SES (i.e. population-weighed quintiles (1 to 5) of the Carstairs deprivation index for each ward (see section 5.2.5)). Region and SES were included as categorical explanatory factors in the regression models. To test for a 'dose-response' effect, each rate was also modelled as a continuous log-linear trend on the SES category numbers.

For each broad diagnostic group, and each of the three census decades, the following Poisson regression models were fitted to the age-sex-standardised annual rate in each census ward:

Model 1. Separate rate for each combination of region and SES.
Model 2. Multiplicative effects of region and SES, i.e. (1) without an interaction term.
Model 3. Separate rate for each SES category, with no effect of region.
Model 4. Separate rate for each region, with no effect of SES.
Model 5. Separate rate for each region, with a parallel SES trend in each region.

Model comparisons were as follows.

Model 1 v Model 2: Heterogeneity of SES effects between regions

Model 2 v Model 3: Heterogeneity of region-adjusted rates between SES categories

Model 2 v Model 4: Heterogeneity of SES-adjusted rates between regions

The Stata commands used to fit these models are listed in Appendix 3.

Almost none of the relevant model comparisons detected statistically significant heterogeneity of SES effects between regions; the only (marginally) significant result was in the test for CNS tumours during 1996-2005 (p=0.049). The IRR for each region and SES category (with estimated 95% confidence interval) was therefore estimated from the model containing region, SES category, age group, sex, and interactions between age and sex, without interactions between region and SES (i.e. Model (2) in the list above, rather than Model (1)). The tests for heterogeneity of SES effects by region are not reported in the main tables of results (Section 5.3).

The rates predicted by Model (2) were presented in bar charts to illustrate changes in the geographical patterns of rates between census decades. The rates by region were directly standardised [116] by age, sex and SES, and the rates by SES were directly standardised by age, sex and region. The chosen common distribution was the uniform distribution, i.e. numbers of children in each of the age groups proportional to the number of years of age contributing to each age group, equal numbers of males and females, and equal numbers of children in each SES category or region, as appropriate.

The SES trend was estimated as the IRR (with estimated 95% confidence interval) for an increase of one unit of the SES score (1 to 5) in a model that contains age group, sex, interactions between age and sex, region and SES as a continuous variable, i.e. Model (5) in the list above.

Figure 5.2(a) Flow-chart for calculation of step models for variation in rates over time.

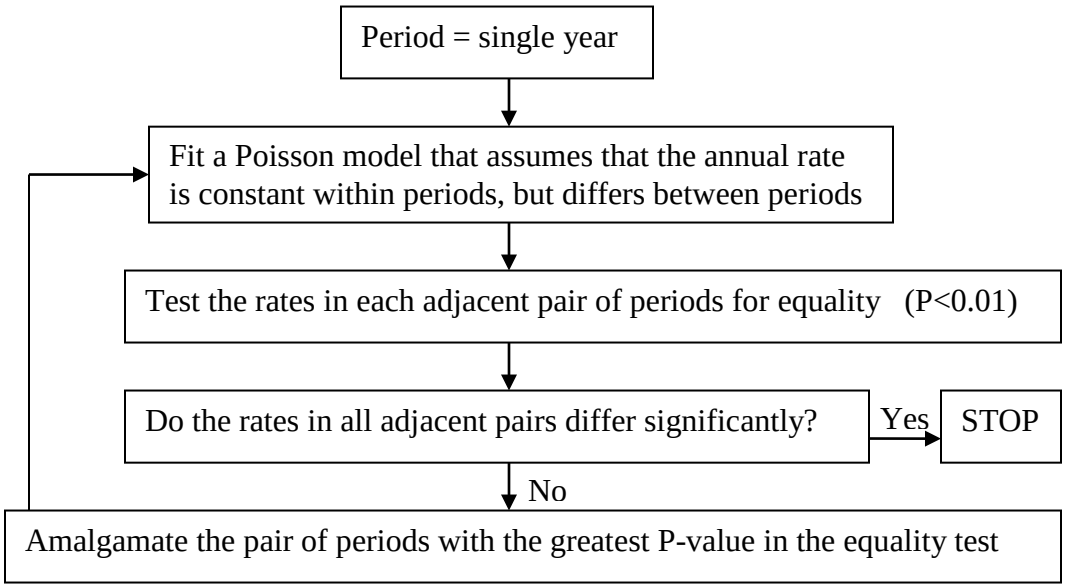


Table 5.2(a). Population (thousands) by age group, sex and groups of four 12-month birth cohorts centred on 1 January, Britain 1966-67 to 1989-90.

		Period of birth					
	From:	1966-67	1970-71	1974-75	1978-79	1982-83	1986-87
	To:	1969-70	1973-74	1977-78	1981-82	1985-86	1989-90
Age	Sex						
0	M	1818	1620	1325	1425	1439	1518
	F	1740	1533	1256	1353	1370	1452
1-4	M	7218	6409	5259	5665	5758	6065
	F	6890	6067	4987	5387	5490	5807
5-9	M	8954	7928	6547	7123	7237	7612
	F	8493	7501	6206	6785	6914	7283
10-14	M	8907	7886	6587	7102	7265	7662
	F	8450	7487	6261	6820	6943	7298
0-14	M	26896	23844	19719	21315	21699	22856
	F	25572	22589	18710	20345	20717	21840

Table 5.2(b). Population (thousands) by age group, sex and groups of five calendar years of diagnosis, Britain 1966 to 2005.

		Period of diagnosis							
	From:	1966	1971	1976	1981	1986	1991	1996	2001
	To:	1970	1975	1980	1985	1990	1995	2000	2005
Age	Sex								
0	M	2293	1970	1689	1780	1888	1893	1760	1698
	F	2195	1864	1601	1696	1803	1804	1674	1617
1-4	M	9397	8607	6914	6974	7318	7645	7276	6770
	F	9026	8160	6550	6631	6985	7316	6918	6456
5-9	M	11063	11535	10445	8538	8807	9247	9553	9028
	F	10535	10952	9892	8090	8392	8844	9118	8599
10-14	M	9827	11044	11545	10381	8587	8793	9286	9612
	F	9224	10480	10936	9858	8156	8439	8871	9124
0-14	M	32580	33156	30593	27672	26601	27579	27875	27108
	F	30980	31455	28979	26275	25337	26404	26582	25797

Table 5.2(c). Simplified diagnostic classification based on ICCC3 [111], for Chapter 5.

Simplified classification	ICCC3	Number of cases by decade of diagnosis				Total
		1966-75	1976-85	1986-95	1996-05	1966-2005
Leukaemia	I					
Lymphoid	a	3302	3331	3524	3777	13934
Myeloid	bcd	878	752	764	880	3274
Unspecified	e	457	68	68	49	642
Lymphoma	II					
Hodgkin	a	521	608	515	687	2331
Non-Hodgkin	bc	733	719	757	815	3024
Unspecified	de	109	61	33	21	224
CNS tumours	III *					
Glioma	abd	1750	1935	2098	2362	8145
Embryonal	c	634	634	660	709	2637
Germ-cell *	(Xa)	55	117	137	164	473
Other specified	e	246	276	328	482	1332
Unspecified	f	525	146	196	168	1035
PNS cancer †	IV					
-	ab	975	728	916	933	3552
Retinoblastoma ‡	V					
Unilateral	a	275	201	282	267	1025
Bilateral	a	155	137	154	127	573
Renal cancer	VI					
-	abc	861	716	783	854	3214
Hepatic cancer	VII					
-	abc	92	101	127	163	483
Bone cancer	VIII					
Osteosarcoma	a	354	342	298	319	1313
Ewing	c	165	289	230	244	928
Other/unspecified	bde	54	49	44	39	186
Soft-tissue sarcoma	IX					
Rhabdomyosarcoma	a	421	515	561	512	2009
Other specified	bcd	243	217	367	417	1244
Unspecified	e	111	56	61	68	296
Gonadal/germ-cell **	X					
Gonadal	cde	193	223	210	203	829
Non-gonadal non-CNS	b	83	70	107	135	395
Melanoma/carcinoma #	XI					
Melanoma	d	50	94	146	123	413
Thyroid carcinoma	b	43	58	56	106	263
Carcinoma NOS	acf	152	155	124	148	579
Other/unspec. cancer	XII					
-	ab	73	41	93	90	297
Total		13510	12639	13639	14862	54650

Excludes skin carcinoma (XIe), and non-CNS disease formerly classified as non-malignant.
† = peripheral nervous system cancer, i.e. almost entirely neuroblastoma.
‡ = unilateral subtype includes a few cases of unknown laterality.
* = CNS germ-cell cancers transferred from group X. ** = Non-CNS gonadal/germ-cell cancer.
# = some carcinomas are included in other groups. NOS = not otherwise specified.

Table 5.2(d). Diagnostic groups for which the test of heterogeneity of time trend by sex was statistically significant (P<0.05).

Analysis	Diagnostic group	Age group	No. of cases	P<0.05
By year of birth	Lymphoma	5-9	1062	0.0495
	Lymphoma	0-14	3353	0.004
	Hepatic cancer	10-14	45	0.046
	Non-CNS solid cancer	0-14	13623	0.023
	Total	0-14	32004	0.020
By year of diagnosis	Lymphoma	10-14	2804	0.035
	Retinoblastoma	1-4	893	0.031
	Gonadal/germ-cell cancer	5-9	132	0.007
	Non-CNS solid cancer	0-14	23178	0.040
	Total	0-14	54650	0.047

5.3 Results and discussion for individual diagnostic groups

Detailed results are given separately for each of 14 diagnostic groups. These consist of the 12 main categories shown in Table 5.2(c), together with two larger groups: non-CNS solid cancer (i.e. all cases except leukaemia and CNS tumours), and total cases.

As shown in Table 5.2(c), most of the 12 main categories have two or more subtypes, generally based on histology. The subtypes of 'non-CNS solid cancer' are defined to be the 10 categories consisting of all the main categories except leukaemia and CNS tumours. The subtypes of the 'total cases' group are defined to be leukaemia, CNS tumours, and non-CNS solid cancer.

The results for Britain by year of birth (i.e. 12-month birth cohort) 1966-67 to 1989-90 are presented as follows.

- standardised incidence rates for successive groups of four 12-month birth cohorts
- estimated annual average percentage change, assuming a log-linear time trend in the rate for 12-month birth cohorts
- graph of the distribution of age at diagnosis by single year of age, for successive groups of eight 12-month birth cohorts
- graph of the standardised rate by 12-month birth cohort, with a step model suggesting possible timing for changes in rate.

The results for Britain by year of diagnosis 1966-2005 are presented as follows.

- standardised incidence rates for successive 5-year diagnosis periods
- estimated annual average percentage change, assuming a log-linear time trend in the rate by year of diagnosis
- graph of the distribution of the age at diagnosis by single year of age, for successive decades of diagnosis
- graph of the standardised rate by single year of diagnosis, with a step model suggesting possible timing for changes in rate and an indication of the timing of important changes in diagnostic and registration methods (see Table 5.1)
- for categories that have subtypes, graphs of rates for each subtype by 5-year diagnosis period, within age groups

The results of the geographical analysis for England and Wales by census ward for decades of diagnosis centred on successive UK censuses (1976-85, 1986-95, 1996-2005) are as follows.

- for leukaemia, CNS tumours and non-CNS solid cancer, a comparison of rates by region and by socio-economic status (SES), presented as incidence rate ratios and as graphs of standardised rates.

The trend models are used to estimate time trends in the recorded incidence rates. The fit of these models was adequate except where otherwise stated in the text. The other analyses are used to assess the possibility of diagnostic and registration artefact as an explanation of the time trends.

Not all the differences discussed in Sections 5.3.1 to 5.3.14 are tested formally, and some, although of interest, may not be statistically significant.

5.3.1 Leukaemia

5.3.1.1 Year of birth

See Tables 5.3.1.1 (a) to (c), and Figures 5.3.1.1 (a) and (b).

By year of birth, there was an overall increasing time trend of 0.7% per year (95% confidence interval 0.4 to 1.0). In age groups 1-4 and 10-14 there were time trends of 0.9% (0.5 to 1.3) and 1.2% (0.6 to 1.8) per year, respectively. In age group 0, there was a non-significant increase of 0.8% (-0.4 to 2.0). In age group 5-9 the Poisson model did not fit ($p<0.01$), and there was no apparent time trend (0.0% per year) (Table 5.3.1.1(c)).

As shown in Figure 5.3.1.1(a), the rates at ages 4 to 7 decreased between the first 8-year birth period (1966-67 to 1973-74) and the second (1974-75 to 1981-82), consistent with the lack of time trend in the age 5-9 group. There was little change in the rates by single year of age from 0 to 3, and the rates at ages over 8 increased slightly. Between the second birth period and the third (82-83 to 89-90), the rates appear to have increased fairly consistently at all ages.

As shown in Figure 5.3.1.1(b), there were a few small peaks in incidence over time, for example in children born in 1973-75, 1985-86 and 1988-89. The step model suggests only one step, which coincides with the peak at the birth year 1985-86.

5.3.1.2 Year of diagnosis

See Tables 5.3.1.2 (a) to (c), Figures 5.3.1.2 (a) to (f), and Figures 5.3.14.2 (c) to (f).

By year of diagnosis, there was an overall increasing time trend of 0.7% per year (95% confidence interval 0.6 to 0.9). At ages 0, 1-4, 5-9 and 10-14 there were time trends of 1.4% (0.9 to 2.0), 0.8% (0.6 to 1.0), 0.7% (0.5 to 1.0) and 0.5% (0.2 to 0.8) per year, respectively. The trends in the different age groups differed significantly ($p=0.024$). (Table 5.3.1.2(c)).

As shown in Figure 5.3.1.2(a), the large increase at age 0 occurred mainly in the most recent decade of diagnosis. From the first decade to the second, there was a large increase at age 3 and little or no increase over age 7.

As shown in Figure 5.3.1.2(b), there were several small peaks in incidence over time, most obviously in 1976, 1990 and 2002. The step model suggests increases at 1971 (coinciding with the introduction of the revised scheme for cancer registration), 1990, and 2002 (in the year following the action plan for cancer registration).

Figures 5.3.1.2 (c) to (f) clearly show a reduction in the proportion of cases of unspecified subtype from 1966-70 to 1971-75, in every age group. At age 0 the transfer was apparently to the myeloid subtype, and a substantial proportion (5-10%) of cases continued to be unspecified until the most recent decade. At older ages the transfer was mainly to the lymphoid subtype, and the proportion of unspecified cases was very small after 1971-75.

The striking increase at age 0, which is seen in the rates shown in Table 5.3.1.2(c) and reflected in the trend estimate, occurred in both the lymphoid and the myeloid subtypes (Figure 5.3.1.2(c)). At older ages, the myeloid subtype changed little over time, whereas the lymphoid leukaemia rate increased steadily from 1986-90 onwards (Figures 5.3.1.2 (d) to (f)). At ages 1-4 and 5-9 the lymphoid leukaemia rate levelled off or decreased slightly from 1976-80 to 1981-85.

5.3.1.3 Geographical analysis

See Table 5.3.1.3 and Figures 5.3.1.3 (a) and (b).

In all regions except the South West, the SES-adjusted rate was higher in 1996-2005 than in 1976-85. (Figure 5.3.1.3(a)).

Within each of the three census decades, with the exception of the South West in 1996-2005 (which had a slightly lower rate), Wales was the region with the lowest SES-adjusted rate: relative to the South East, the IRRs for Wales were 0.87 (0.74 to 1.02), 0.85

(0.72 to 1.00) and 0.86 (0.74 to 1.01). Rates in London and the South East were relatively high in all three decades. There was statistically significant heterogeneity by region only in 1996-2005 (p=0.025). (Table 5.3.1.3 and Figure 5.3.1.3(a)).

In all five SES categories, the region-adjusted rate was higher in 1996-2005 than in 1976-85. (Figure 5.3.1.3(b)).

Within each of the three census decades, after adjusting for regional differences, there was a statistically significant trend with SES. The IRR for each unit increase in SES category was 0.97 (0.94 to 0.99) in 1976-85, 0.97 (0.95 to 0.995) in 1986-95, and 0.96 (0.94 to 0.99) in 1996-2005. (Table 5.3.1.3 and Figure 5.3.1.3(b)). This implies that in all three census decades the standardised leukaemia rate was about 9% lower in the most deprived 40% of the childhood population than in the most affluent 40%. There was statistically significant heterogeneity by SES category in 1976-85 (p=0.015) and 1996-2005 (p=0.017) (Table 5.3.1.3).

5.3.1.4 Discussion

Both by year of birth and by year of diagnosis there was an overall increasing time trend of 0.7% per year.

For the earliest decade, the analysis by year of diagnosis is consistent with artefact. The first step indicated by the step model coincides with the introduction of the revised scheme for general cancer registration in 1971. There was a noticeable increase at age 3 from the first to the second decade, and relatively little increase at older ages, perhaps suggesting diagnosis at an earlier stage of disease. The reduction in the proportion of cases of unspecified subtype is clearly artefactual, and is probably related to methods for registration, not diagnosis, since most of the change occurred between 1966-70 and 1971-75. The differences in trend between age groups by year of birth are hard to interpret; they might represent changes in age at diagnosis, or diagnostic shifts - perhaps including transfer to lymphoma (see Section 5.3.2).

In the later decades, there is very little evidence for artefact. The step changes in rate by year of diagnosis do not coincide with changes in methods for diagnosis and registration (except perhaps for the registration Action Plan of 2001 – see below). In particular, there is no indication of an effect of the widespread use of immunophenotyping methods from around 1986 on either the proportions of the subtypes (except possibly at age 0) or the overall rates (Figures 5.3.1.2 (c) to (f)).

By year of diagnosis over the whole time period, the time trend was steepest in the younger age groups, and particularly in infants: 1.4% per year at age 0, compared with 0.8% at age 1-4, 0.7% at age 5-9, and 0.5% per year at age 10-14. It is possible that transfer to lymphoma between the first and second decades might contribute to the slightly lower time trend estimate for leukaemia in older children (see Section 5.3.2.3). A new observation is the large increase in the rates at age 0 for 2001-05 compared to 1996-2000 (Figure 5.3.1.2(c)), in both the myeloid and the lymphoid subtypes.

Childhood leukaemia rates were higher in more affluent communities within England and Wales, as expected from previous studies based on NRCT data. The comparison of the SES trend between census decades is new, and it is striking that the trend is almost the same in all three decades, and persists when regional differences are allowed for.

The SES-adjusted rates apparently increased over the three decades in almost all the regions. The history of registration methods suggests that registration might have been relatively incomplete in Wales and the Thames region in earlier decades: the low rates in Wales, relative to the South East, are consistent with this idea, but there is very little sign of incomplete registration in London and the South East. The emergence of statistically significant regional differences in the most recent decade is interesting, and might perhaps be related to the apparent step change at 2001 in some way.

As previously reported [32], the two earlier small peaks in recorded incidence by year of diagnosis, in 1976 and 1990, followed seasonal influenza epidemics: this association may well be due to other factors, or to chance, but might perhaps be causal. No known relevant change in methods for diagnosis or registration occurred at those times. By year of birth, the small peaks in incidence for children born in 1973-74, 1985-86 and 1988-89

might be indirect effects of the peaks in incidence by year of diagnosis in 1976 and 1990, since the peak age for diagnosis of childhood leukaemia is 1-5. Otherwise, they might be related to some real causal factor acting around the time of birth in these years, or they might be due to chance.

The peak in 2002 by year of diagnosis does not appear to be related to influenza, since there was no influenza epidemic between 1991 and 2005. In 2002, but not in 1976 or 1990, peaks in recorded incidence were also seen in some other diagnostic groups (lymphoma, retinoblastoma, renal cancer and bone cancer; see the relevant Sections below). One possible explanation is the Action Plan for cancer registration that was launched in 2001 with the intention of improving completeness of registration. Nevertheless it seems surprising that this initiative should have had such a sudden and relatively large effect, particularly for leukaemia, which is probably the diagnostic group least likely to be under-registered (see Chapter 4).

Leukaemia: by 12-month birth cohort 1966-67 to 1989-90, Britain
Tables 5.3.1.1 (a) to (c).

Time trend analysis. 66-70 is the 48-month birth cohort from 1 July 1966 to 30 June 1970, etc.

Age	0		1-4		5-9		10-14		0-14	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	50	52	519	399	318	257	218	153	1105	861
70-74	48	44	511	372	294	215	175	144	1028	775
74-78	44	32	386	278	245	171	166	138	841	619
78-82	42	36	410	351	197	190	196	141	845	718
82-86	34	48	457	354	298	188	205	136	994	726
86-90	45	57	535	413	285	205	233	171	1098	846
Total	263	269	2818	2167	1637	1226	1193	883	5911	4545

a) Number of cases by age, sex and grouped birth cohort.

Age	0		1-4		5-9		10-14		ASR	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	27.5	29.9	71.9	57.9	35.5	30.3	24.5	18.1	41.0	33.6
70-74	29.6	28.7	79.7	61.3	37.1	28.7	22.2	19.2	43.0	34.2
74-78	33.2	25.5	73.4	55.7	37.4	27.6	25.2	22.0	42.7	33.1
78-82	29.5	26.6	72.4	65.2	27.7	28.0	27.6	20.7	39.7	35.4
82-86	23.6	35.0	79.4	64.5	41.2	27.2	28.2	19.6	45.9	35.1
86-90	29.6	39.3	88.2	71.1	37.4	28.1	30.4	23.4	48.1	38.8

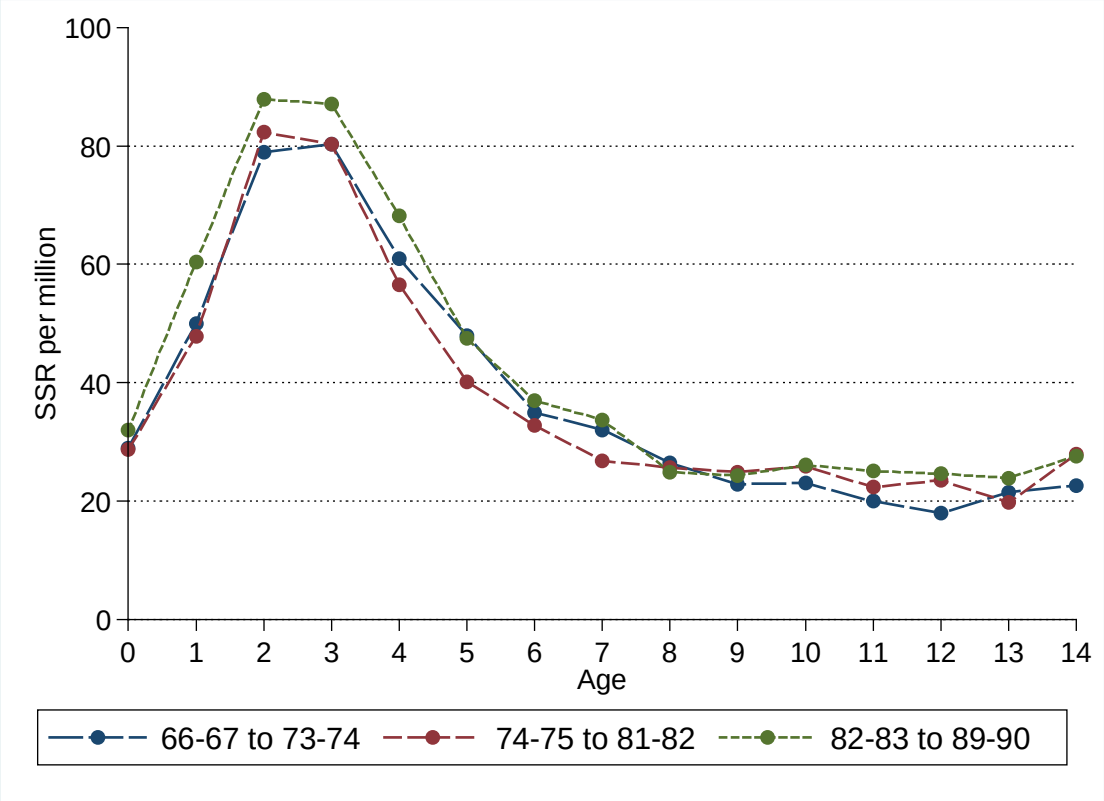
b) Incidence rate per million by age group, sex and grouped birth cohort.

Age	0	1-4	5-9	10-14	ASSR
Born					
66-70	28.7	64.9	32.9	21.3	37.3
70-74	29.2	70.5	32.9	20.7	38.6
74-78	29.3	64.6	32.5	23.6	37.9
78-82	28.0	68.8	27.8	24.1	37.5
82-86	29.3	71.9	34.2	23.9	40.5
86-90	34.4	79.7	32.8	26.9	43.4
Trend	-	***	-	***	***
AAPC	0.77	0.88	0.01	1.16	0.69
CI	-0.42 to 1.97	0.49 to 1.27	*-0.50 to 0.52*	0.55 to 1.77	0.42 to 0.96
Fit	-	-	**	-	-

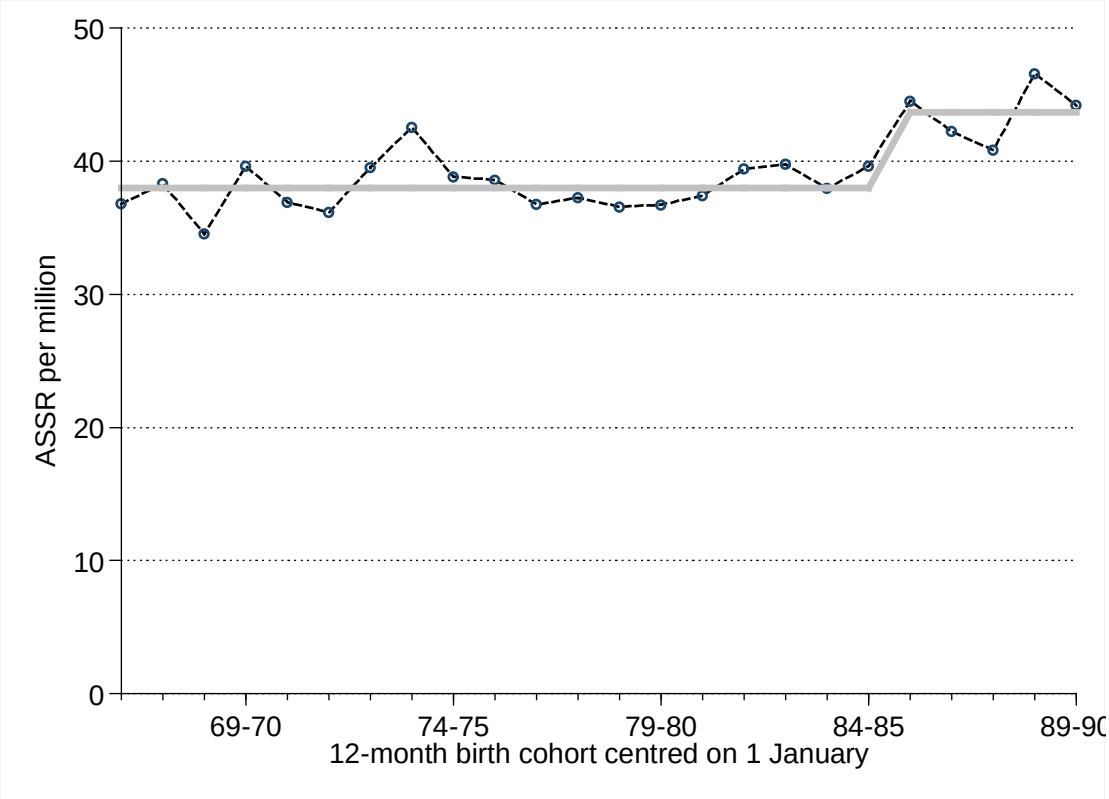
c) Sex-standardised incidence rate per million by age group and grouped birth cohort.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.018.

- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Leukaemia: by 12-month birth cohort 1966-67 to 1989-90, Britain
Figures 5.3.1.1 (a) and (b).



a) Standardised rate by single year of age at diagnosis, for successive birth periods.



b) Standardised rate by 12-month birth cohort: actual (dotted), step model (solid) line.

Leukaemia: by year of diagnosis 1966-2005, Britain
Tables 5.3.1.2 (a) to (c).

Time trend analysis.

Age/sex	0		1-4		5-9		10-14		0-14	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	64	62	595	481	319	244	244	210	1222	997
1971-75	58	54	664	470	401	316	275	180	1398	1020
1976-80	50	42	538	401	382	273	261	230	1231	946
1981-85	54	49	509	419	287	221	252	183	1102	872
1986-90	51	77	586	471	301	244	213	170	1151	962
1991-95	63	60	636	468	350	239	247	180	1296	947
1996-00	69	60	605	523	371	274	251	177	1296	1034
2001-05	76	84	584	477	374	277	281	223	1315	1061
Total	485	488	4717	3710	2785	2088	2024	1553	10011	7839

a) Number of cases by age group, sex, and period of diagnosis.

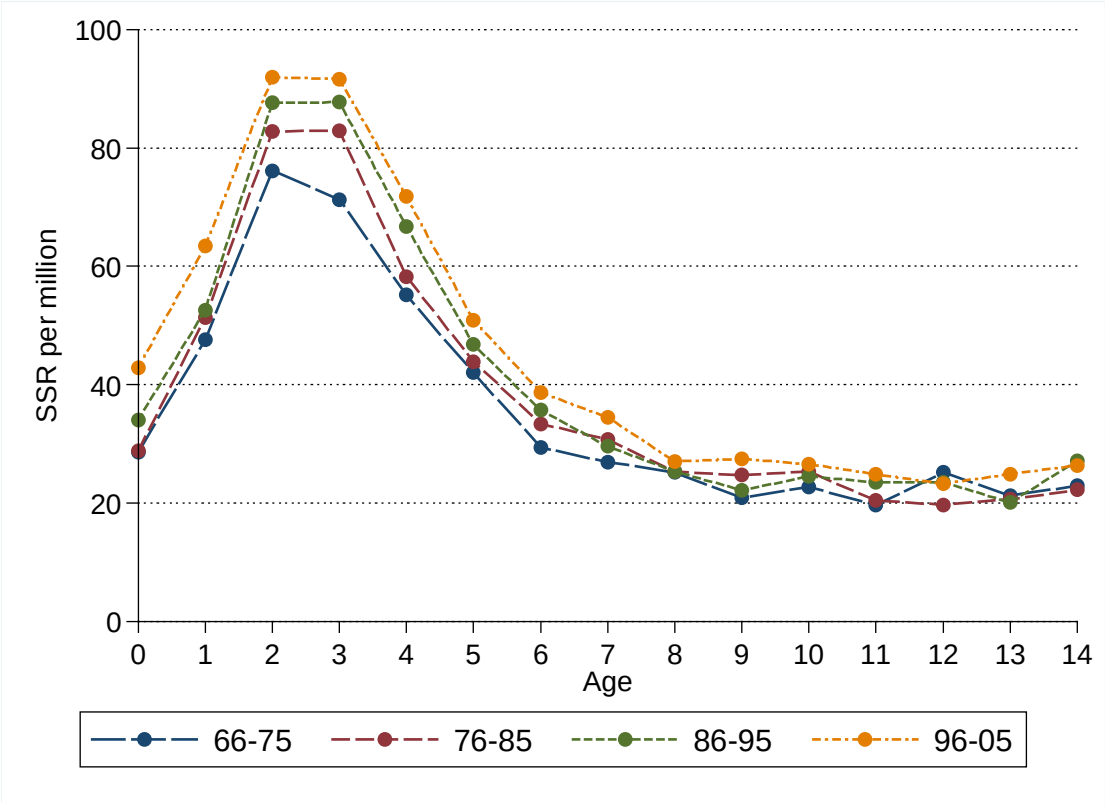
Age/sex	0		1-4		5-9		10-14		ASR	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	27.9	28.2	63.3	53.3	28.8	23.2	24.8	22.8	36.6	31.4
1971-75	29.4	29.0	77.2	57.6	34.8	28.9	24.9	17.2	42.4	32.6
1976-80	29.6	26.2	77.8	61.2	36.6	27.6	22.6	21.0	42.5	34.3
1981-85	30.3	28.9	73.0	63.2	33.6	27.3	24.3	18.6	40.8	34.1
1986-90	27.0	42.7	80.1	67.4	34.2	29.1	24.8	20.8	42.8	37.5
1991-95	33.3	33.3	83.2	64.0	37.8	27.0	28.1	21.3	46.4	35.4
1996-00	39.2	35.8	83.2	75.6	38.8	30.0	27.0	20.0	46.7	39.2
2001-05	44.8	51.9	86.3	73.9	41.4	32.2	29.2	24.4	49.5	42.0

b) Incidence rate per million by age group, sex and period of diagnosis.

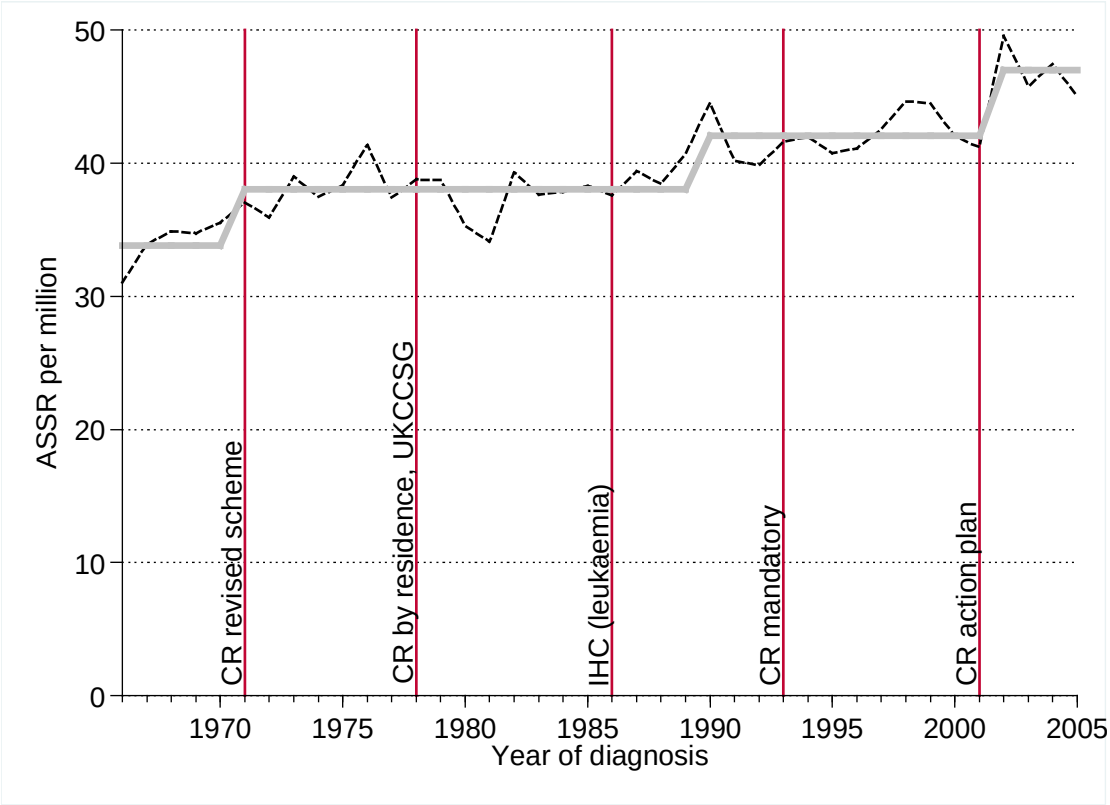
Age	0	1-4	5-9	10-14	ASSR
Diagnosed					
1966-70	28.1	58.3	26.0	23.8	34.0
1971-75	29.2	67.4	31.8	21.0	37.5
1976-80	27.9	69.5	32.1	21.8	38.4
1981-85	29.6	68.1	30.5	21.4	37.4
1986-90	34.9	73.8	31.6	22.8	40.1
1991-95	33.3	73.6	32.4	24.7	40.9
1996-00	37.5	79.4	34.4	23.5	43.0
2001-05	48.3	80.1	36.8	26.8	45.8
Trend	***	***	***	**	***
AAPC	1.41	0.78	0.71	0.47	0.73
CI	0.86 to 1.96	0.60 to 0.96	0.47 to 0.95	0.19 to 0.76	0.61 to 0.86
Fit	-	-	-	-	-

c) Sex-standardised incidence rate per million by age group and period of diagnosis.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.024.
- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Leukaemia: by year of diagnosis 1966-2005, Britain
Figures 5.3.1.2 (a) and (b).

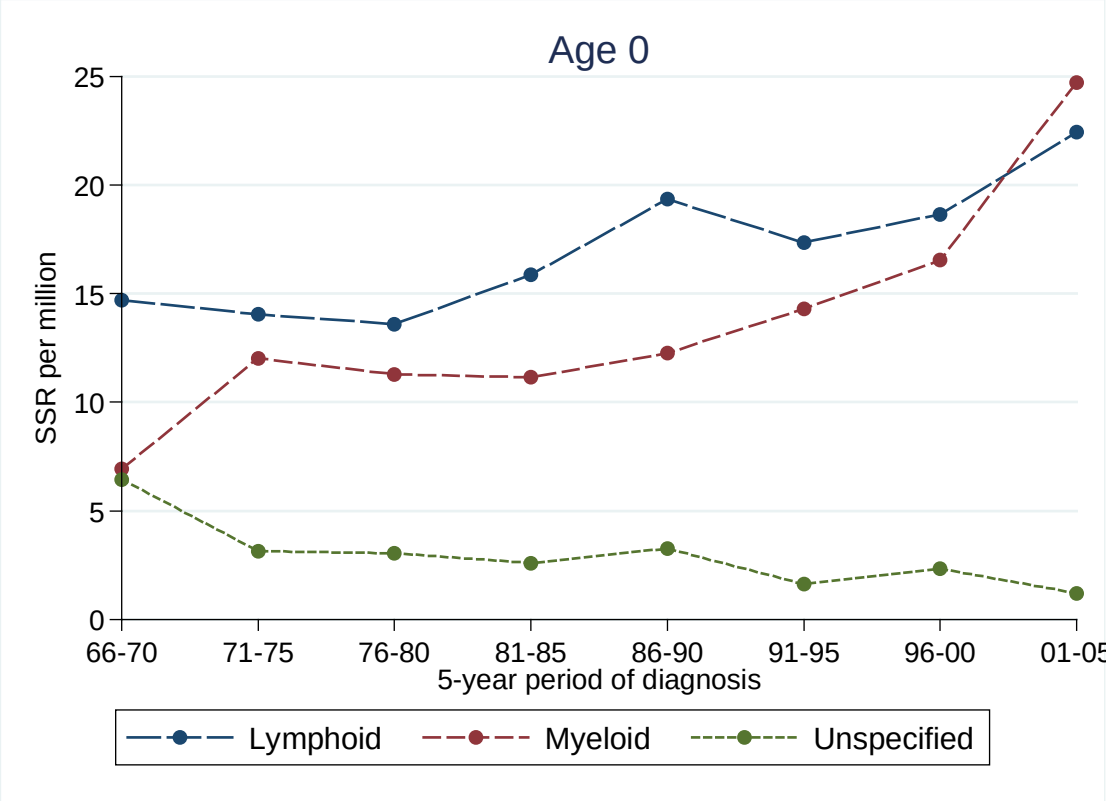


a) Standardised rate by single year of age at diagnosis, for successive diagnosis periods.

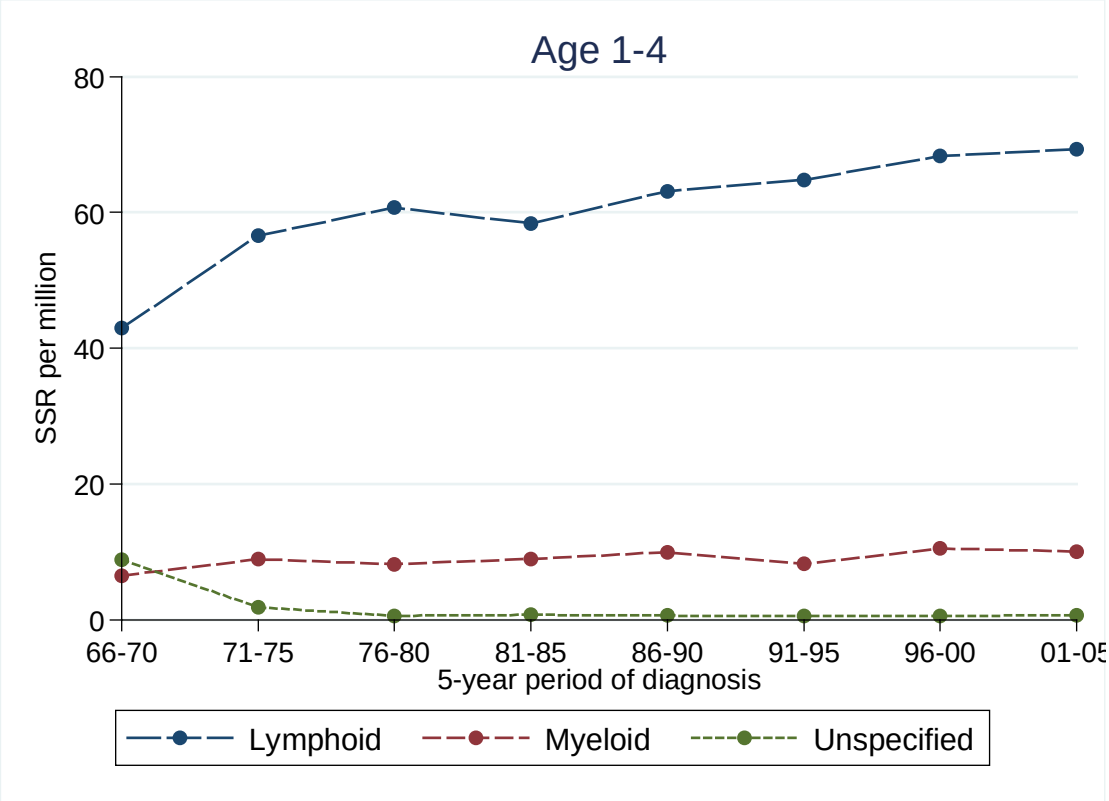


b) Standardised rate by year of diagnosis: actual (dotted), step model (solid) line.

Leukaemia: by year of diagnosis 1966-2005, Britain
Figures 5.3.1.2 (c) and (d).

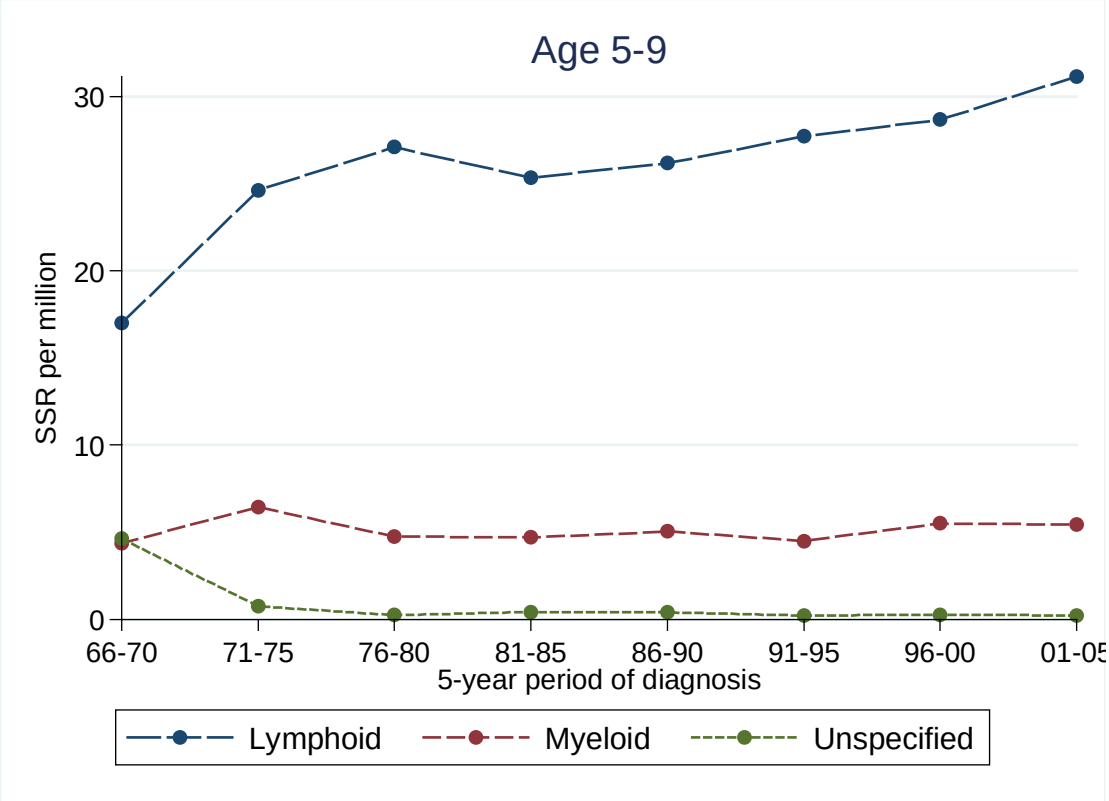


c) Standardised rate at age 0, by subtype and 5-year period of diagnosis.

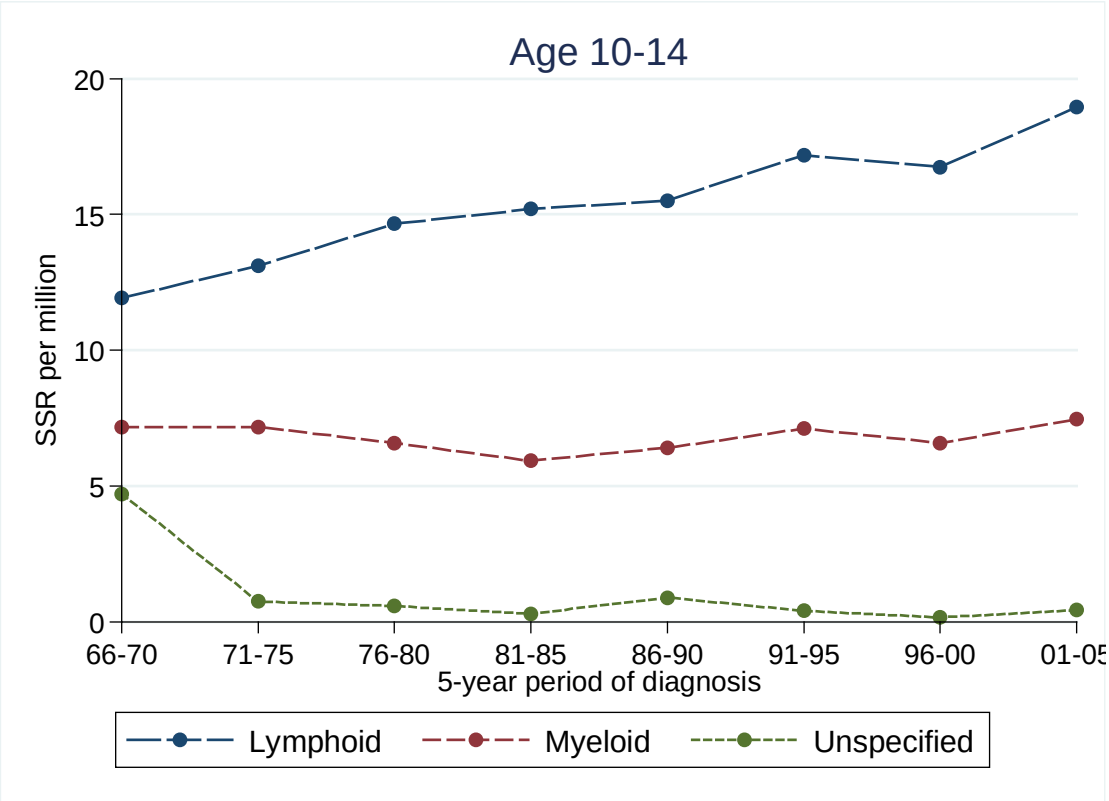


d) Standardised rate at age 1-4, by subtype and 5-year period of diagnosis.

Leukaemia: by year of diagnosis 1966-2005, Britain
Figures 5.3.1.2 (e) and (f).



e) Standardised rate at age 5-9, by subtype and 5-year period of diagnosis.



f) Standardised rate at age 10-14, by subtype and 5-year period of diagnosis.

Leukaemia: by year of diagnosis 1976-2005, England and Wales.
Table 5.3.1.3.

Geographical analysis by decade of diagnosis.

Decade	1976-85		1986-95		1996-2005	
Estimates	IRR	95% CI	IRR	95% CI	IRR	95% CI
Region:						
North East	0.98	0.83 to 1.16	0.94	0.80 to 1.11	1.01	0.86 to 1.18
North West	0.89	0.79 to 1.01	0.89	0.79 to 1.00	0.99	0.89 to 1.11
York/Humber	0.92	0.80 to 1.05	1.00	0.88 to 1.14	0.95	0.84 to 1.08
E Midlands	0.95	0.82 to 1.09	0.96	0.83 to 1.10	0.96	0.85 to 1.10
W Midlands	1.00	0.88 to 1.13	0.99	0.87 to 1.12	0.94	0.83 to 1.06
Eastern	0.92	0.80 to 1.04	0.93	0.82 to 1.05	0.87	0.77 to 0.99
London	0.97	0.85 to 1.10	1.04	0.92 to 1.17	1.04	0.92 to 1.16
South East	1.00	n/a	1.00	n/a	1.00	n/a
South West	1.07	0.93 to 1.22	1.05	0.92 to 1.19	0.83	0.73 to 0.94
Wales	0.87	0.74 to 1.02	0.85	0.72 to 1.00	0.86	0.74 to 1.01
SES:						
1=affluent	1.00	n/a	1.00	n/a	1.00	n/a
2	1.07	0.97 to 1.18	1.01	0.91 to 1.11	1.03	0.93 to 1.13
3	0.94	0.85 to 1.04	0.98	0.89 to 1.08	0.94	0.86 to 1.04
4	0.93	0.84 to 1.03	0.91	0.82 to 1.01	0.91	0.82 to 1.00
5=deprived	0.91	0.82 to 1.02	0.91	0.82 to 1.02	0.88	0.80 to 0.98
SES trend:						
Estimates	0.97	0.94 to 0.99	0.97	0.95 to .995	0.96	0.94 to 0.99
Trend	**		*		**	
P (Region)	0.252		0.103		0.025	
P (SES)	0.015		0.135		0.017	
Fit	-		-		-	

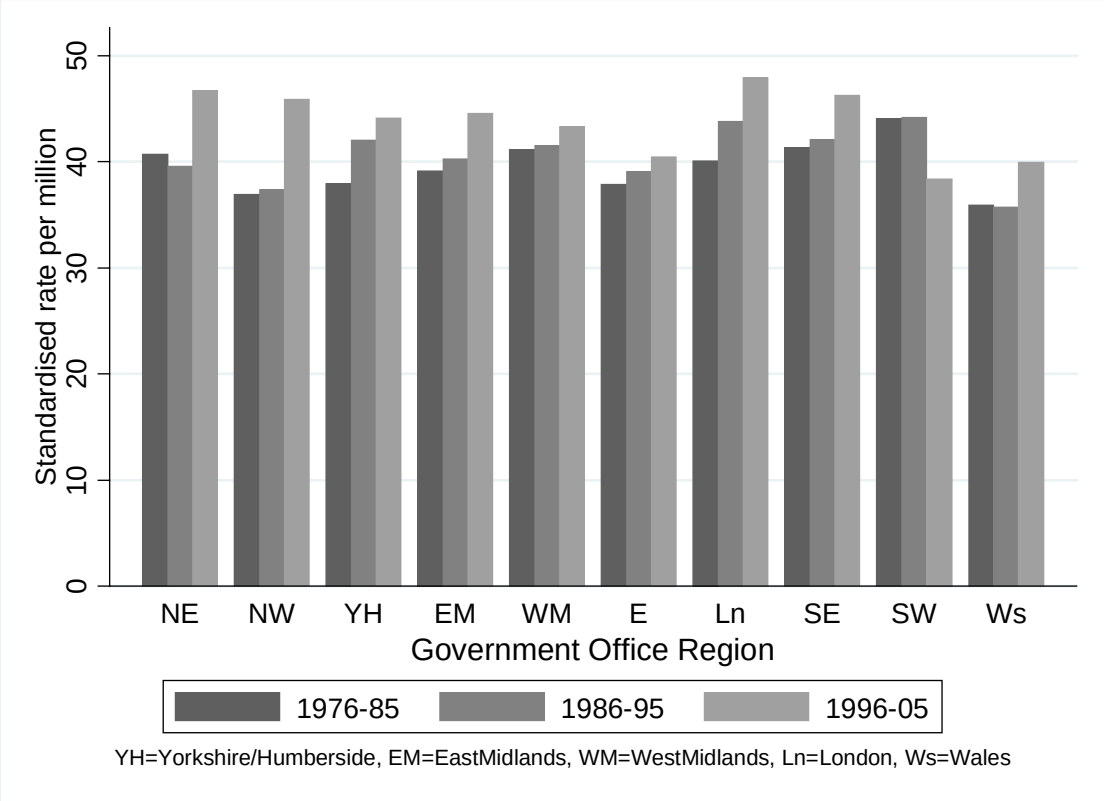
IRR: incidence rate ratio, standardised by age group and sex, for each Government Office Region and SES category (from a Poisson regression model that includes both region and SES as categorical factors), by decade of diagnosis, with estimated 95% confidence interval (CI). Reference categories: South East region; SES category 1 (most affluent).

P (Region): significance level of test for heterogeneity of IRRs between regions.
P (SES): significance level of test for heterogeneity of IRRs between SES categories.
Fit: significance level of deviance test for lack of fit to the categorical model.

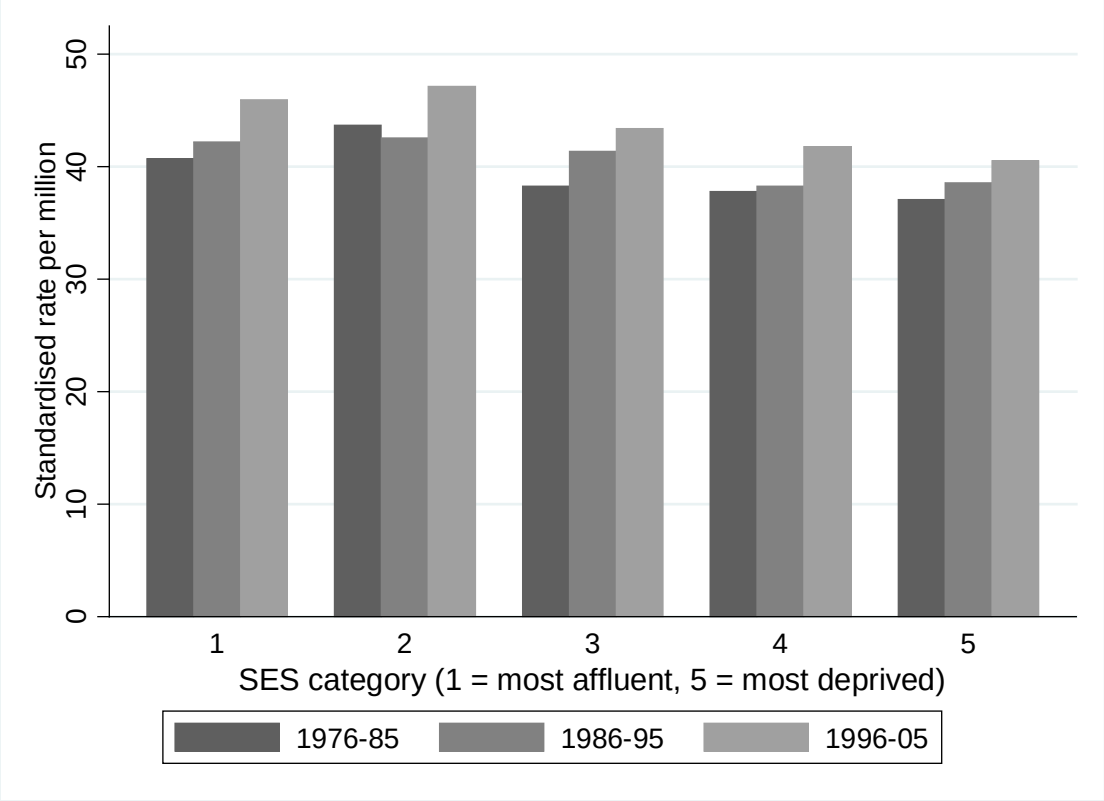
SES trend: IRR for an increase of one SES category, with estimated 95% CI (from a Poisson regression model that includes region as a categorical factor, and the SES category number as a continuous factor).

- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Leukaemia: by year of diagnosis 1976-2005, England and Wales.
Figures 5.3.1.3 (a) and (b).



a) SES-standardised ASSR by Government Office Region and decade of diagnosis.



b) Region-standardised ASSR by SES category and decade of diagnosis.

5.3.2 Lymphoma

5.3.2.1 Year of birth

See Tables 5.3.2.1 (a) to (c), and Figures 5.3.2.1 (a) and (b).

By year of birth, there was an overall increasing time trend of 0.6% per year (95% confidence interval 0.2 to 1.1). In age group 10-14 there was a time trend of 1.0% (0.3 to 1.7) per year. In age groups 1-4 and 5-9 there were non-significant increases of 0.8% (-0.4 to 2.0), 0.3% (-0.6 to 1.1) respectively. At age 0 the Poisson model did not fit ($p<0.05$); there was a decrease of -5.8% per year on average (Table 5.3.2.1(c)).

As shown in Figure (a), the clearest increase in rate occurred at ages 13 and 14, for children born in the most recent of the three periods of birth. As shown in Figure 5.3.2.1(b), there were some small peaks and troughs in the overall rate; the step model suggests only one increasing step, which follows the trough in birth year 1976-77.

5.3.2.2 Year of diagnosis

See Tables 5.3.2.2 (a) to (c), Figures 5.3.2.2 (a) to (f), and Figures 5.3.13.2 (c) to (f).

By year of diagnosis, there was an overall increase of 0.8% per year on average, but there was evidence for lack of fit of the Poisson model ($p<0.05$). In age groups 5-9 and 10-14 there were increasing time trends of 0.6% (0.2 to 1.0) and 1.2% (0.9 to 1.6) per year, respectively; in age group 1-4 there was a non-significant increase of 0.3% (-0.2 to 0.9); at age 0 there was a decreasing time trend of -3.5% (-5.6 to -1.5) per year (Table 5.3.2.2(c)).

As shown in Figure 5.3.2.2(a), there were relatively large increases in rate from 1966-75 to 1976-85 for children diagnosed at ages 8-12, and from 1986-95 to 1996-2005 for children diagnosed at ages 13-14. The step model suggests increases at 1976 and 1997, with a large peak and trough in 2001-02 (Figure 5.3.2.2(b)).

As shown in Figures 5.3.2.2 (c) to (f), in every age group the proportion of unspecified cases was low in 1966-70 and very low from 1971-75 onwards. There was perhaps a suggestion of diagnostic transfer between subtypes: at ages 5-9 and 10-14 the rates for Hodgkin and non-Hodgkin appear to mirror each other from 1981-85 onwards. An exception is that at age 10-14 there was a particularly large increase from 1996-2000 to 2001-05 for girls diagnosed with Hodgkin lymphoma.

5.3.2.3 Discussion

By year of birth and by year of diagnosis there were overall increases of 0.6% and 0.8% per year respectively.

The decreasing time trend in lymphoma diagnosed at age 0 was mainly due to a decrease in rate from 1976-80 to 1981-85 (see Table 5.3.2.2(c) and Figures 5.3.2.2(c) and 5.3.13.2 (c)). Although based on very small numbers of cases (Table 5.3.2.1(a)), this is almost certainly diagnostic transfer of some kind; perhaps to neuroblastoma, following the introduction of catecholamine testing around 1975 (see Sections 5.3.4 and 5.3.13), or to Langerhans cell histiocytosis, a disorder that until recently was not classified as malignant [1].

The increase in rate by year of diagnosis from 1966-75 to 1976-85 for children diagnosed at ages 8-12 (Figure 5.3.2.2(a)) could perhaps represent diagnostic transfer from T-precursor lymphoid leukaemia, as predicted from the history of diagnosis methods (Section 2.5.10). The timing is plausible, in that the UKCCSG clinical trials that set a consistent boundary between leukaemia and lymphoma began in 1977. There was little or no increase in the leukaemia rates for the same age group and time periods (Figure 5.3.1.2(a)), and T-precursor is a relatively frequent subtype of lymphoid leukaemia in this age group [1]. Transfer of this kind might explain the increase of about 15% indicated by the step model at 1976 (Figure 5.3.2.2(b)), which would be well within the predicted maximum effect of 22% (Section 2.5.10).

The graphs by age group (Figures 5.3.2.2(e) and 5.3.2.2(f)) suggest that there may have been some diagnostic transfer between Hodgkin and non-Hodgkin lymphoma: since

1981-85 the rates have tended to mirror each other, particularly for males. This might represent changes in diagnostic fashion for cases where the diagnosis by morphology is uncertain.

The step model includes an increase in rate in 1997 (Figure 5.3.2.2(b)), and Figures 5.3.2.2 (a) and (f) show that this was mainly for the oldest children. This is consistent with the possibility that improved scanning methods led to earlier diagnosis of lymphoma patients who previously would not have been diagnosed until after the age of 15. Hodgkin lymphoma, in particular, is very much more common in the age groups 15-19 and 20-24 than in the age group 10-14 [119]. The 'nodular sclerosing' subtype is relatively frequent in girls and older children [1]: this might explain the particularly large increase in Hodgkin lymphoma in girls during 2001-05.

There may also have been some diagnostic transfer to lymphoma from other types of non-CNS solid cancer (see Section 5.3.13).

The sharp peak and trough in 2001 and 2002 are hard to explain, except perhaps as some effect of the Action Plan of 2001, which aimed to improve completeness of cancer registration.

Lymphoma: by 12-month birth cohort 1966-67 to 1989-90, Britain
Tables 5.3.2.1 (a) to (c).

Time trend analysis. 66-70 is the 48-month birth cohort from 1 July 1966 to 30 June 1970, etc.

Age	0		1-4		5-9		10-14		0-14	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	11	3	70	31	173	48	206	99	460	181
70-74	5	9	69	22	140	36	191	94	405	161
74-78	4	3	49	18	105	25	159	81	317	127
78-82	8	4	57	31	139	35	175	87	379	157
82-86	0	3	53	27	124	48	197	99	374	177
86-90	2	1	69	32	135	54	189	133	395	220
Total	30	23	367	161	816	246	1117	593	2330	1023

a) Number of cases by age, sex and grouped birth cohort.

Age	0		1-4		5-9		10-14		ASR	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	6.0	1.7	9.7	4.5	19.3	5.7	23.1	11.7	17.1	7.1
70-74	3.1	5.9	10.8	3.6	17.7	4.8	24.2	12.6	17.0	7.1
74-78	3.0	2.4	9.3	3.6	16.0	4.0	24.1	12.9	16.1	6.8
78-82	5.6	3.0	10.1	5.8	19.5	5.2	24.6	12.8	17.8	7.7
82-86	0.0	2.2	9.2	4.9	17.1	6.9	27.1	14.3	17.2	8.5
86-90	1.3	0.7	11.4	5.5	17.7	7.4	24.7	18.2	17.3	10.1

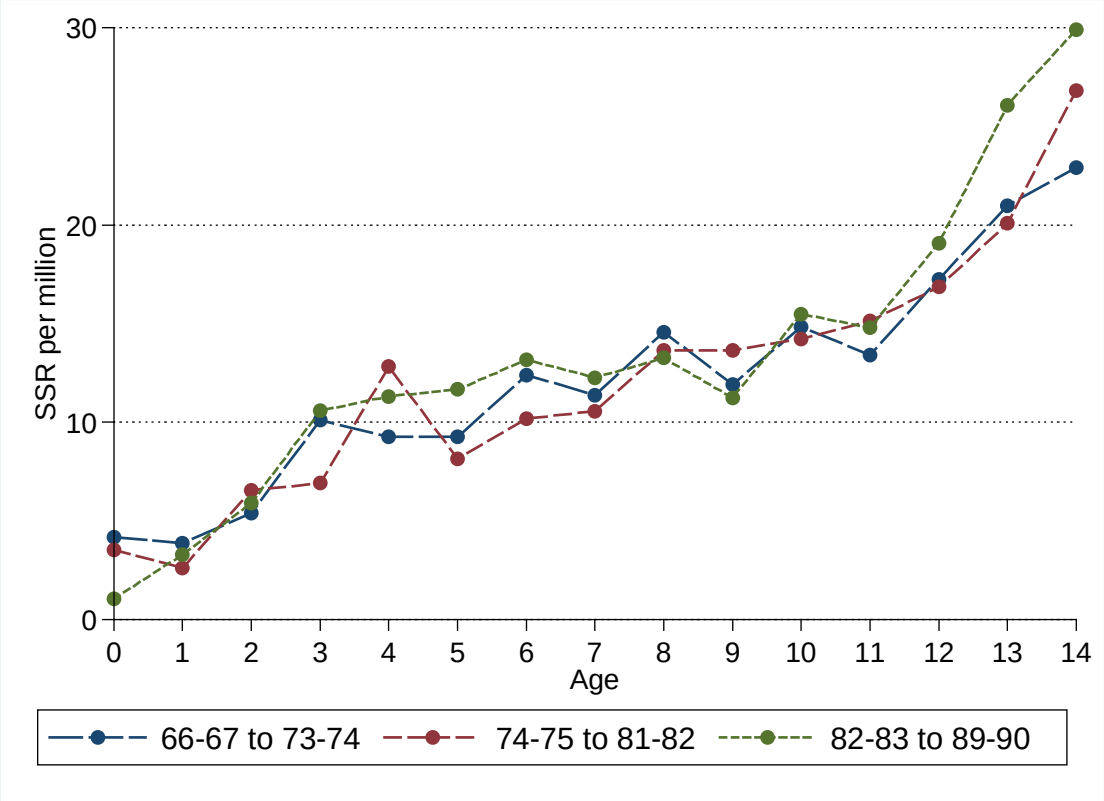
b) Incidence rate per million by age group, sex and grouped birth cohort.

Age	0	1-4	5-9	10-14	ASSR
Born					
66-70	3.9	7.1	12.5	17.4	12.1
70-74	4.5	7.2	11.2	18.4	12.1
74-78	2.7	6.5	10.0	18.5	11.4
78-82	4.3	7.9	12.3	18.7	12.7
82-86	1.1	7.1	12.0	20.7	12.9
86-90	1.0	8.4	12.6	21.4	13.7
Trend	**	-	-	**	*
AAPC	-5.76	0.79	0.28	0.98	0.62
CI	*-9.49 to -1.88*	-0.41 to 1.99	-0.55 to 1.13	0.32 to 1.65	0.15 to 1.10
Fit	*	-	-	-	-

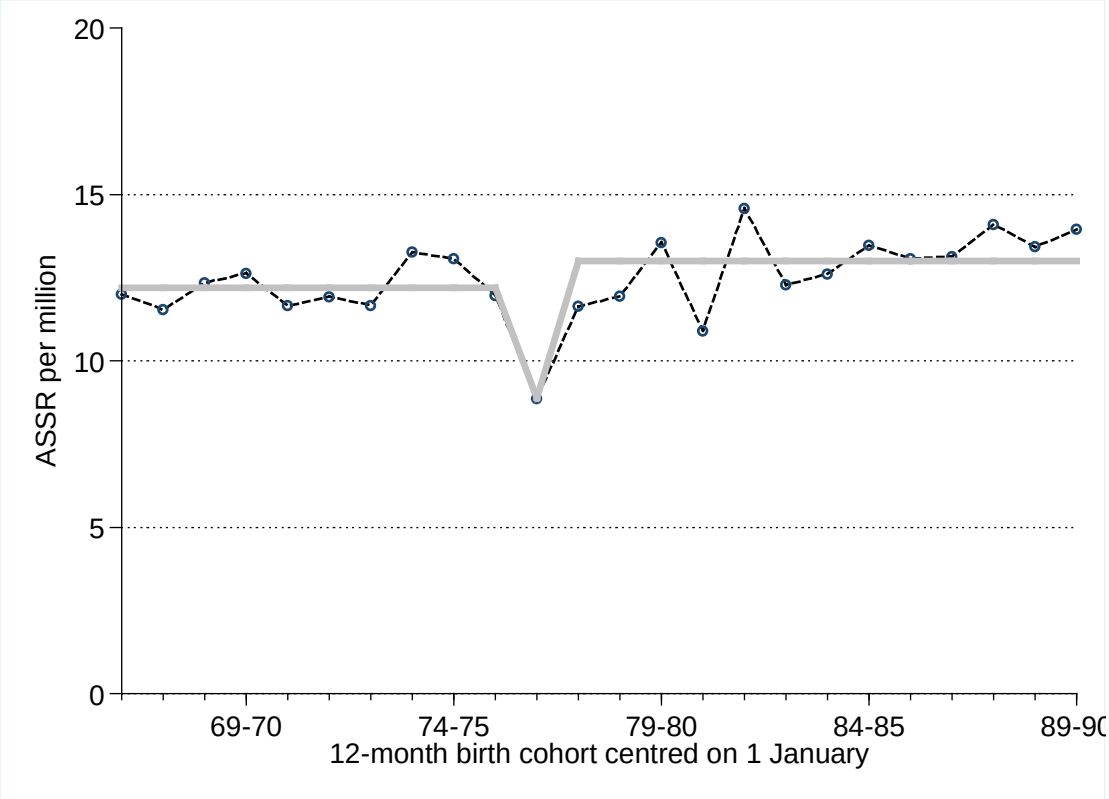
c) Sex-standardised incidence rate per million by age group and grouped birth cohort.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.005.

- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Lymphoma: by 12-month birth cohort 1966-67 to 1989-90, Britain
Figures 5.3.2.1 (a) and (b).



a) Sex-standardised rate by single year of age at diagnosis, for successive birth periods.



b) Standardised rate by 12-month birth cohort: actual (dotted), step model (solid) line.

Lymphoma: by year of diagnosis 1966-2005, Britain
Tables 5.3.2.2 (a) to (c).

Time trend analysis.

Age/sex	0		1-4		5-9		10-14		0-14	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	12	3	95	42	171	56	204	91	482	192
1971-75	5	9	83	36	172	66	211	107	471	218
1976-80	10	7	74	25	203	54	251	122	538	208
1981-85	2	3	66	34	138	33	245	121	451	191
1986-90	3	1	70	37	160	50	200	103	433	191
1991-95	4	0	77	36	172	59	222	111	475	206
1996-00	1	3	86	30	176	69	246	129	509	231
2001-05	4	2	74	33	177	52	267	174	522	261
Total	41	28	625	273	1369	439	1846	958	3881	1698

a) Number of cases by age group, sex, and period of diagnosis.

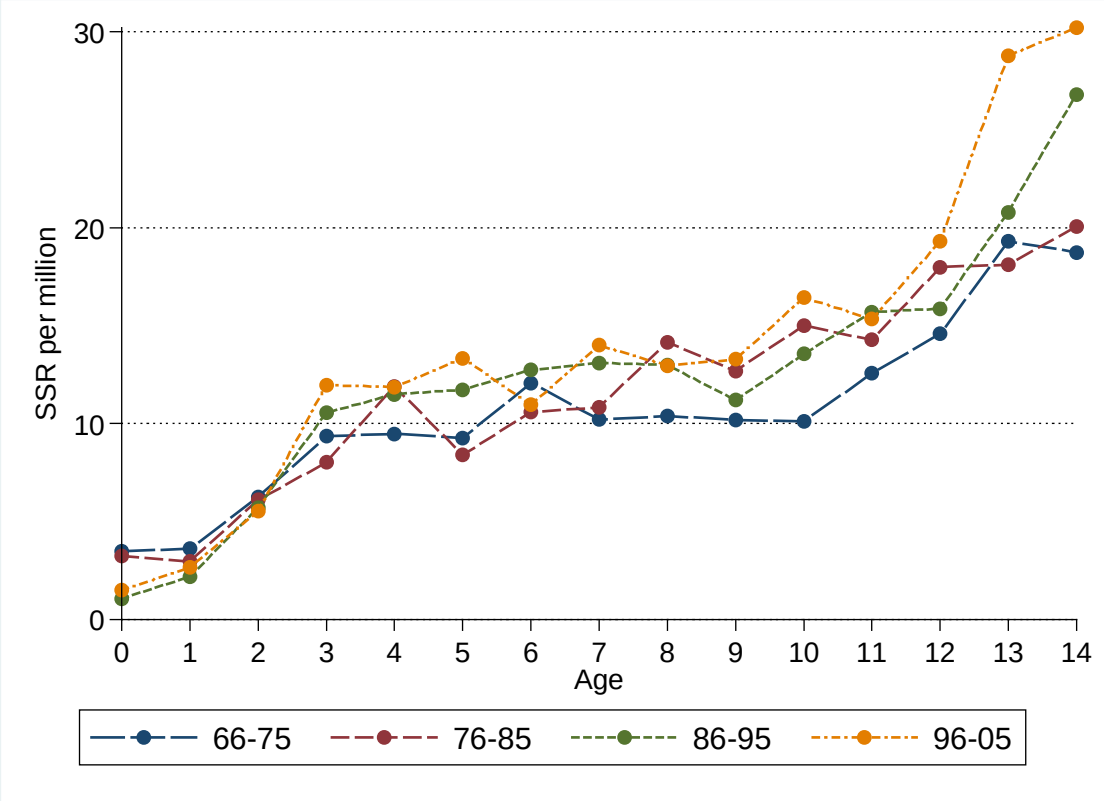
Age/sex	0		1-4		5-9		10-14		ASR	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	5.2	1.4	10.1	4.7	15.5	5.3	20.8	9.9	15.1	6.4
1971-75	2.5	4.8	9.6	4.4	14.9	6.0	19.1	10.2	14.1	6.9
1976-80	5.9	4.4	10.7	3.8	19.4	5.5	21.7	11.2	17.0	6.8
1981-85	1.1	1.8	9.5	5.1	16.2	4.1	23.6	12.3	15.9	6.9
1986-90	1.6	0.6	9.6	5.3	18.2	6.0	23.3	12.6	16.5	7.6
1991-95	2.1	0.0	10.1	4.9	18.6	6.7	25.2	13.2	17.4	7.9
1996-00	0.6	1.8	11.8	4.3	18.4	7.6	26.5	14.5	18.2	8.6
2001-05	2.4	1.2	10.9	5.1	19.6	6.0	27.8	19.1	18.9	9.8

b) Incidence rate per million by age group, sex and period of diagnosis.

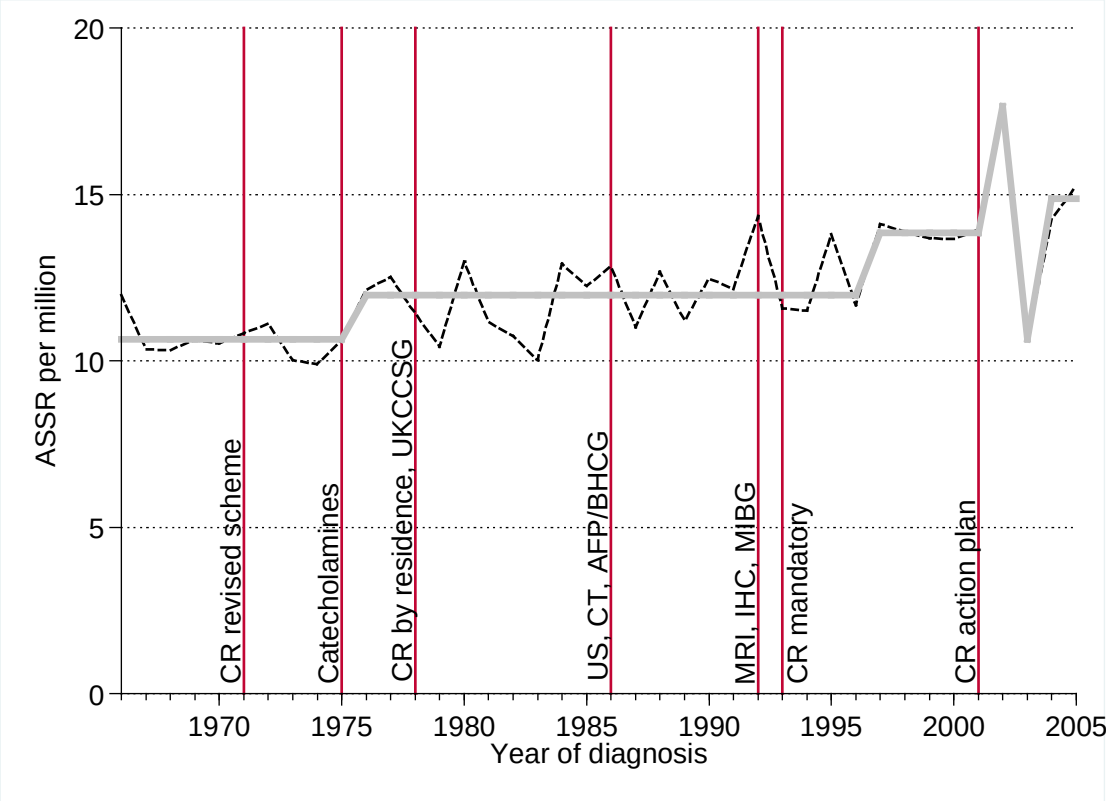
Age	0	1-4	5-9	10-14	ASSR
Diag.					
1966-70	3.3	7.4	10.4	15.3	10.8
1971-75	3.7	7.0	10.5	14.7	10.5
1976-80	5.1	7.3	12.4	16.4	11.9
1981-85	1.4	7.3	10.1	17.9	11.4
1986-90	1.1	7.4	12.1	18.0	12.1
1991-95	1.1	7.5	12.6	19.2	12.7
1996-00	1.2	8.1	13	20.5	13.4
2001-05	1.8	8.0	12.8	23.4	14.3
Trend	**	-	**	***	***
AAPC	-3.54	0.32	0.63	1.24	0.83
CI	-5.58 to -1.45	-0.24 to 0.88	0.24 to 1.03	0.92 to 1.57	*0.60 to 1.06*
Fit	-	-	-	-	*

c) Sex-standardised incidence rate per million by age group and period of diagnosis.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups < 0.001.
- = not significant; * p<0.05, ** p<0.01, *** p<0.001.

Lymphoma: by year of diagnosis 1966-2005, Britain
Figures 5.3.2.2 (a) and (b).

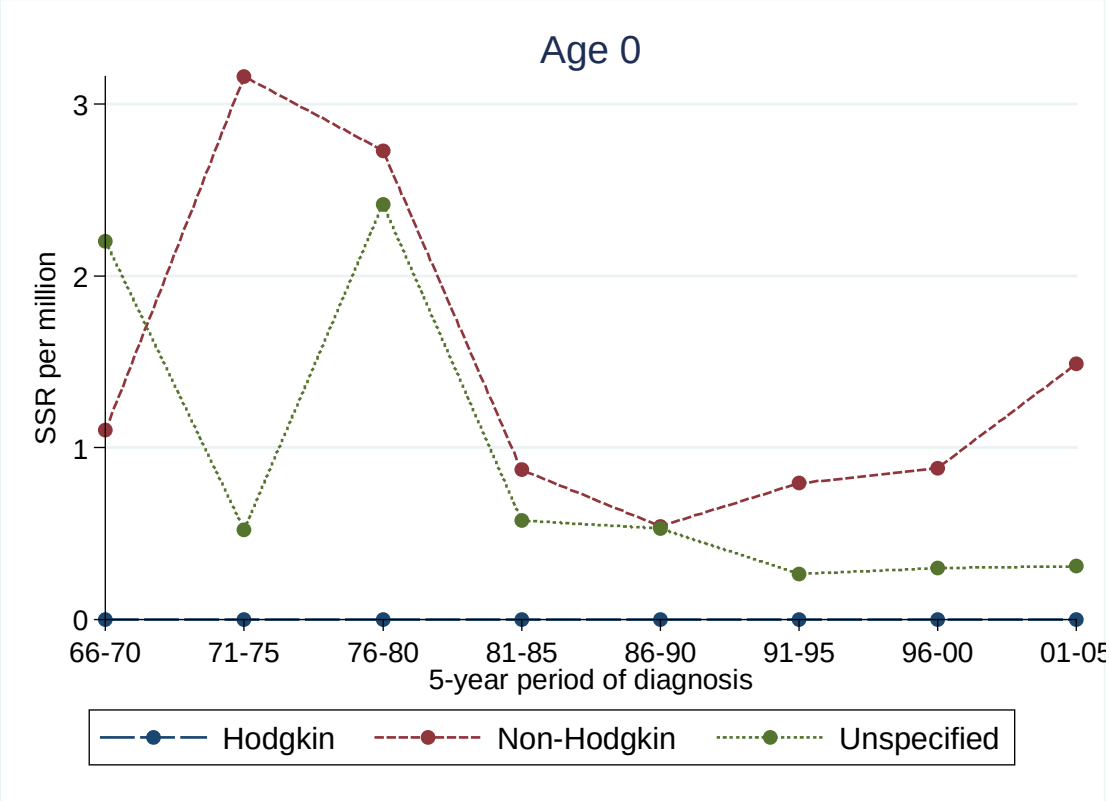


a) Standardised rate by single year of age at diagnosis, for successive diagnosis periods.

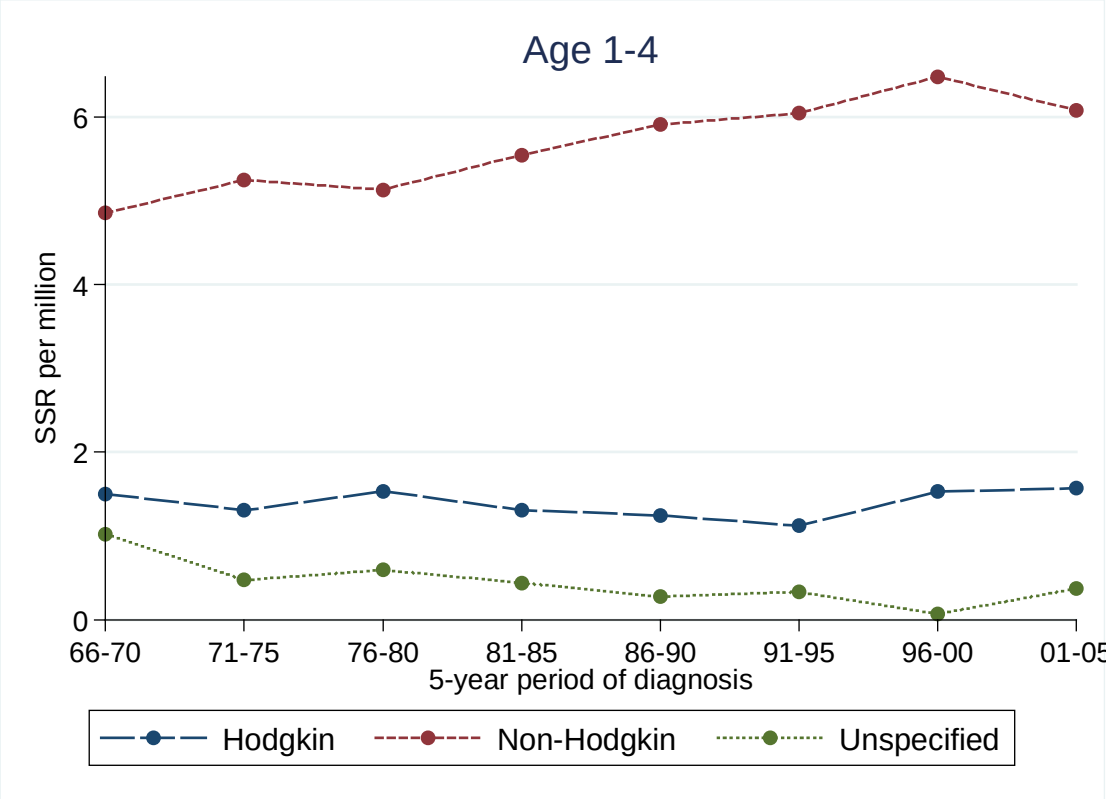


b) Standardised rate by year of diagnosis: actual (dotted), step model (solid) line.

Lymphoma: by year of diagnosis 1966-2005, Britain
Figures 5.3.2.2 (c) and (d).

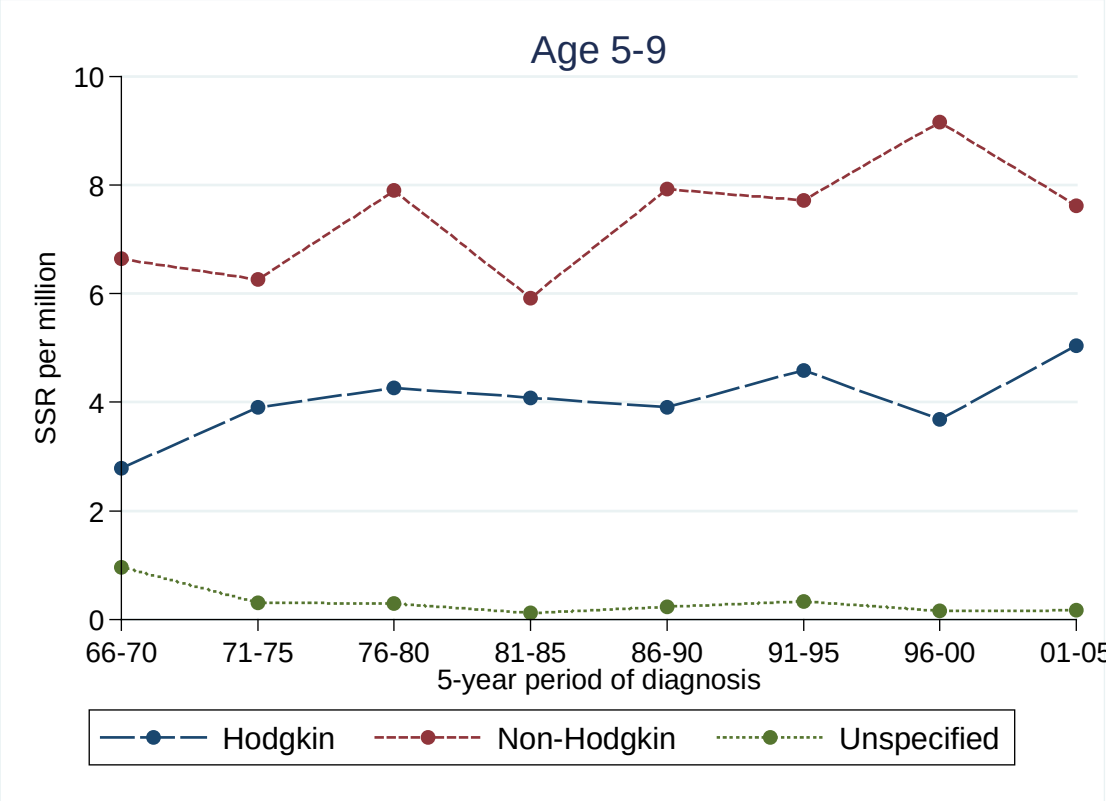


c) Standardised rate at age 0, by subtype and 5-year period of diagnosis.

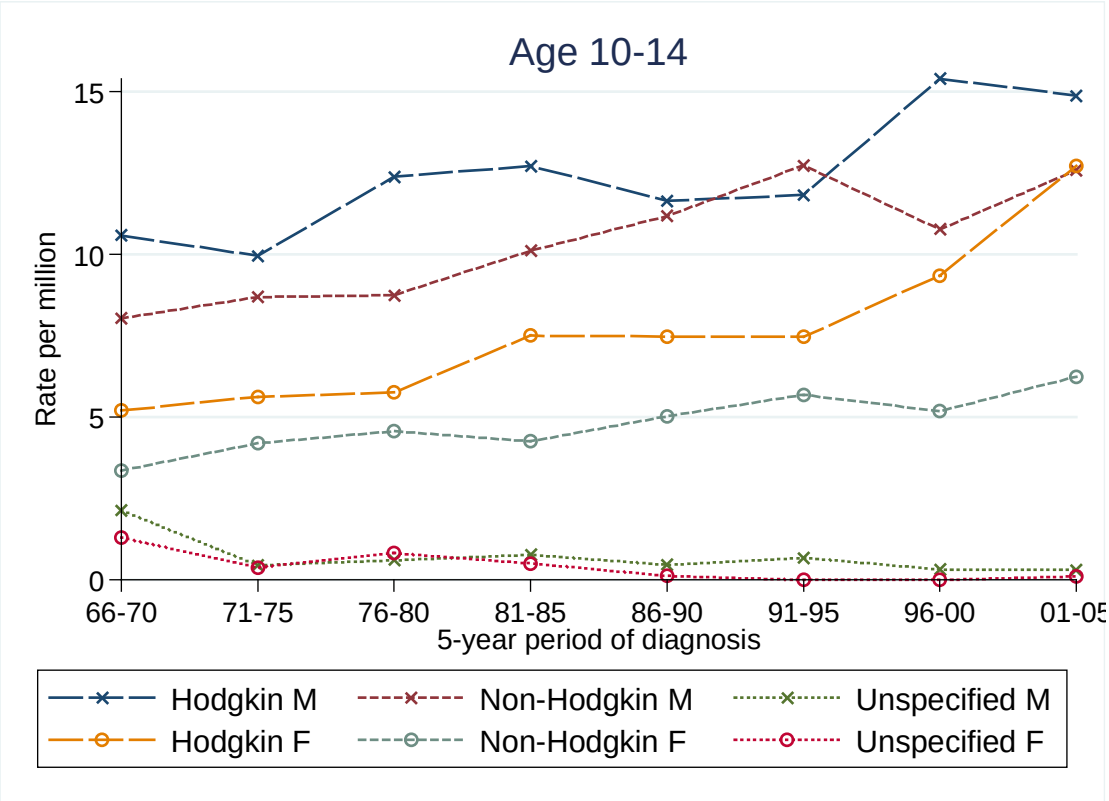


d) Standardised rate at age 1-4, by subtype and 5-year period of diagnosis.

Lymphoma: by year of diagnosis 1966-2005, Britain
Figures 5.3.2.2 (e) and (f).



e) Standardised rate at age 5-9, by subtype and 5-year period of diagnosis.



f) Rate at age 10-14, by subtype and sex, and 5-year period of diagnosis.

5.3.3 Central nervous system (CNS) tumours

5.3.3.1 Year of birth

See Tables 5.3.3.1 (a) to (c), and Figures 5.3.3.1 (a) and (b).

By year of birth, there was an overall increase of 1.2% per year. There was evidence for lack of fit of the Poisson model ($p<0.01$). In age groups 0, 5-9 and 10-14 there were increasing time trends of 1.8% (0.5 to 3.1), 1.3% (0.8 to 1.8) and 1.4% (0.9 to 2.0) per year, respectively (Table 5.3.3.1(c)). In age group 1-4 there was a non-significant increase of 0.5% (-0.1 to 1.1).

According to the step model, the overall rate was higher for children born during the 1980s than for children born during the 1970s (Figure 5.3.3.1(b)).

5.3.3.2 Year of diagnosis

See Tables 5.3.3.2 (a) to (c), Figures 5.3.3.2 (a) to (f), and Figures 5.3.14.2 (c) to (f).

By year of diagnosis, there was an overall increase of 1.3% per year. There was evidence for lack of fit of the Poisson model ($p<0.05$). In age groups 0, 1-4, 5-9 and 10-14 there were increasing time trends of 1.8% (1.2 to 2.4), 1.2% (1.0 to 1.5), 1.1% (0.9 to 1.4) and 1.5% (1.2 to 1.7) per year, respectively (Table 5.3.3.2(c)).

The step model indicates relatively small increases in the overall rate in 1975 and 1983, followed by a more striking increase in 1992 (Figure 5.3.3.2(b)).

Figures 5.3.3.2 (c) to (f) clearly show reductions in the proportion of cases of unspecified subtype for 1976-80 compared to 1971-75 and 1966-70. In all age groups the transfer was mainly to the glioma subtype.

5.3.3.3 Geographical analysis

See Tables 5.3.3.3 and Figures 5.3.3.3 (a) and (b).

In all regions, the SES-adjusted rate was higher in 1996-2005 than in 1976-85. (Figure 5.3.3.3(a)).

Within each of the three census decades, with the exception of the West Midlands in 1996-2005, London was the region with the lowest SES-adjusted rate: relative to the South East, the IRRs for London were 0.85 (0.73 to 1.00), 0.85 (0.74 to 0.98) and 0.95 (0.83 to 1.08).

In 1996-2005 there appeared to be some heterogeneity by region ($p=0.004$, Table 5.3.3.3), although there was some evidence for lack of model fit ($p<0.05$); the standardised rate per million ranged from 31 in the West Midlands to 42 in the South West (Figure 5.3.3.3(a)). There were particularly large rate increases from the second to the third census decade in the North East, Eastern and South West regions.

In all five SES categories, the region-adjusted rate was higher in 1996-2005 than in 1976-85. (Figure 5.3.3.3(b)).

Within each of the three census decades, after adjusting for regional differences, there was no statistically significant trend with SES, or heterogeneity between SES categories. The SES trend estimates for the three census decades were 1.00 (0.97 to 1.03), 0.98 (0.95 to 1.003) and 1.00 (0.97 to 1.02).

5.3.3.4 Discussion

By year of birth and year of diagnosis, the overall rate increased by 1.2% and 1.3% per year on average, respectively.

The change in rates by year of birth was largest in the youngest and oldest age groups, which are probably the most likely to have been under-registered in earlier years.

The reduction in the proportion of unspecified tumours in the first decade of the study period (Figures 5.3.3.2 (c) to (f)) is probably an artefact of coding. CNS tumours without histology, but with clinical or radiological features of glioma, were generally coded as 'unspecified CNS tumour' in the OSCC, rather than 'unspecified glioma' as in the CCRG era.

By year of diagnosis, some of the increase indicated by the step model at 1975 could be a delayed effect of the revised scheme for cancer registration that was introduced in 1971. Catecholamine testing for neuroblastoma is another possible factor: in the early years of the study period intracranial/intraspinal cancers of the 'embryonal' type, which would now be classified as CNS tumours, were apparently sometimes diagnosed as neuroblastoma without histological or biochemical proof (see Chapter 2).

Neither the early reduction in the proportion of unspecified cases, nor the increase in 1975, is likely to be an effect of the introduction of CT scanning, because CT was not in routine use for childhood CNS tumours until about 1986 (see Chapter 2). However, CT may explain the small increase suggested by the step model in 1983.

The step model indicates a relatively large increase in 1992. The most obvious explanation is the introduction of MRI scanning. As discussed in Chapter 2, MRI is better than CT for detecting CNS tumours in the posterior fossa and spinal cord, such as brain stem glioma, astrocytoma and medulloblastoma, and would be expected to lead to the detection of tumours at an earlier stage of disease. The timing is exactly as predicted, although the apparent size of the effect is slightly surprising.

Another possible explanation of this increase is the introduction of mandatory cancer registration in 1993. When registration was voluntary, CNS tumours may have been more likely than other childhood cancers to miss registration, because they were sometimes diagnosed and treated entirely in surgical units not specialising in oncology. Mandatory registration may have encouraged better communication between these units and the cancer registries (see Sections 5.3.5 and 5.3.11).

The lack of statistically significant regional differences during 1976-85 and 1986-95 suggests that completeness of diagnosis and registration of CNS tumours did not vary systematically by region in these decades. The consistently low rates for London are as predicted from the history of registration methods, but the relatively high rates for Wales and the South East are not. The large increases between 1986-95 and 1996-2005 in some regions, and the variation between regions in 1996-2005, suggest that the changes represented by the step increase in 1992 were not evenly spread over England and Wales. Perhaps mandatory registration had more effect in some regional registries than others, or perhaps provision of new MRI scanners varied by region, or both.

These analyses find no evidence of an association between SES and region-adjusted recorded incidence of CNS tumours.

CNS tumours: by 12-month birth cohort 1966-67 to 1989-90, Britain

Tables 5.3.3.1(a) to (c).

Time trend analysis. 66-70 is the 48-month birth cohort from 1 July 1966 to 30 June 1970, etc.

Age	0		1-4		5-9		10-14		0-14	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	46	32	237	185	284	220	240	184	807	621
70-74	40	29	195	181	257	198	206	159	698	567
74-78	29	31	179	136	189	181	193	134	590	482
78-82	36	35	189	168	225	194	238	206	688	603
82-86	38	45	201	166	263	227	212	213	714	651
86-90	44	46	208	183	300	256	265	202	817	687
Total	233	218	1209	1019	1518	1276	1354	1098	4314	3611

a) Number of cases by age, sex and grouped birth cohort.

Age	0		1-4		5-9		10-14		ASR	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	25.3	18.4	32.8	26.9	31.7	25.9	26.9	21.8	30.0	24.3
70-74	24.7	18.9	30.4	29.8	32.4	26.4	26.1	21.2	29.3	25.1
74-78	21.9	24.7	34.0	27.3	28.9	29.2	29.3	21.4	29.9	25.8
78-82	25.3	25.9	33.4	31.2	31.6	28.6	33.5	30.2	32.3	29.6
82-86	26.4	32.9	34.9	30.2	36.3	32.8	29.2	30.7	32.9	31.4
86-90	29.0	31.7	34.3	31.5	39.4	35.1	34.6	27.7	35.7	31.5

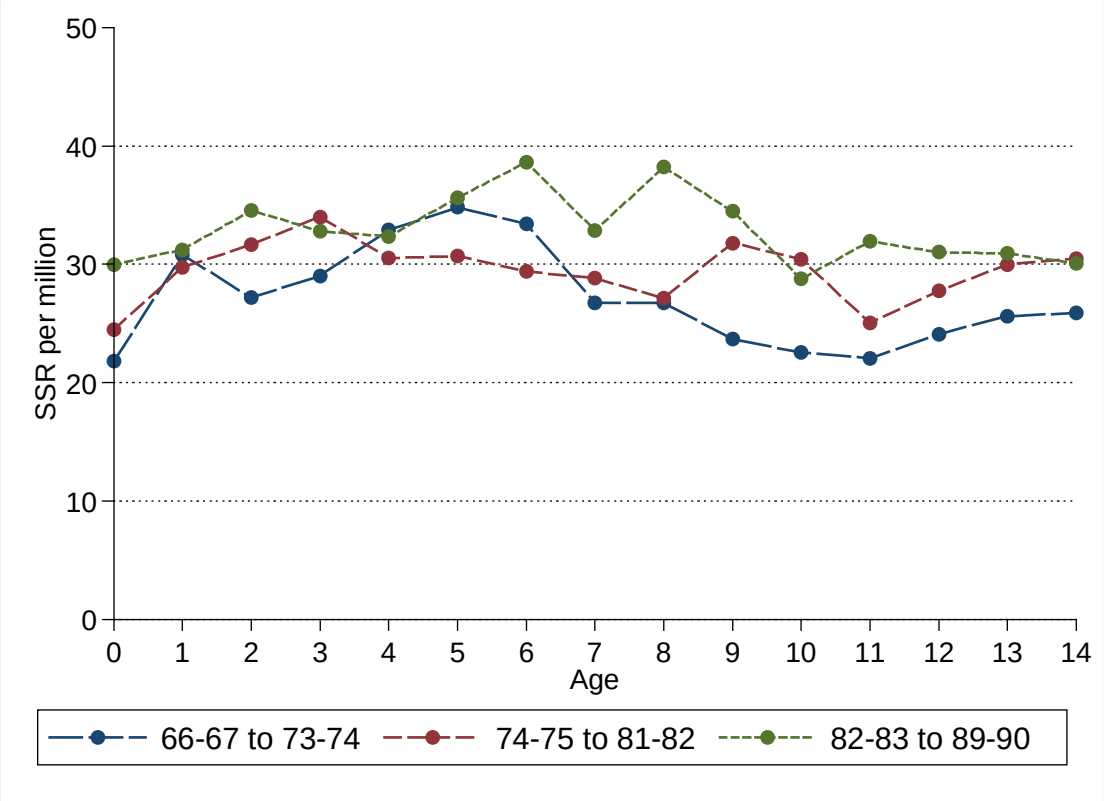
b) Incidence rate per million by age group, sex and grouped birth cohort.

Age	0	1-4	5-9	10-14	ASSR
Born					
66-70	21.8	29.8	28.8	24.4	27.1
70-74	21.8	30.1	29.4	23.7	27.2
74-78	23.3	30.7	29.0	25.4	27.8
78-82	25.6	32.3	30.1	31.9	31.0
82-86	29.6	32.6	34.6	29.9	32.2
86-90	30.3	32.9	37.3	31.1	33.6
Trend	**	-	***	***	***
AAPC	1.79	0.53	1.30	1.44	1.15
CI	0.48 to 3.11	-0.05 to 1.12	0.77 to 1.82	0.88 to 2.00	*0.84 to 1.46*
Fit	-	-	-	-	**

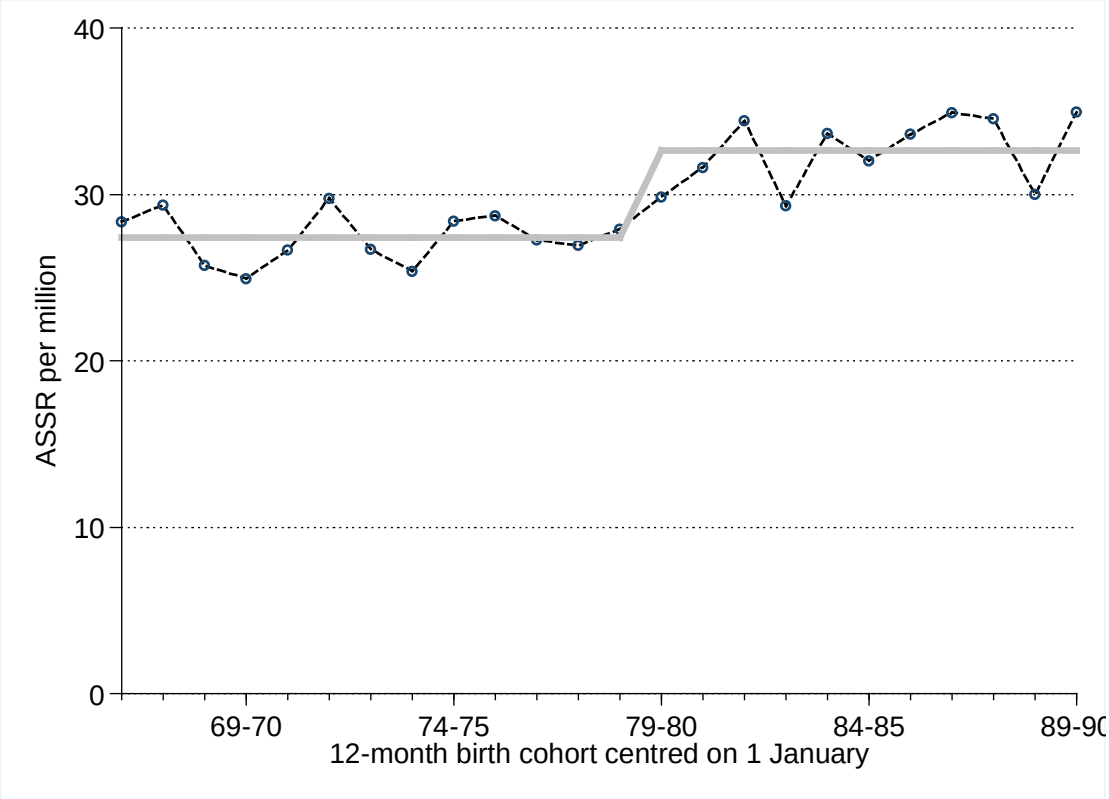
c) Sex-standardised incidence rate per million by age group and grouped birth cohort.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.088.

- = not significant; * p<0.05, ** p<0.01, *** p<0.001.

CNS tumours: by 12-month birth cohort 1966-67 to 1989-90, Britain
Figures 5.3.3.1 (a) and (b).



a) Standardised rate by single year of age at diagnosis, for successive birth periods.



b) Standardised rate by 12-month birth cohort: actual (dotted), step model (solid) line.

CNS tumours: by year of diagnosis 1966-2005, Britain
Tables 5.3.3.2 (a) to (c).

Time trend analysis.

Age/sex	0		1-4		5-9		10-14		0-14	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	60	41	283	224	307	263	210	168	860	696
1971-75	44	34	264	213	352	262	266	219	926	728
1976-80	42	38	226	205	322	260	300	241	890	744
1981-85	51	54	234	188	260	207	273	207	818	656
1986-90	49	57	261	204	278	265	248	184	836	710
1991-95	74	61	275	263	337	313	297	253	983	890
1996-00	69	60	292	245	373	322	281	251	1015	878
2001-05	64	59	311	267	363	284	381	263	1119	873
Total	453	404	2146	1809	2592	2176	2256	1786	7447	6175

a) Number of cases by age group, sex, and period of diagnosis.

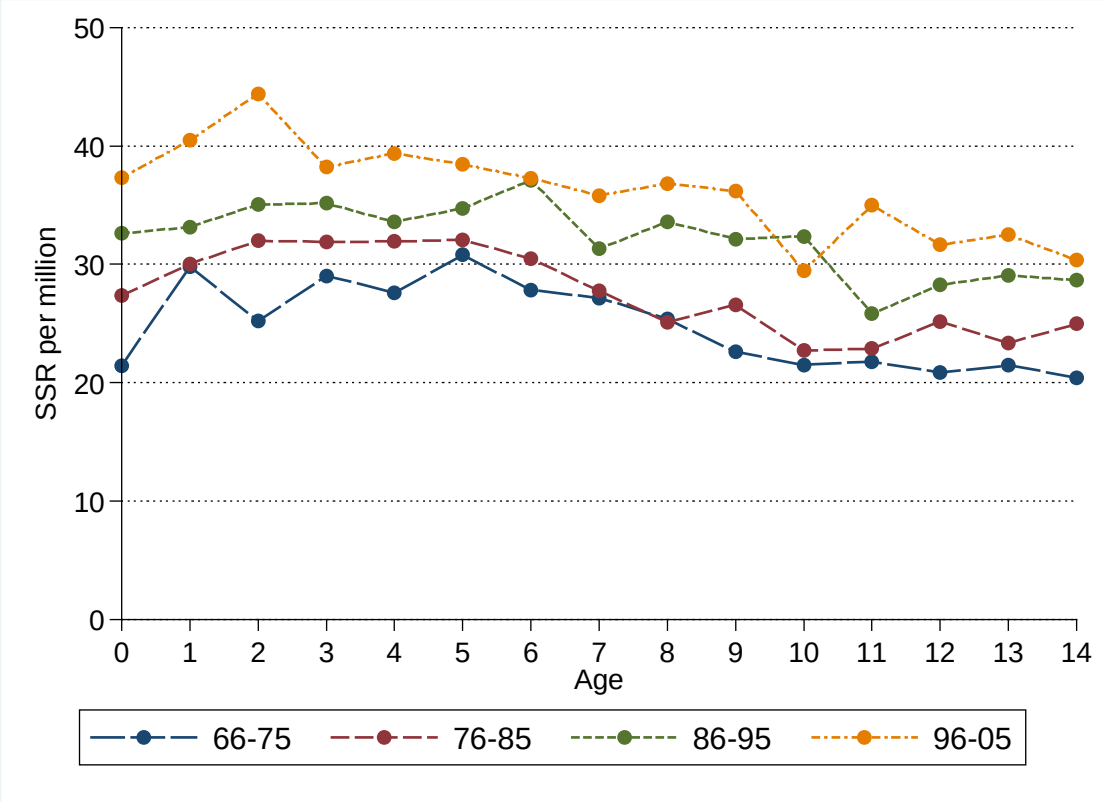
Age/sex	0		1-4		5-9		10-14		ASR	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70										
1971-75	26.2	18.7	30.1	24.8	27.8	25.0	21.4	18.2	26.1	22.3
1976-80	22.3	18.2	30.7	26.1	30.5	23.9	24.1	20.9	27.9	23.1
1981-85	24.9	23.7	32.7	31.3	30.8	26.3	26.0	22.0	29.3	26.0
1986-90	28.6	31.8	33.6	28.4	30.5	25.6	26.3	21.0	29.8	25.2
1991-95	26.0	31.6	35.7	29.2	31.6	31.6	28.9	22.6	31.4	27.9
1996-00	39.1	33.8	36.0	35.9	36.4	35.4	33.8	30.0	35.6	33.6
2001-05	39.2	35.8	40.1	35.4	39.0	35.3	30.3	28.3	36.4	33.0

b) Incidence rate per million by age group, sex and period of diagnosis.

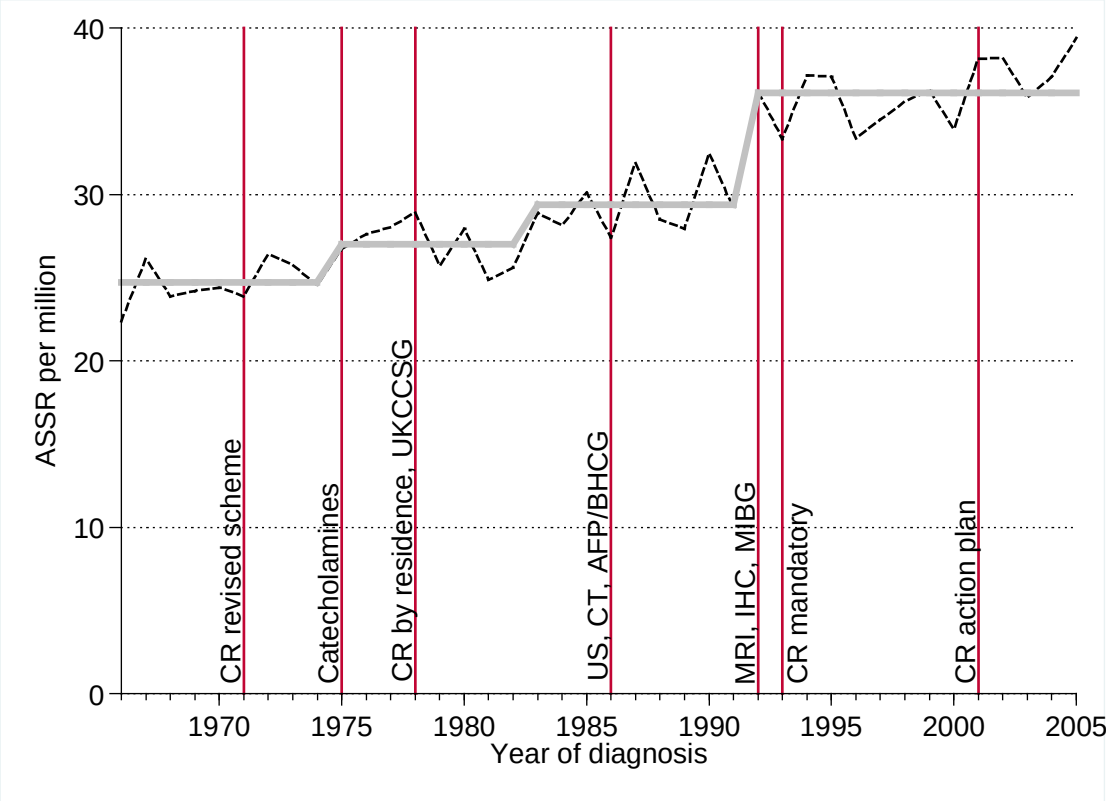
Age	0	1-4	5-9	10-14	ASSR
Diagnosed					
1966-70	22.4	27.5	26.4	19.8	24.2
1971-75	20.3	28.4	27.2	22.5	25.5
1976-80	24.3	32.0	28.6	24.0	27.7
1981-85	30.2	31.0	28.0	23.6	27.5
1986-90	28.8	32.4	31.6	25.7	29.7
1991-95	36.5	36.0	35.9	31.9	34.6
1996-00	37.5	37.8	37.2	29.3	34.7
2001-05	37.1	43.6	36.6	34.2	37.7
Trend	***	***	***	***	***
AAPC	1.83	1.24	1.13	1.46	1.30
CI	1.24 to 2.42	0.97 to 1.51	0.89 to 1.37	1.19 to 1.73	*1.15 to 1.45*
Fit	-	-	-	-	*

c) Sex-standardised incidence rate per million by age group and period of diagnosis.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.088.
- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

CNS tumours: by year of diagnosis 1966-2005, Britain
Figures 5.3.3.2 (a) and (b).

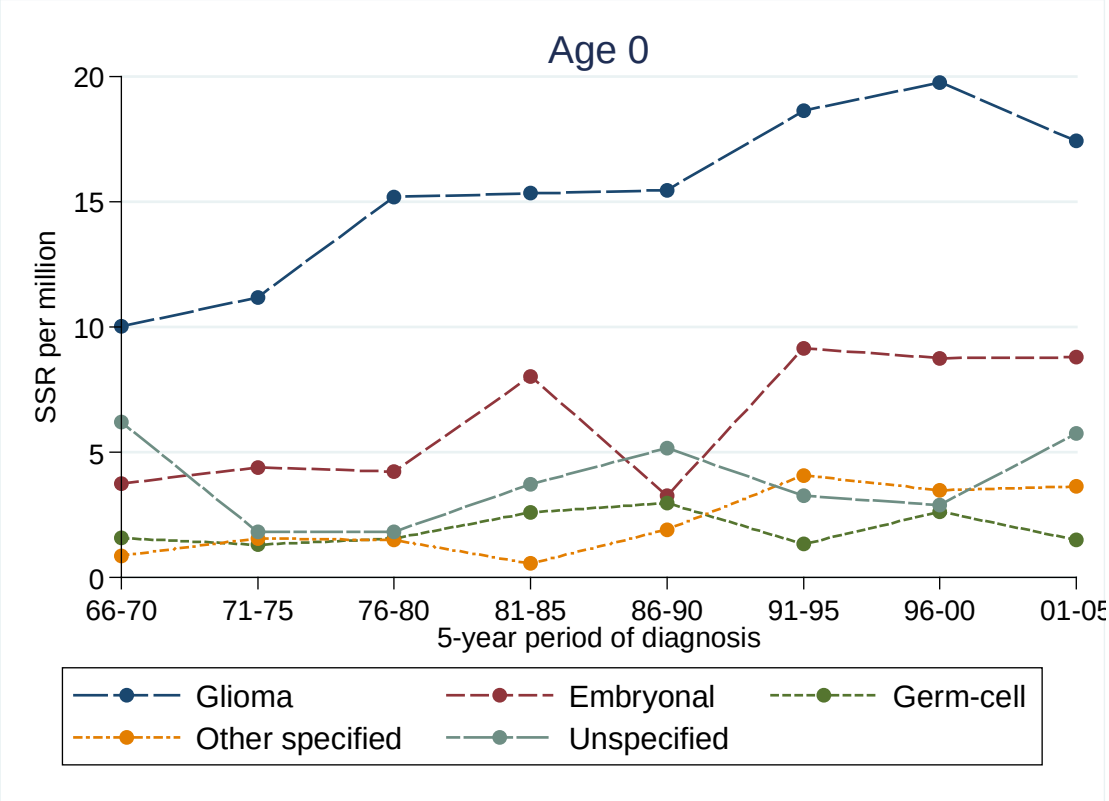


a) Standardised rate by single year of age at diagnosis, for successive diagnosis periods.

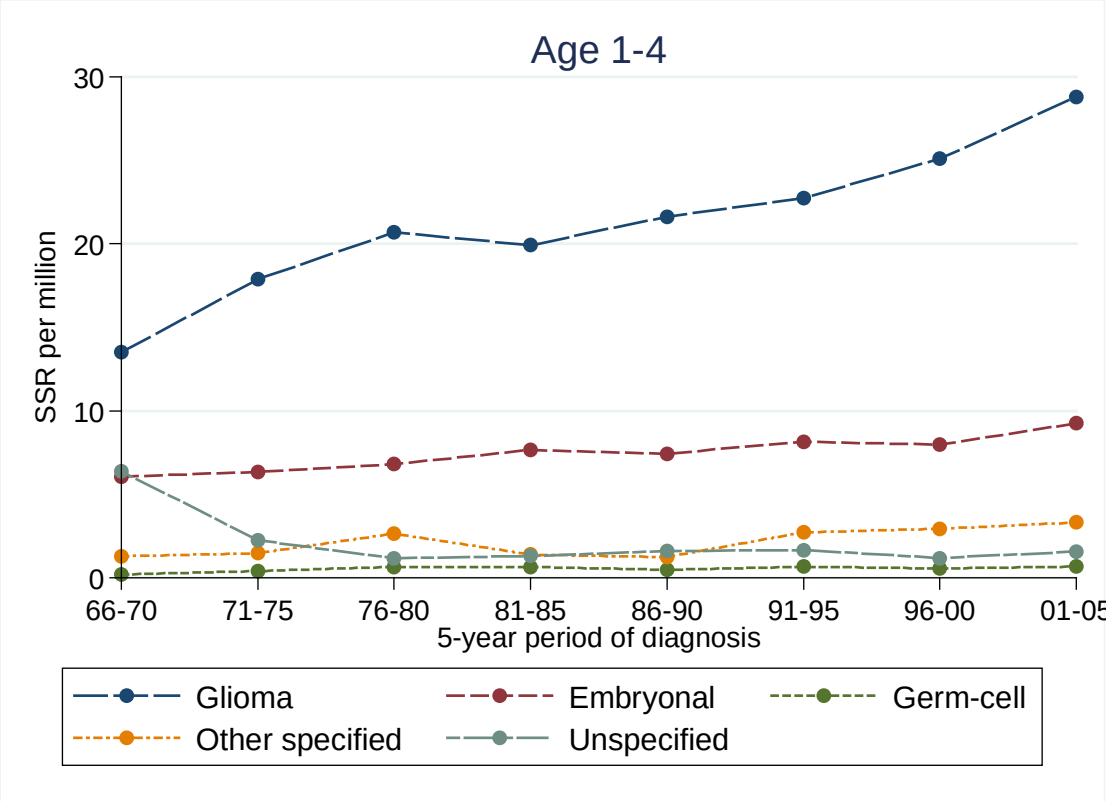


b) Standardised rate by year of diagnosis: actual (dotted), step model (solid) line.

CNS tumours: by year of diagnosis 1966-2005, Britain
Figures 5.3.3.2 (c) and (d).

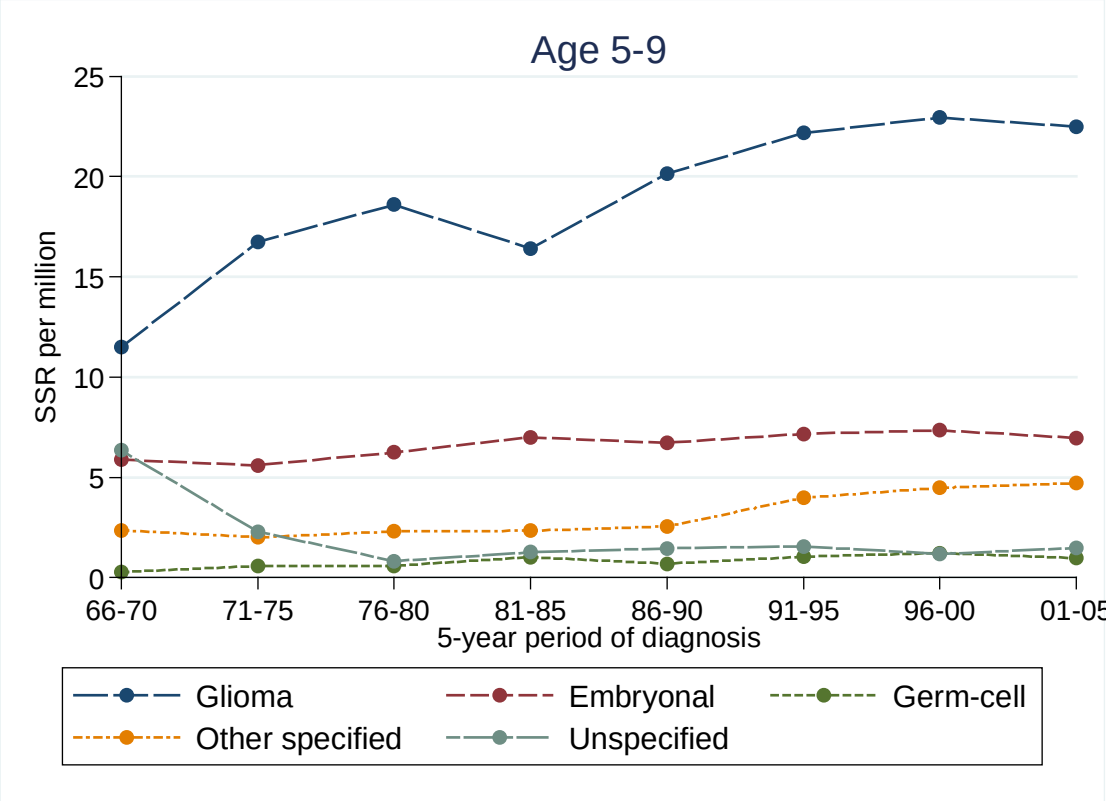


c) Standardised rate at age 0, by subtype and 5-year period of diagnosis.

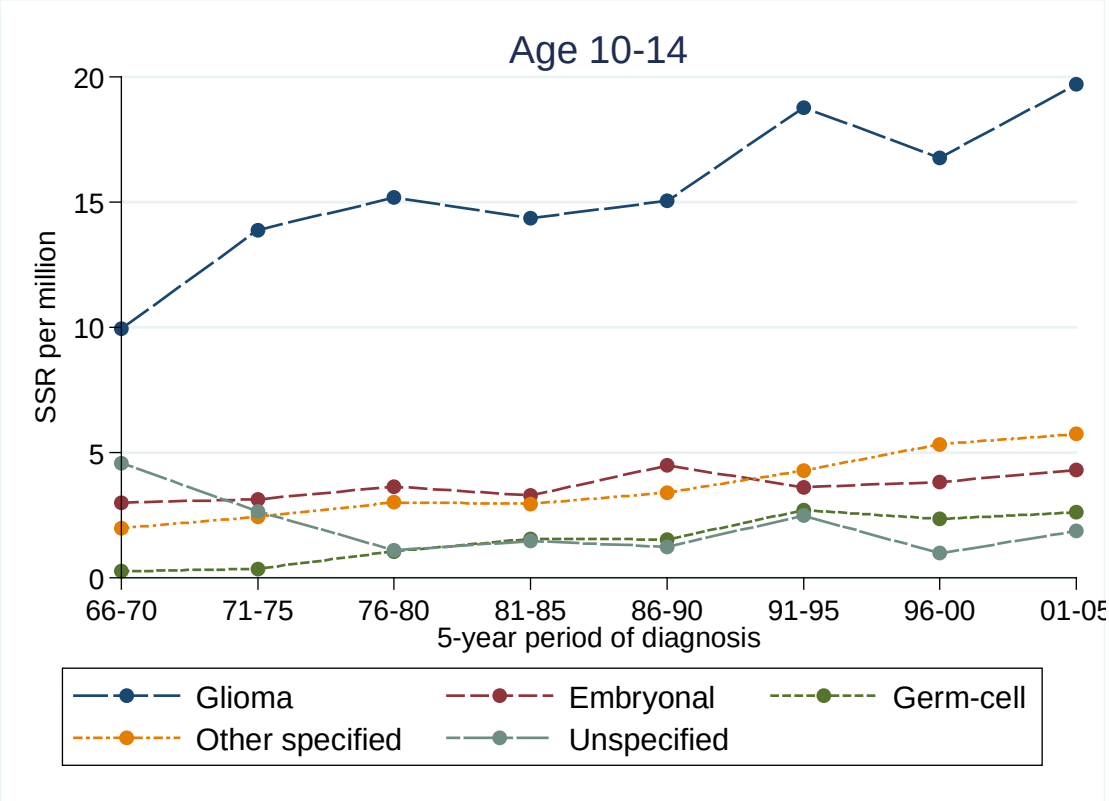


d) Standardised rate at age 1-4, by subtype and 5-year period of diagnosis.

CNS tumours: by year of diagnosis 1966-2005, Britain
Figures 5.3.3.2 (e) and (f).



e) Standardised rate at age 5-9, by subtype and 5-year period of diagnosis.



f) Standardised rate at age 10-14, by subtype and 5-year period of diagnosis.

CNS tumours: by year of diagnosis 1976-2005, England and Wales.
Table 5.3.3.3.

Geographical analysis by decade of diagnosis.

Decade	1976-85		1986-95		1996-2005	
Estimates	IRR	95% CI	IRR	95% CI	IRR	95% CI
Region:						
North East	1.04	0.86 to 1.26	0.88	0.73 to 1.06	1.17	0.99 to 1.38
North West	1.06	0.92 to 1.22	0.99	0.87 to 1.13	1.02	0.90 to 1.16
York/Humber	1.02	0.87 to 1.19	1.00	0.87 to 1.16	0.99	0.86 to 1.14
E Midlands	0.95	0.80 to 1.12	0.98	0.84 to 1.15	1.13	0.98 to 1.30
W Midlands	0.98	0.85 to 1.15	0.96	0.83 to 1.10	0.88	0.76 to 1.01
Eastern	0.94	0.81 to 1.10	0.87	0.75 to 1.00	1.06	0.93 to 1.21
London	0.85	0.73 to 1.00	0.85	0.74 to 0.98	0.95	0.83 to 1.08
South East	1.00	n/a	1.00	n/a	1.00	n/a
South West	1.07	0.91 to 1.25	0.99	0.85 to 1.14	1.19	1.04 to 1.36
Wales	0.99	0.82 to 1.20	0.97	0.81 to 1.15	1.02	0.87 to 1.21
SES:						
1=affluent	1.00	n/a	1.00	n/a	1.00	n/a
2	0.92	0.81 to 1.03	1.03	0.92 to 1.15	0.93	0.84 to 1.03
3	0.90	0.80 to 1.02	0.99	0.88 to 1.10	0.93	0.84 to 1.03
4	0.92	0.82 to 1.04	0.92	0.82 to 1.03	1.02	0.92 to 1.13
5=deprived	0.99	0.88 to 1.12	0.94	0.83 to 1.06	0.93	0.83 to 1.04
SES trend:						
Estimates	1.00	0.97 to 1.03	0.98	0.95 to1.003	1.00	0.97 to 1.02
Trend	-		-		-	
P (Region)	0.239		0.240		0.004	
P (SES)	0.290		0.306		0.192	
Fit	-		-		*	

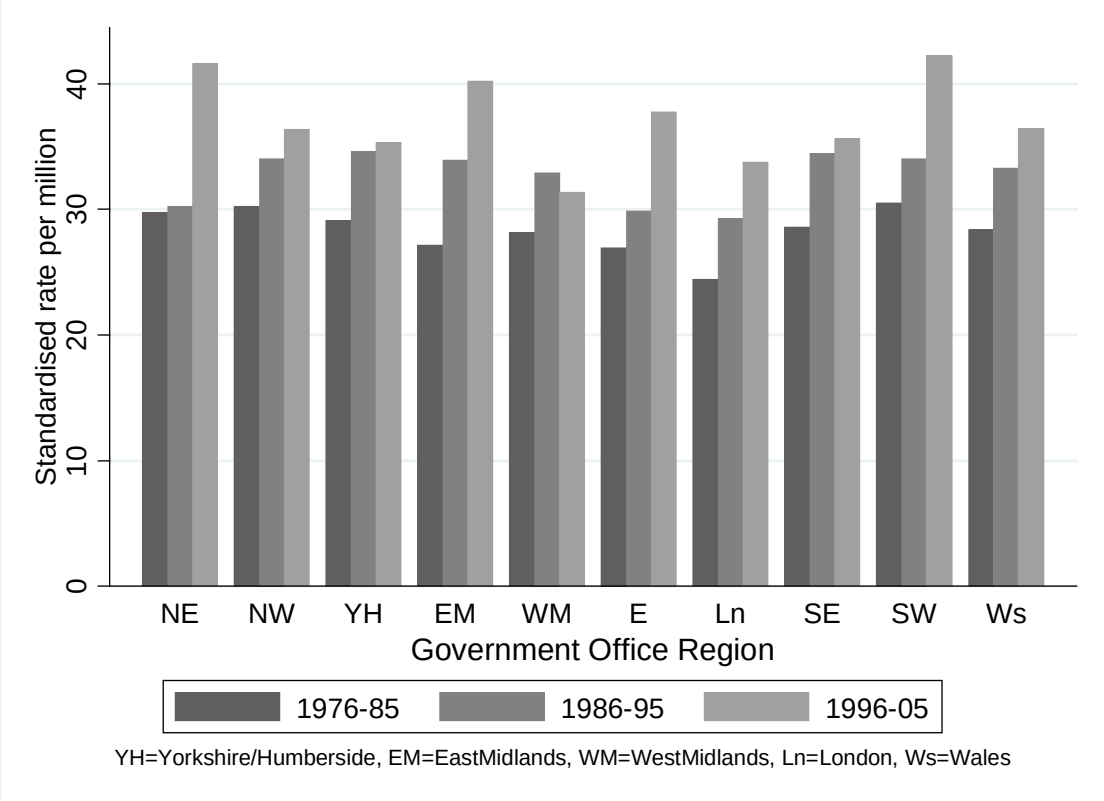
IRR: incidence rate ratio, standardised by age group and sex, for each Government Office Region and SES category (from a Poisson regression model that includes both region and SES as categorical factors), by decade of diagnosis, with estimated 95% confidence interval (CI). Reference categories: South East region; SES category 1 (most affluent).

P (Region): significance level of test for heterogeneity of IRRs between regions.
P (SES): significance level of test for heterogeneity of IRRs between SES categories.
Fit: significance level of deviance test for lack of fit to the categorical model.

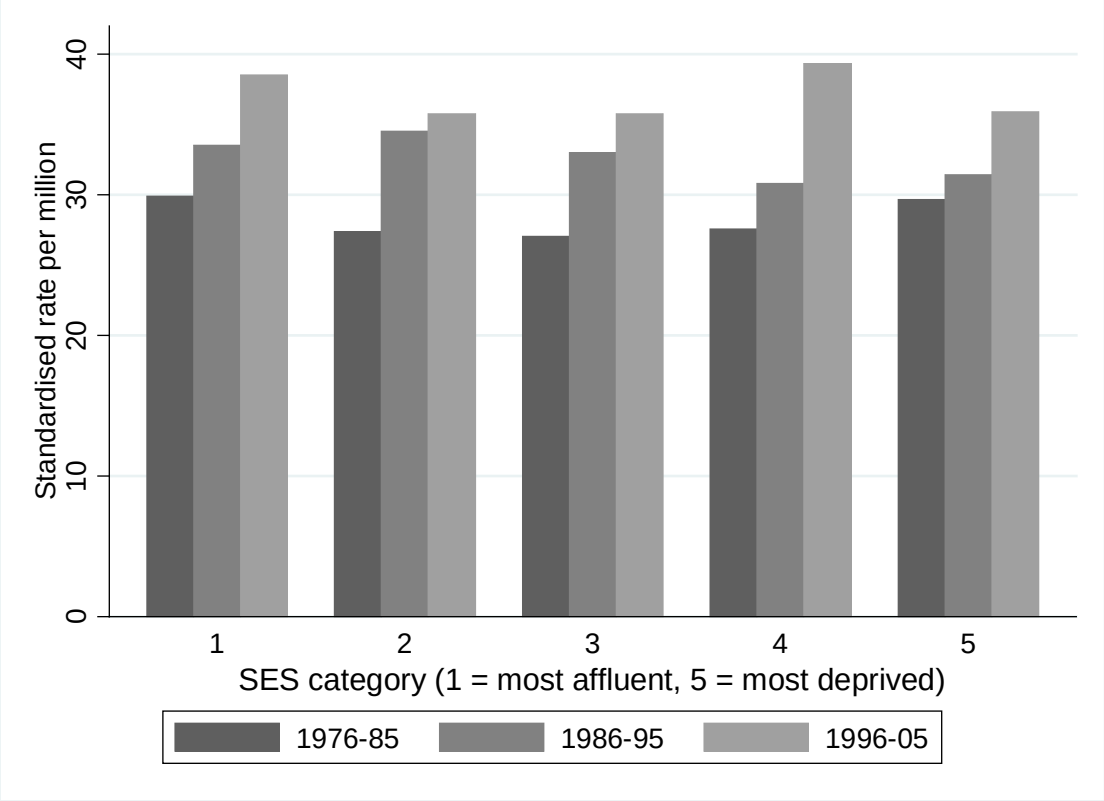
SES trend: IRR for an increase of one SES category, with estimated 95% CI (from a Poisson regression model that includes region as a categorical factor, and the SES category number as a continuous factor).

- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

CNS tumours: by year of diagnosis 1976-2005, England and Wales.
Figures 5.3.3.3 (a) and (b).



a) SES-standardised ASSR by Government Office Region and decade of diagnosis.



b) Region-standardised ASSR by SES category and decade of diagnosis.

5.3.4 Peripheral nervous system (PNS) cancer

This group consists almost entirely of neuroblastoma.

5.3.4.1 Year of birth

See Tables 5.3.4.1 (a) to (c), and Figures 5.3.4.1 (a) and (b).

By year of birth, there was an increasing time trend of 1.4% per year (0.7 to 2.0). In age groups 0 and 1-4 there were increasing time trends of 1.5% (0.3 to 2.7) and 1.7% (0.9 to 2.5) and per year, respectively. In age group 5-9 there was a non-significant increase of 0.3% (-1.4 to 2.0). In age group 10-14 there was evidence for lack of fit of the Poisson model ($p<0.05$), and there was a decrease of -0.7% per year on average (Table 5.3.4.1(c)).

According to the step model, the overall rate was higher for children born during the 1980s than for those born during the 1970s (Figure 5.3.4.1(b)).

5.3.4.2 Year of diagnosis

See Tables 5.3.4.2 (a) to (c), Figures 5.3.4.2 (a) and (b), and Figures 5.3.13.2 (c) to (f).

By year of diagnosis, there was an overall increase of 0.6% per year, with very strong evidence for lack of fit of the Poisson model ($p<0.001$). In age groups 0 and 1-4 there were increasing time trends of 1.7% (1.1 to 2.2) and 0.9% (0.5 to 1.3) per year, respectively, while in age groups 5-9 and 10-14 there were decreasing time trends of -0.8% (-1.6 to -0.1) and -3.9% (-5.2 to -2.5) per year. (Table 5.3.4.2(c)).

Figures 5.3.4.2 (a) and 5.3.13.2 (c) to (f) show the decrease in rates for older children between the first and second decades, and the striking increase at age 0 between the third and fourth decades.

The step model indicates an increase at 1986 (Figure 5.3.4.2(b)).

5.3.4.3 Discussion

By year of birth and by year of diagnosis the rates increased by 1.4% and 0.6% per year on average, respectively. The large difference between these two AAPCs reflects the different time periods covered by the two analyses, and the plateau that followed the fairly sudden increase in rates during the 1980s. There was strong evidence for lack of fit to the overall trend model by year of diagnosis: this is not surprising, since there were increasing trends at ages 0 and 1-4, and decreasing trends at ages 5-9 and 10-14.

The step in rates by year of diagnosis at 1986 (and by year of birth at 1980-81, since most neuroblastoma is diagnosed at ages 0-5) closely matches the pre-specified timing of the routine use of ultrasound scanning in paediatric oncology. This is entirely consistent with the suggestion that the use of ultrasound resulted in the diagnosis of many cases of neuroblastoma that would previously have regressed spontaneously without ever being recognized (see Chapter 2).

Some relatively small changes in rate may be explained by diagnostic transfer affecting just a few cases per year. Figure 5.3.13.2(c) suggests that transfer from lymphoma might explain part of the increase in PNS cancer at age 0 from 1976-80 to 1981-85. The decrease between 1971-75 and 1976-80 in PNS cancer at ages 5-9 and 10-14 is consistent with Marsden and Steward's suggestion that neuroblastoma might have been over-diagnosed before the introduction of catecholamine testing in 1975 (Section 2.5.2). Figures 5.3.13.2 (e) and (f), 5.3.8.2 (e) and (f), and 5.3.9.2 (e) and (f), suggest transfer to bone (Ewing) and soft-tissue sarcoma (rhabdomyosarcoma). Some diagnostic transfer to CNS tumours is also possible: there was an increase in CNS tumours in the same age groups at the same time (see Section 5.3.3, and Tables 5.3.3.2(c) and 5.3.4.2(c)).

PNS cancer: by 12-month birth cohort 1966-67 to 1989-90, Britain

Tables 5.3.4.1 (a) to (c).

Time trend analysis. 66-70 is the 48-month birth cohort from 1 July 1966 to 30 June 1970, etc.

Age	0		1-4		5-9		10-14		0-14	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	44	52	114	88	35	24	8	8	201	172
70-74	48	37	93	67	22	15	3	5	166	124
74-78	39	28	81	65	17	12	5	4	142	109
78-82	54	41	83	88	38	21	7	5	182	155
82-86	56	37	96	93	23	20	2	4	177	154
86-90	43	56	129	94	25	19	6	6	203	175
Total	284	251	596	495	160	111	31	32	1071	889

a) Number of cases by age, sex and grouped birth cohort.

Age	0		1-4		5-9		10-14		ASR	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	24.2	29.9	15.8	12.8	3.9	2.8	0.9	0.9	7.4	6.7
70-74	29.6	24.1	14.5	11.0	2.8	2.0	0.4	0.7	6.9	5.4
74-78	29.4	22.3	15.4	13.0	2.6	1.9	0.8	0.6	7.2	5.8
78-82	37.9	30.3	14.7	16.3	5.3	3.1	1.0	0.7	8.5	7.7
82-86	38.9	27.0	16.7	16.9	3.2	2.9	0.3	0.6	8.2	7.5
86-90	28.3	38.6	21.3	16.2	3.3	2.6	0.8	0.8	8.9	8.0

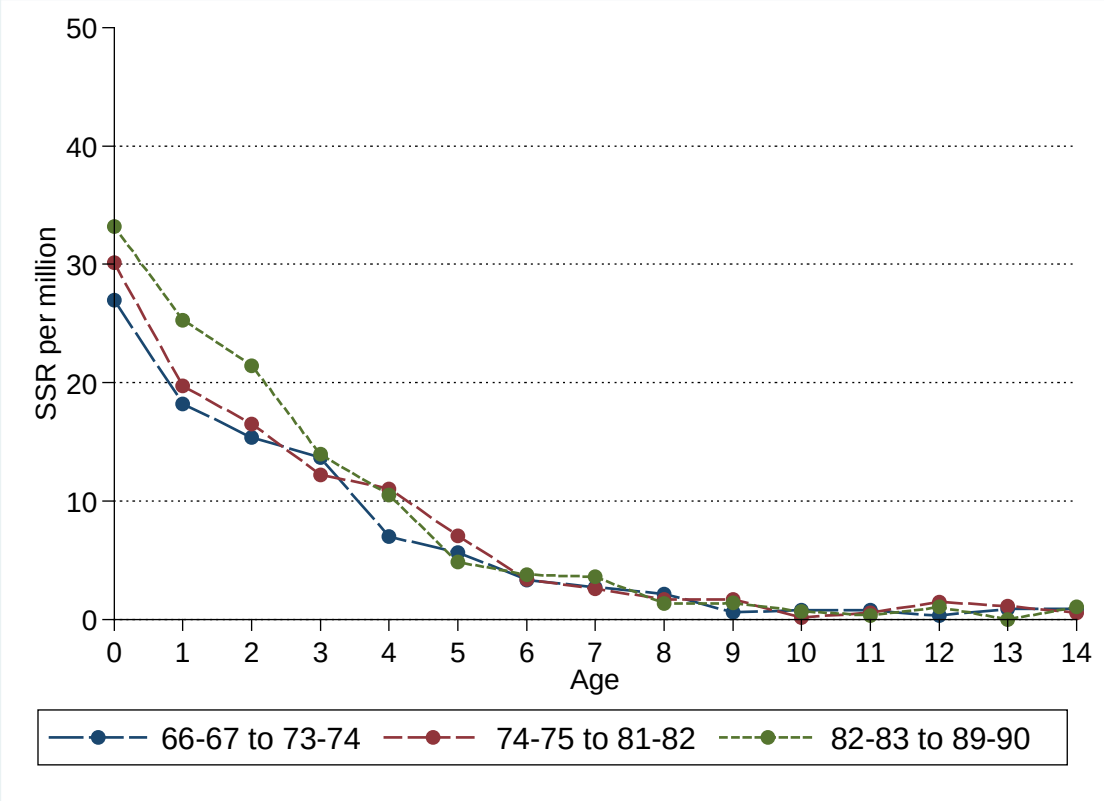
b) Incidence rate per million by age group, sex and grouped birth cohort.

Age	0	1-4	5-9	10-14	ASSR
Born					
66-70	27.0	14.3	3.4	0.9	7.0
70-74	26.9	12.8	2.4	0.5	6.2
74-78	25.9	14.2	2.3	0.7	6.5
78-82	34.1	15.5	4.2	0.9	8.1
82-86	33.0	16.8	3.0	0.4	7.8
86-90	33.4	18.7	2.9	0.8	8.5
Trend	*	***	-	-	***
AAPC	1.46	1.69	0.29	-0.68	1.36
CI	0.27 to 2.67	0.85 to 2.54	-1.36 to 1.98	*-4.06 to 2.82*	0.73 to 1.99
Fit	-	-	-	*	-

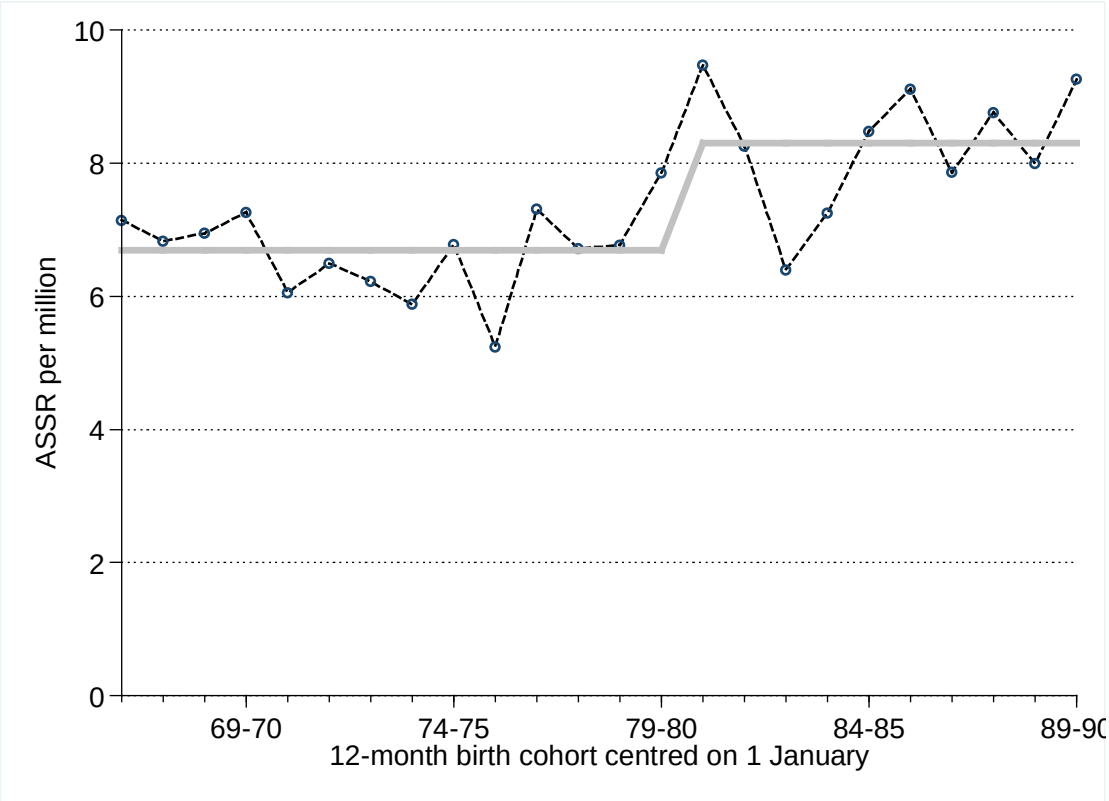
c) Sex-standardised incidence rate per million by age group and grouped birth cohort.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.320.

- = not significant; * p<0.05, ** p<0.01, *** p<0.001.

PNS cancer: by 12-month birth cohort 1966-67 to 1989-90, Britain
Figures 5.3.4.1 (a) and (b).



a) Standardised rate by single year of age at diagnosis, for successive birth periods.



b) Standardised rate by 12-month birth cohort: actual (dotted), step model (solid) line.

PNS cancer: by year of diagnosis 1966-2005, Britain
Tables 5.3.4.2 (a) to (c).

Time trend analysis.

Age/sex	0		1-4		5-9		10-14		0-14	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	54	70	146	117	53	45	21	19	274	251
1971-75	55	47	127	95	55	28	27	16	264	186
1976-80	56	33	102	79	29	24	11	14	198	150
1981-85	69	54	97	106	26	14	7	7	199	181
1986-90	60	70	153	120	34	33	8	4	255	227
1991-95	78	45	135	115	29	19	7	6	249	185
1996-00	64	70	156	104	33	28	4	4	257	206
2001-05	88	85	112	113	27	27	10	8	237	233
Total	524	474	1028	849	286	218	95	78	1933	1619

a) Number of cases by age group, sex, and period of diagnosis.

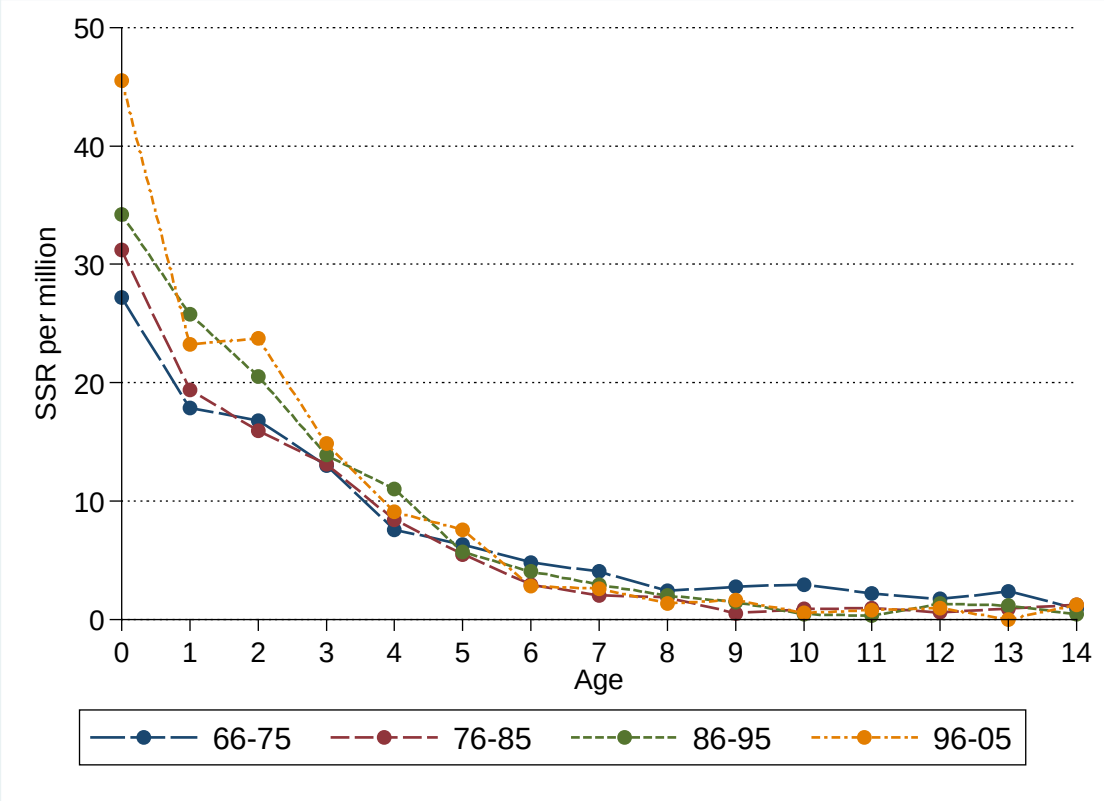
Age/sex	0		1-4		5-9		10-14		ASR	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	23.6	31.9	15.5	13	4.8	4.3	2.1	2.1	8	7.7
1971-75	27.9	25.2	14.8	11.6	4.8	2.6	2.4	1.5	8.2	6.1
1976-80	33.1	20.6	14.8	12.1	2.8	2.4	1.0	1.3	7.4	5.8
1981-85	38.8	31.8	13.9	16.0	3.0	1.7	0.7	0.7	7.5	7.2
1986-90	31.8	38.8	20.9	17.2	3.9	3.9	0.9	0.5	9.3	8.6
1991-95	41.2	24.9	17.7	15.7	3.1	2.1	0.8	0.7	8.8	6.8
1996-00	36.4	41.8	21.4	15.0	3.5	3.1	0.4	0.5	9.4	8.0
2001-05	51.8	52.6	16.5	17.5	3.0	3.1	1.0	0.9	9.2	9.5

b) Incidence rate per million by age group, sex and period of diagnosis.

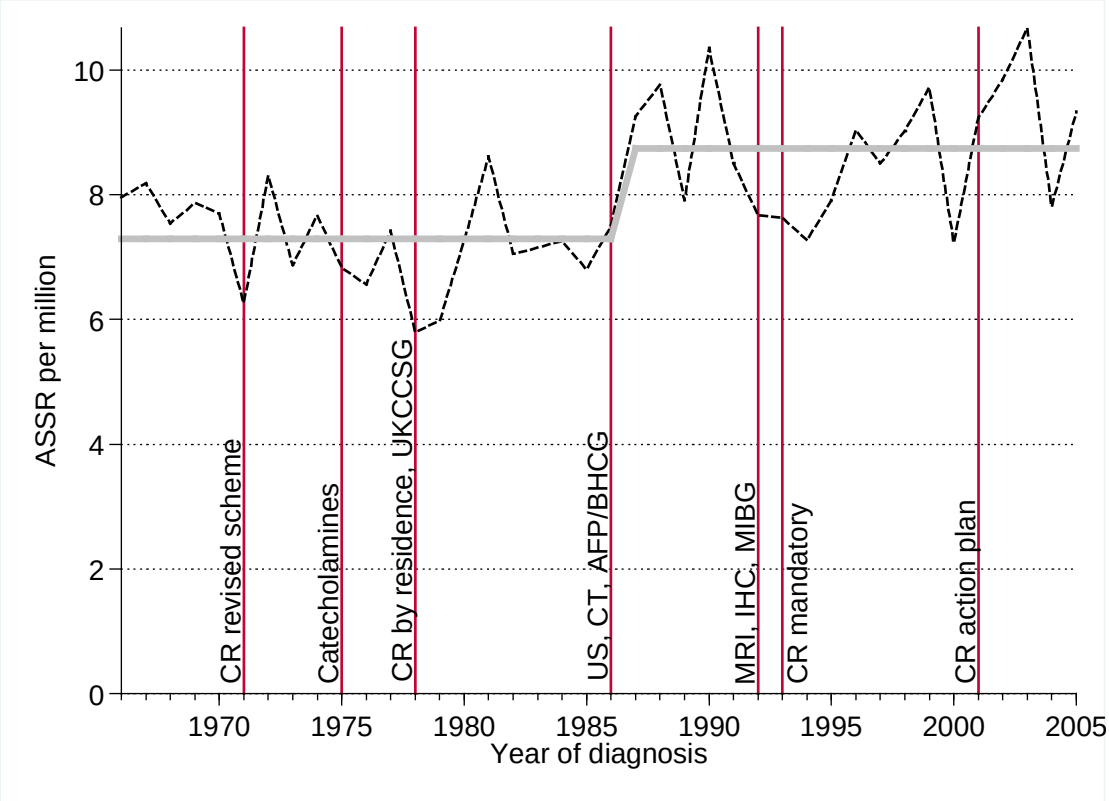
Age	0	1-4	5-9	10-14	ASSR
Diagnosed					
1966-70	27.7	14.2	4.5	2.1	7.9
1971-75	26.6	13.2	3.7	2.0	7.2
1976-80	26.9	13.4	2.6	1.1	6.6
1981-85	35.3	14.9	2.4	0.7	7.4
1986-90	35.3	19.0	3.9	0.7	9.0
1991-95	33.1	16.7	2.6	0.8	7.8
1996-00	39.1	18.2	3.3	0.4	8.7
2001-05	52.2	17.0	3.1	1.0	9.4
Trend	***	***	*	***	***
AAPC	1.65	0.88	-0.84	-3.85	0.63
CI	1.11 to 2.19	0.49 to 1.27	-1.59 to -0.10	-5.20 to -2.49	*0.35 to 0.91*
Fit	-	-	-	-	***

c) Sex-standardised incidence rate per million by age group and period of diagnosis.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups < 0.001.
- = not significant; * p<0.05, ** p<0.01, *** p<0.001.

PNS cancer: by year of diagnosis 1966-2005, Britain
Figures 5.3.4.2 (a) and (b).



a) Standardised rate by single year of age at diagnosis, for successive diagnosis periods.



b) Standardised rate by year of diagnosis: actual (dotted), step model (solid) line.

5.3.5 Retinoblastoma

5.3.5.1 Year of birth

See Tables 5.3.5.1 (a) to (c), and Figures 5.3.5.1 (a) and (b).

By year of birth, overall, there was a non-significant increase of 0.7% per year (-0.2 to 1.7). In age group 0 there was an increasing time trend of 1.8% (0.4 to 3.3) per year. In age group 1-4 there was little change: -0.2% (-1.4 to 1.0) per year (Table 5.3.5.1(c)). In age group 5-14 there was a non-significant increase of 2.9% (-1.2 to 7.1) per year. The differences in trend between age groups were not quite statistically significant (p=0.067).

Between the first and the second 8-year period of birth, there was a decrease in the rate at ages 1-5, and an increase at age 0. Between the second and third periods, there were small increases at all individual ages up to 6. (Table 5.3.5.1(c) and Figure 5.3.5.1(a)).

The step model indicates no change in rate (Figure 5.3.5.1(b)).

5.3.5.2 Year of diagnosis

See Tables 5.3.5.2 (a) to (c), and Figures 5.3.5.2 (a) to (f)

By year of diagnosis, there was an overall time trend of 0.6% (0.2 to 1.1) per year. In age groups 0 and 5-14, there were increasing time trends of 1.1% (0.4 to 1.8) and 2.3% (0.4 to 4.4) per year, respectively. In age group 1-4 there was little change 0.2% (-0.4 to 0.7). The differences in trend between age groups were statistically significant (p=0.025). (Table 5.3.5.2(c)).

Figures 5.3.5.2 (a) and 5.3.5.2 (c) to (e) show the decrease in rates at ages 1-4 between the first and second decades, in both unilateral and bilateral cases, and the increase at age 0, which was of approximately the same size. From the second to the third decade, in all age groups, there were increases in unilateral cases, but not in bilateral cases (Figures 5.3.5.2 (c) to (e)). There was little change from the third to the fourth decade.

Figure 5.3.5.2(d) shows the rates in age group 1-4 separately for boys and girls, because the trend estimate in this age group differed significantly by sex (see Table 5.2 (d)). The increase in rate appears to be greater for girls than boys, particularly for unilateral cases.

The step model indicates an increase at 1993. (Figure 5.3.5.2(b)).

Among cases diagnosed in the first year of life, the proportion diagnosed in the first month of life was higher in 1986-2005 than in 1966-85 (Figure 5.3.5.2 (f)).

5.3.5.3 Discussion

By year of birth and by year of diagnosis the rates increased by 0.7% (non-significant) and 0.6% (significant) per year on average, respectively.

By year of birth, there is clear evidence of a change in age at diagnosis. Children born from 1974-75 to 1989-90 were more likely to be diagnosed in infancy than those born from 1966-67 to 1973-74 (Figure 5.3.5.1(a)). This change also appears in the analysis by year of diagnosis from the first to the second decade of the study period (Figure 5.3.5.2(a)). It may be related to the introduction of US and CT, both of which can aid the diagnosis of retinoblastoma. It does not seem to be entirely due to better monitoring of known retinoblastoma families, since the effect is seen as strongly in unilateral as in bilateral cases (Figures 5.3.5.2(c) to (e)), and unilateral patients are much less likely to have a positive family history. However, monitoring might explain the increase from 1966-85 to 1986-2005 in the proportion of cases diagnosed in the first month of life (Figure 5.3.5.2(f)).

Table 5.3.5.2(c) and Figures 5.3.5.2(a) and 5.3.5.2(d) show that from 1976-85 to 1986-95 there was an increase in rate at ages 1-4 of about 30%, which derived mainly from unilateral, not bilateral disease; the apparent difference between girls than boys (Figure 5.3.5.2(d)) is hard to interpret, and may be due to chance. The increase does not seem to represent a change in age at diagnosis, because there was little sign of a compensating reduction in other age groups. Mandatory registration from 1993 is a possible

explanation: retinoblastoma patients treated outside the main retinoblastoma centres may have been more likely to be missed when registration was voluntary, particularly if seen by ophthalmologists rather than oncologists. The proportion of patients referred to specialist centres increased at around this time; for example, the centre at St Bartholomew's Hospital dates from 1983. Moreover, the use of ultrasound may have enabled diagnosis of some tumours that previously would have regressed spontaneously. All these explanations are consistent with the observation that the increase was mainly in unilateral cases, i.e. less severe disease, usually without a family history.

Retinoblastoma: by 12-month birth cohort 1966-67 to 1989-90, Britain
Tables 5.3.5.1 (a) to (c).

Time trend analysis. 66-70 is the 48-month birth cohort from 1 July 1966 to 30 June 1970, etc.

Age	0		1-4		5-9		10-14		0-14	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	28	33	55	51	1	1	1	0	85	85
70-74	22	21	61	46	5	7	0	0	88	74
74-78	27	31	30	31	3	3	0	0	60	65
78-82	29	25	32	38	3	3	1	0	65	66
82-86	44	33	42	37	6	2	1	0	93	72
86-90	36	24	42	52	3	4	1	1	82	81
Total	186	167	262	255	21	20	4	1	473	443

a) Number of cases by age, sex and grouped birth cohort.

Age	0		1-4		5-9		10-14		ASR	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	15.4	19.0	7.6	7.4	0.1	0.1	0.1	0.0	3.1	3.3
70-74	13.6	13.7	9.5	7.6	0.6	0.9	0.0	0.0	3.7	3.2
74-78	20.4	24.7	5.7	6.2	0.5	0.5	0.0	0.0	3.0	3.5
78-82	20.4	18.5	5.6	7.1	0.4	0.4	0.1	0.0	3.1	3.3
82-86	30.6	24.1	7.3	6.7	0.8	0.3	0.1	0.0	4.3	3.5
86-90	23.7	16.5	6.9	9.0	0.4	0.5	0.1	0.1	3.6	3.7

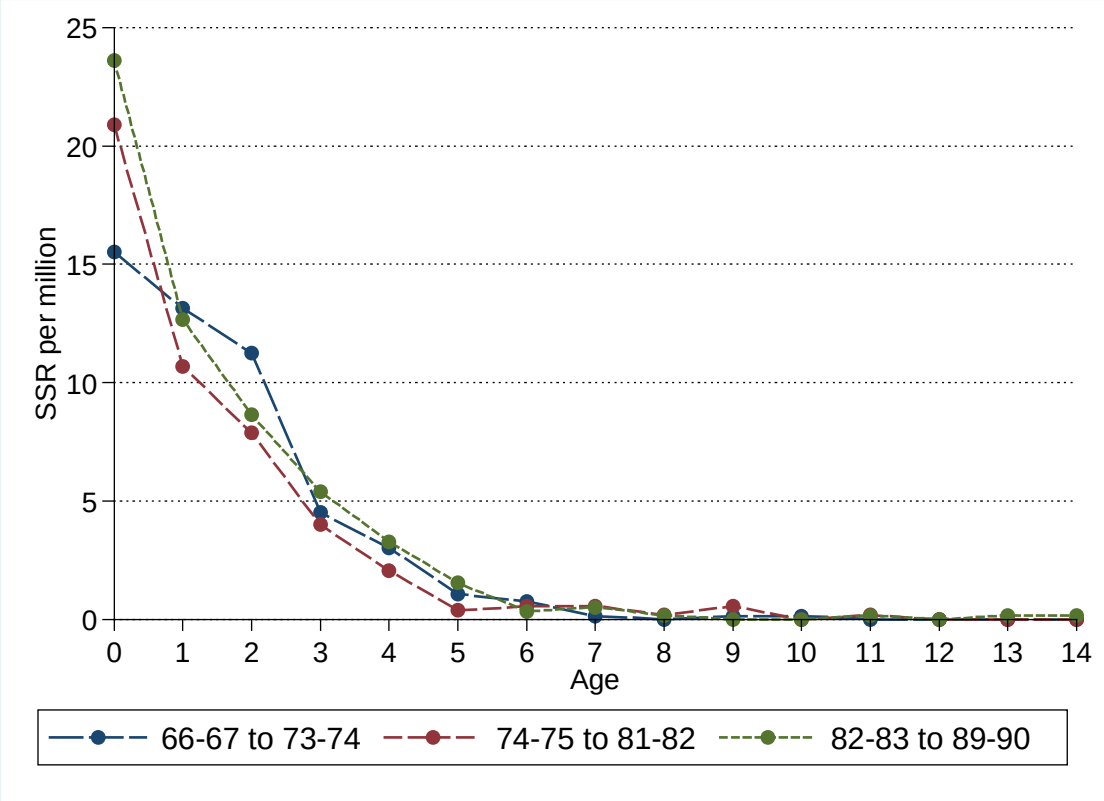
b) Incidence rate per million by age group, sex and grouped birth cohort.

Age	0	1-4	5-9	10-14	ASSR
Born					
66-70	17.2	7.5	0.1	0.1	3.2
70-74	13.6	8.5	0.8	0.0	3.4
74-78	22.5	6.0	0.5	0.0	3.2
78-82	19.4	6.4	0.4	0.1	3.2
82-86	27.3	7.0	0.6	0.1	3.9
86-90	20.1	7.9	0.5	0.1	3.7
Trend	*	-	-		-
AAPC	1.83	-0.19	2.87		0.73
CI	0.36 to 3.33	-1.39 to 1.02	-1.23 to 7.14		-0.17 to 1.65
Fit	-	-	-		-

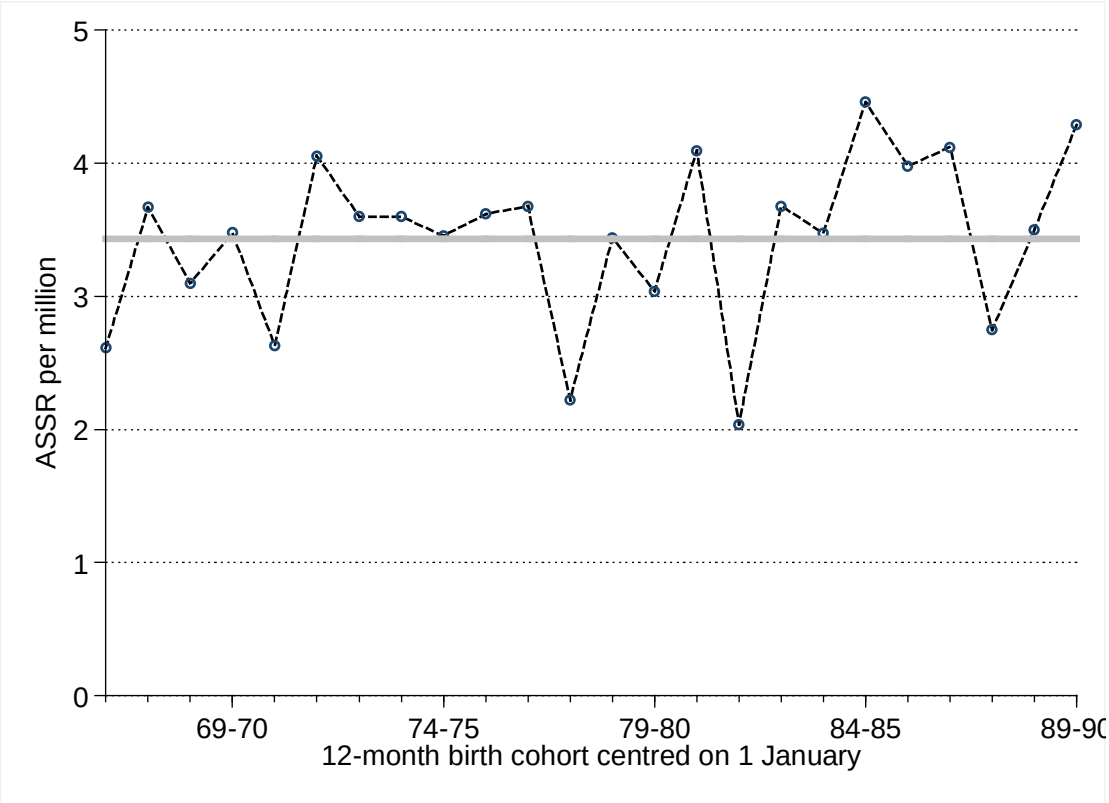
c) Sex-standardised incidence rate per million by age group and grouped birth cohort.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.067.

- = not significant; * p<0.05, ** p<0.01, *** p<0.001.

Retinoblastoma: by 12-month birth cohort 1966-67 to 1989-90, Britain
Figures 5.3.5.1 (a) and (b).



a) Standardised rate by single year of age at diagnosis, for successive birth periods.



b) Standardised rate by 12-month birth cohort: actual (dotted), step model (solid) line.

Retinoblastoma: by year of diagnosis 1966-2005, Britain
Tables 5.3.5.2 (a) to (c).

Time trend analysis.

Age/sex	0		1-4		5-9		10-14		0-14	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	37	43	76	66	3	3	1	0	117	112
1971-75	29	27	77	62	2	3	0	1	108	93
1976-80	36	41	39	45	4	6	1	0	80	92
1981-85	45	33	41	41	3	3	0	0	89	77
1986-90	45	33	53	54	8	4	0	0	106	91
1991-95	52	45	62	69	5	5	1	0	120	119
1996-00	48	37	43	53	5	3	1	0	97	93
2001-05	43	35	48	64	3	7	3	1	97	107
Total	335	294	439	454	33	34	7	2	814	784

a) Number of cases by age group, sex, and period of diagnosis.

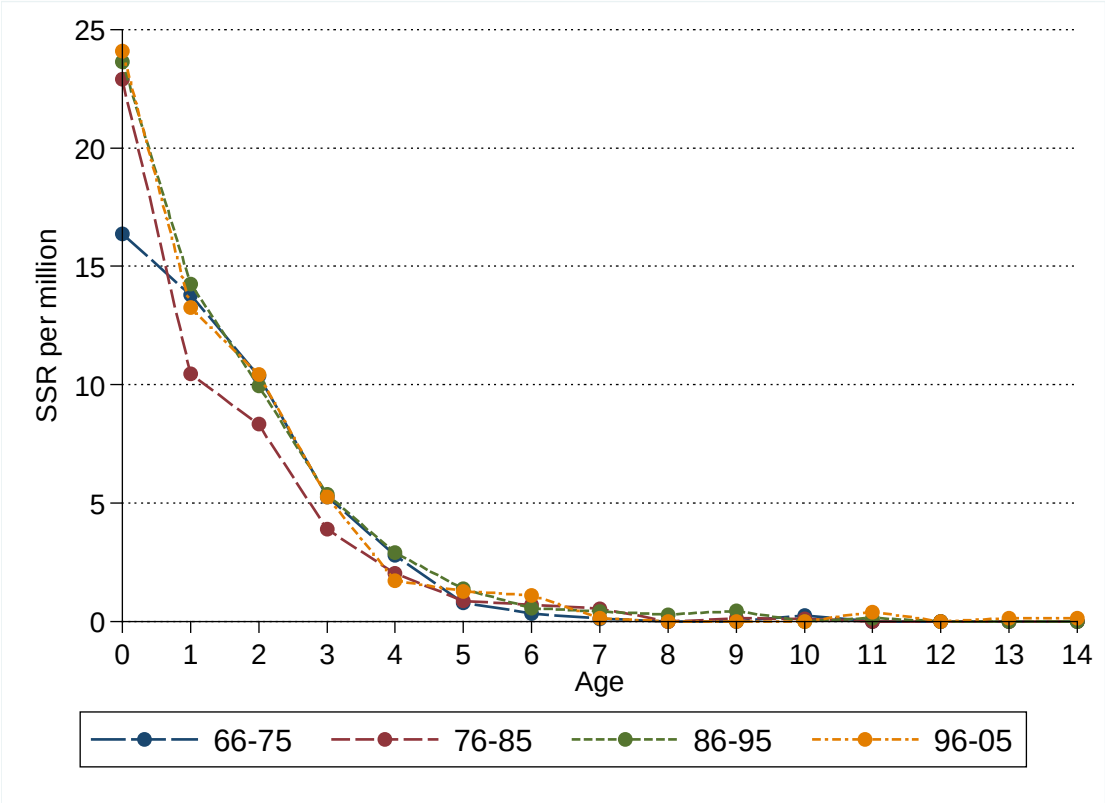
Age/sex	0		1-4		5-9		10-14		ASR	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	16.1	19.6	8.1	7.3	0.3	0.3	0.1	0.0	3.4	3.4
1971-75	14.7	14.5	8.9	7.6	0.2	0.3	0.0	0.1	3.4	3.1
1976-80	21.3	25.6	5.6	6.9	0.4	0.6	0.1	0.0	3.1	3.7
1981-85	25.3	19.5	5.9	6.2	0.4	0.4	0.0	0.0	3.4	3.1
1986-90	23.8	18.3	7.2	7.7	0.9	0.5	0.0	0.0	3.8	3.4
1991-95	27.5	24.9	8.1	9.4	0.5	0.6	0.1	0.0	4.2	4.4
1996-00	27.3	22.1	5.9	7.7	0.5	0.3	0.1	0.0	3.6	3.6
2001-05	25.3	21.6	7.1	9.9	0.3	0.8	0.3	0.1	3.8	4.4

b) Incidence rate per million by age group, sex and period of diagnosis.

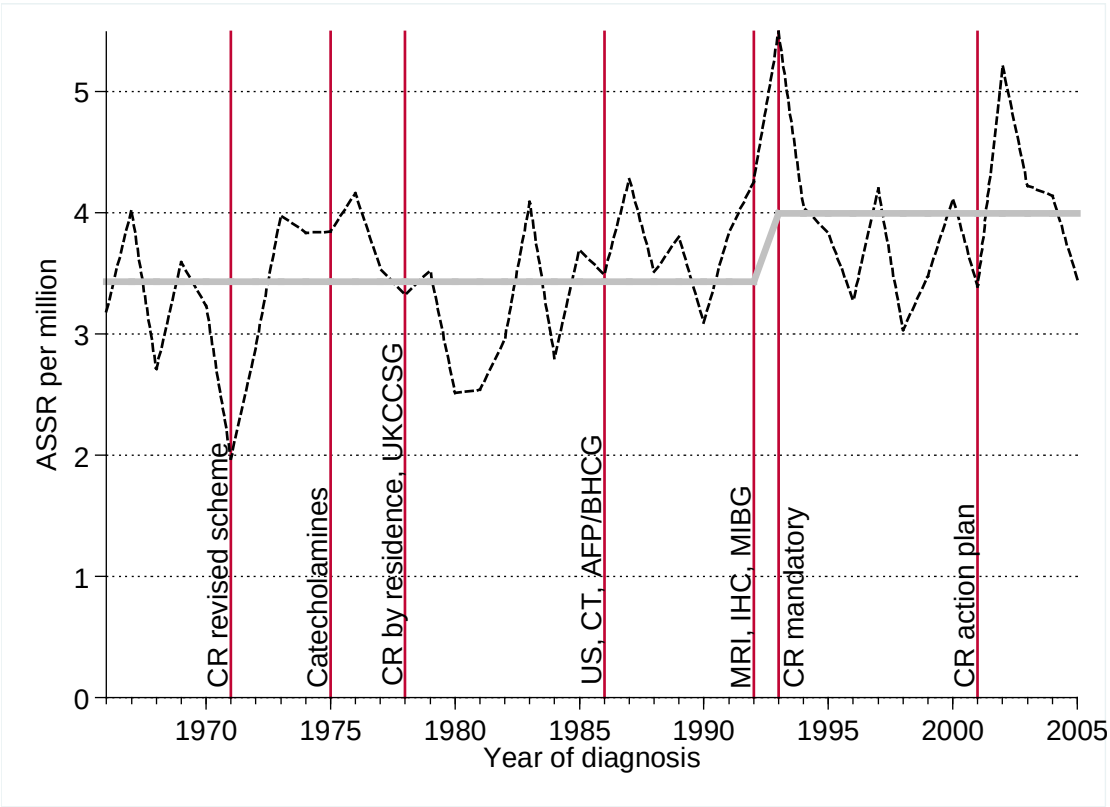
Age	0	1-4	5-9	10-14	ASSR
Diagnosed					
1966-70	17.9	7.7	0.3	0.1	3.4
1971-75	14.6	8.3	0.2	0.0	3.3
1976-80	23.5	6.3	0.5	0.0	3.4
1981-85	22.4	6.0	0.4	0.0	3.2
1986-90	21.1	7.5	0.7	0.0	3.6
1991-95	26.2	8.8	0.6	0.1	4.3
1996-00	24.7	6.8	0.4	0.1	3.6
2001-05	23.5	8.5	0.6	0.2	4.1
Trend	**	-	*		**
AAPC	1.10	0.17	2.33		0.63
CI	0.43 to 1.78	-0.39 to 0.73	0.36 to 4.35		0.21 to 1.05
Fit	-	-	-		-

c) Sex-standardised incidence rate per million by age group and period of diagnosis.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.025.
- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Retinoblastoma: by year of diagnosis 1966-2005, Britain
Figures 5.3.5.2 (a) and (b).

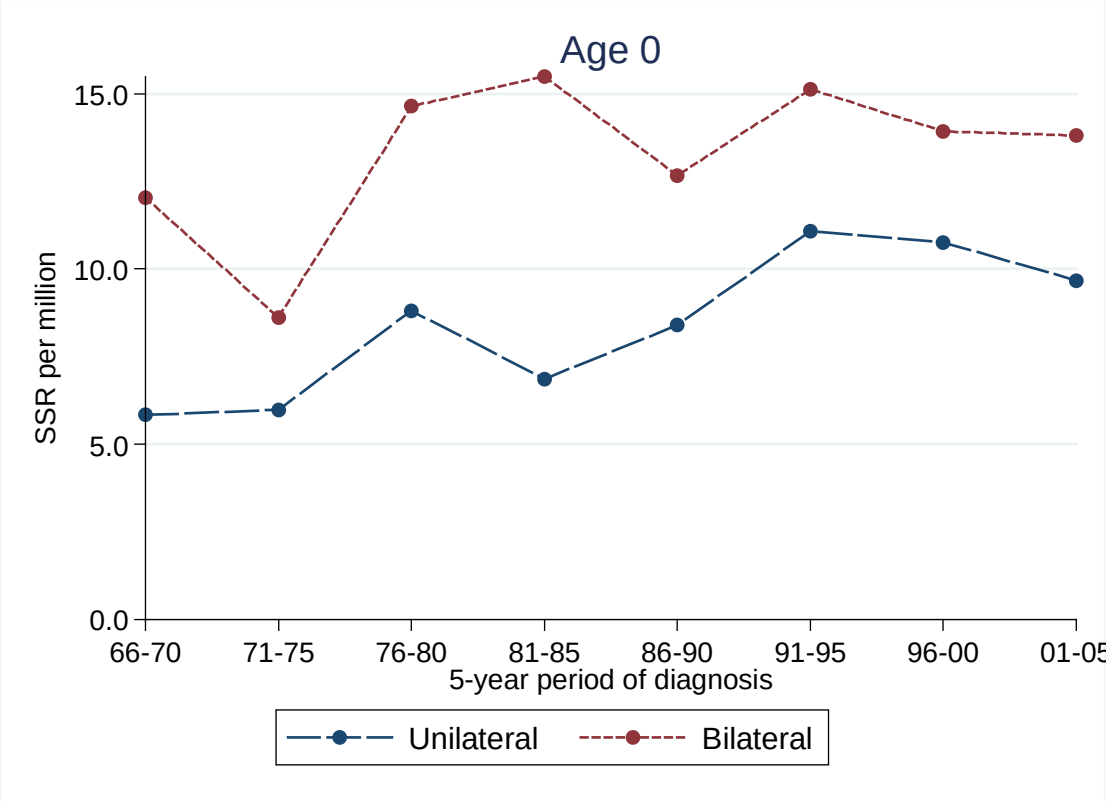


a) Standardised rate by single year of age at diagnosis, for successive diagnosis periods.

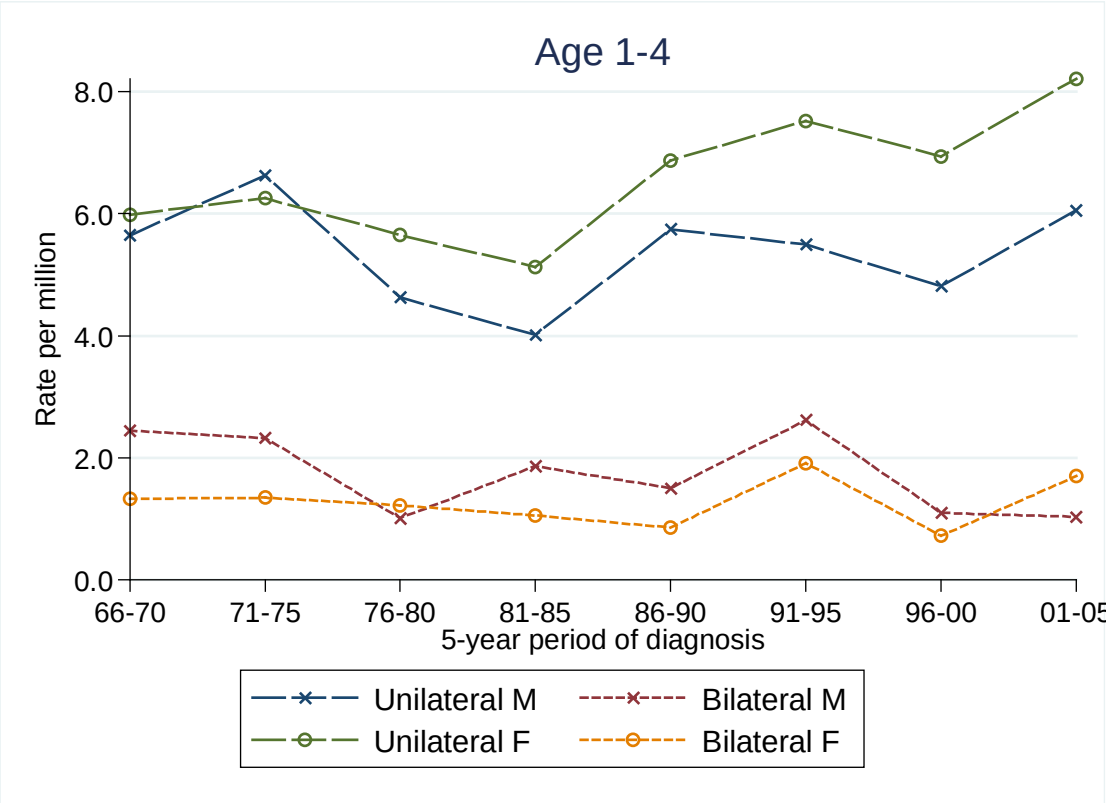


b) Standardised rate by year of diagnosis: actual (dotted), step model (solid) line.

Retinoblastoma: by year of diagnosis 1966-2005, Britain
Figures 5.3.5.2 (c) and (d).

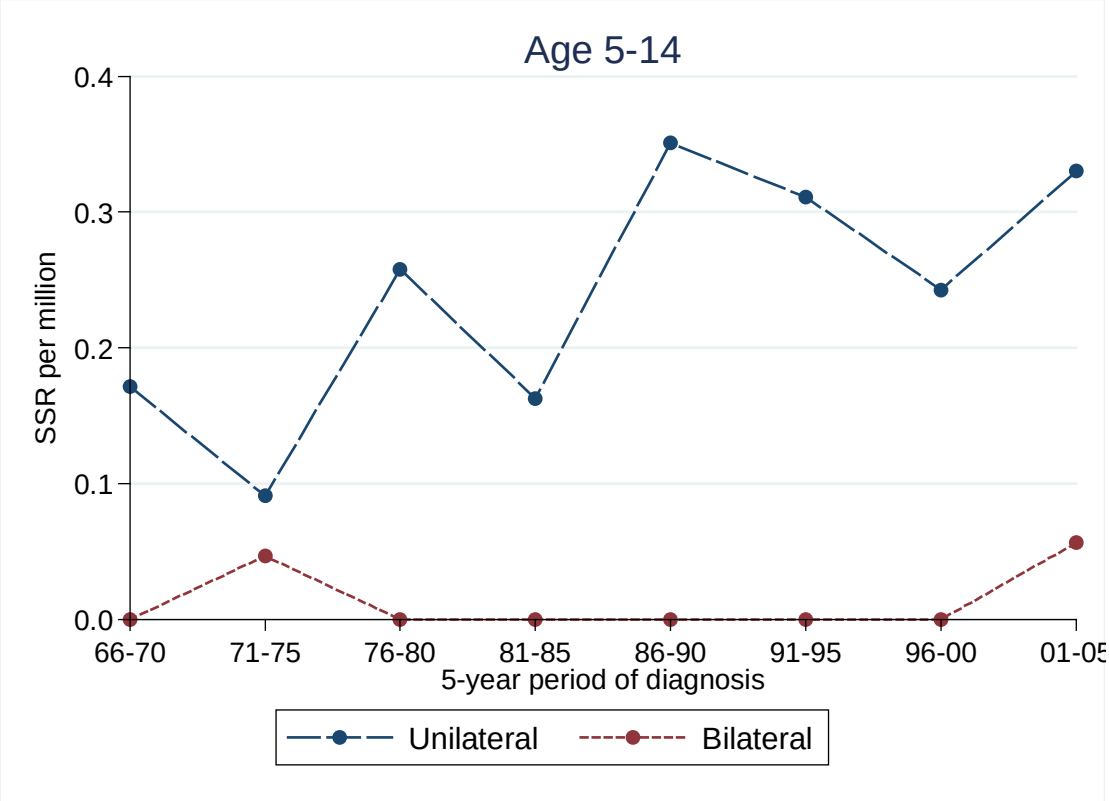


c) Standardised rate at age 0, by subtype and 5-year period of diagnosis.

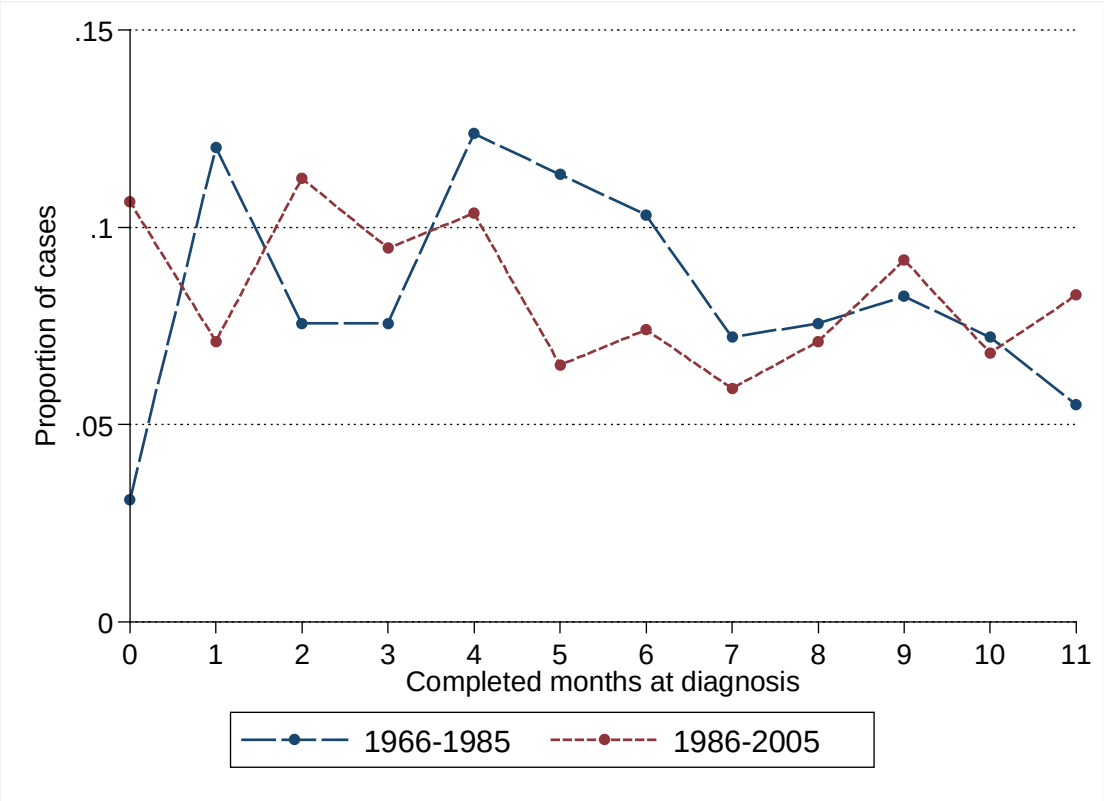


d) Rate at age 1-4, by subtype and sex, and 5-year period of diagnosis.

Retinoblastoma: by year of diagnosis 1966-2005, Britain
Figures 5.3.5.2 (e) and (f).



e) Standardised rate at age 5-14, by subtype and 5-year period of diagnosis.



f) Distribution of cases diagnosed under age 1, by age at diagnosis in completed months.

5.3.6 Renal cancer

5.3.6.1 Year of birth

See Tables 5.3.6.1 (a) to (c), and Figures 5.3.6.1 (a) and (b).

By year of birth, there was a non-significant increase of 0.5% per year (-0.1 to 1.2). In age group 10-14 there was an increasing time trend of 4.1% (1.1 to 7.3) per year. In age groups 0 and 5-9, there were non-significant increases of 0.3% (-1.4 to 2.1) and 0.4% (-1.1 to 1.9). In age group 1-4 there was an increase of 0.4% per year on average, but there was evidence that the Poisson model did not fit ($p<0.05$) (Table 5.3.6.1(c)).

Between the first and the second 8-year period of birth, there was an increase in rate for children diagnosed at ages 1-4, and a slight decrease at age 0. Between the second and third periods, there was an increase at ages 0, 1 and 2, and a decrease at ages 4 and 5. (Figure 5.3.6.1(a)).

The step model indicates a large trough at 1982-83, followed by a slight increase (Figure 5.3.6.1(b)).

5.3.6.2 Year of diagnosis

See Tables 5.3.6.2 (a) to (c), and Figures 5.3.6.2 (a) and (b)

By year of diagnosis, there was an overall time trend of 0.7% (0.4 to 1.0) per year. In age groups 1-4 and 10-14, there were increasing time trends of 0.7% (0.3 to 1.0) and 1.4% (0.01 to 2.8) per year, respectively. (Table 5.3.6.2(c)). In age groups 0 and 5-9 there were non-significant increases of 0.7% (-0.1 to 1.5) and 0.6% (-0.1 to 1.2). The differences in trend between age groups were not statistically significant ($p=0.759$).

Figure 5.3.6.2(a) shows that the rate at ages 0 and 1 decreased between the first and second decades, whereas the rate at age 4 decreased between the second and third decades. From the third to the fourth decade, the rates generally increased.

The step model suggests an increase at 2001 (Figure 5.3.6.2(b)).

5.3.6.3 Discussion

By year of birth and by year of diagnosis the rates increased by 0.5% and 0.7% per year on average, respectively. The difference between these trends is the effect of the large increase in the most recent five-year period of diagnosis.

The increase in rate at ages 1-4 between the first 8-year birth period (1966-67 to 1973-74) and the second (1974-75 to 1981-82) (Figure 5.3.6.1 (a)) also appears in the analysis by year of diagnosis, as an increase at ages 3 and 4 between the first and second decades (Figure 5.3.6.2(a)). It does not appear to be a change in age at diagnosis, because there is little sign of a compensating decrease elsewhere, and it seems too early to be an effect of US scanning (from about 1986). One possibility is that it could represent the start of routine specialist treatment for childhood renal cancer, including chemotherapy, around the time of the start of the UKCCSG. Some relatively mild forms of renal cancer in children can be successfully treated by surgery alone, and might therefore have been more likely to miss registration in the first decade of the study period.

There is clear evidence of a reduction in age at diagnosis in the following period, both by year of birth (from the second birth period to the third) and by year of diagnosis (from the third decade to the fourth): the rates decreased at age 4 and increased at age 2. This may well be an effect of the introduction of US scanning. There was little or no effect on the overall rate, as expected for a diagnosis that is rare in older children.

By year of diagnosis, there was a large increase from 1996-2000 to 2001-05, mainly in the younger age groups, corresponding with a peak in the overall rate in 2002 and a step model increase at 2000. This is puzzling, and looks too large to be explained by chance. The timing of the step coincides with the Action Plan of 2001. Possibly the effort to improve completeness of registration succeeded in finding some patients who previously would not have been registered (perhaps because they were treated exclusively by surgery). This idea is consistent with the earlier increase in the overall rate (which

suggests that registration of childhood renal cancer may not be as straightforward as it seems), and with the increases in some other diagnostic groups at the same time. See Section 5.3.13.

Renal cancer: by 12-month birth cohort 1966-67 to 1989-90, Britain
Tables 5.3.6.1 (a) to (c).

Time trend analysis. 66-70 is the 48-month birth cohort from 1 July 1966 to 30 June 1970, etc.

Age	0		1-4		5-9		10-14		0-14	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	32	19	113	107	33	31	4	4	182	161
70-74	26	21	100	103	36	28	10	5	172	157
74-78	13	21	90	80	24	20	5	9	132	130
78-82	13	22	97	103	26	36	5	9	141	170
82-86	21	12	76	89	27	19	8	8	132	128
86-90	27	26	109	107	31	34	10	11	177	178
Total	132	121	585	589	177	168	42	46	936	924

a) Number of cases by age, sex and grouped birth cohort.

Age	0		1-4		5-9		10-14		ASR	
Sex	M	F	M	F	M	F	M	F	M	F
Born	17.6	10.9	15.7	15.5	3.7	3.7	0.4	0.5	6.7	6.2
66-70	16.0	13.7	15.6	17.0	4.5	3.7	1.3	0.7	7.2	6.9
70-74	9.8	16.7	17.1	16.0	3.7	3.2	0.8	1.4	6.7	6.9
74-78	9.1	16.3	17.1	19.1	3.7	5.3	0.7	1.3	6.6	8.4
78-82	14.6	8.8	13.2	16.2	3.7	2.7	1.1	1.2	6.1	6.2
82-86	17.8	17.9	18.0	18.4	4.1	4.7	1.3	1.5	7.8	8.2
86-90	17.6	10.9	15.7	15.5	3.7	3.7	0.4	0.5	6.7	6.2

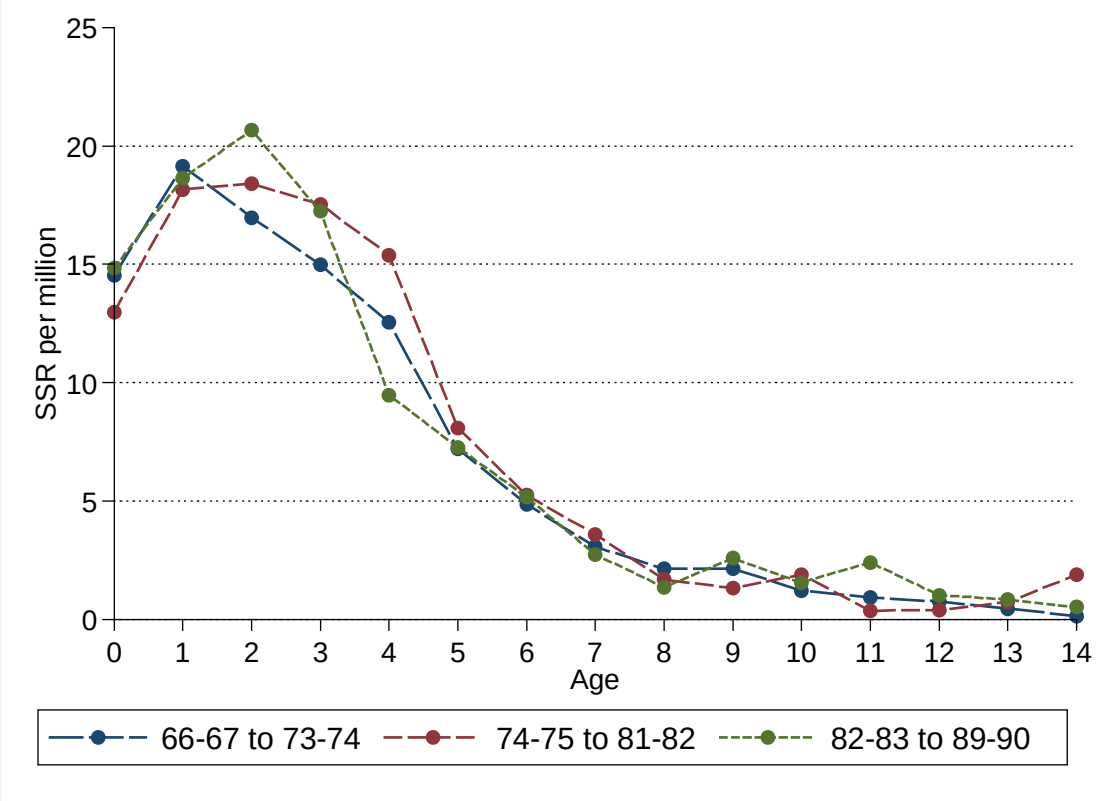
b) Incidence rate per million by age group, sex and grouped birth cohort.

Age	0	1-4	5-9	10-14	ASSR
Born					
66-70	14.3	15.6	3.7	0.5	6.5
70-74	14.9	16.3	4.1	1.0	7.0
74-78	13.3	16.6	3.4	1.1	6.8
78-82	12.7	18.1	4.5	1.0	7.5
82-86	11.7	14.7	3.2	1.1	6.2
86-90	17.8	18.2	4.4	1.4	8.0
Trend	-	-	-	**	-
AAPC	0.34	0.37	0.40	4.10	0.54
CI	-1.37 to 2.08	*-0.43 to 1.17*	-1.07 to 1.89	1.05 to 7.25	-0.10 to 1.18
Fit	-	*	-	-	-

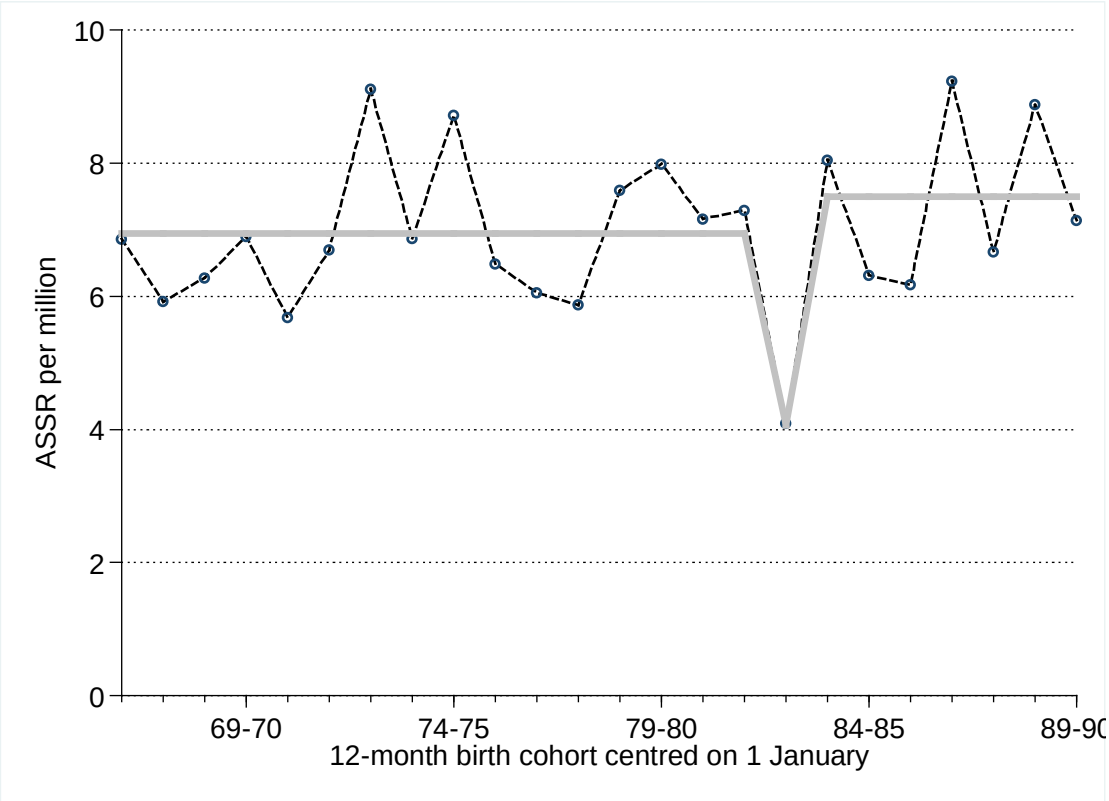
c) Sex-standardised incidence rate per million by age group and grouped birth cohort.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.132.

- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Renal cancer: by 12-month birth cohort 1966-67 to 1989-90, Britain
Figures 5.3.6.1 (a) and (b).



a) Standardised rate by single year of age at diagnosis, for successive birth periods.



b) Standardised rate by 12-month birth cohort: actual (dotted), step model (solid) line.

Renal cancer: by year of diagnosis 1966-2005, Britain
Tables 5.3.6.2 (a) to (c).

Time trend analysis.

Age/sex	0		1-4		5-9		10-14		0-14	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	38	26	136	144	32	45	9	9	215	224
1971-75	33	24	127	127	48	42	9	12	217	205
1976-80	14	29	121	118	42	32	11	9	188	188
1981-85	26	19	107	116	29	32	7	4	169	171
1986-90	31	26	121	123	28	43	5	6	185	198
1991-95	32	22	120	130	42	30	9	15	203	197
1996-00	30	28	132	126	36	37	11	11	209	202
2001-05	34	29	130	138	28	59	10	15	202	241
Total	238	203	994	1022	285	320	71	81	1588	1626

a) Number of cases by age group, sex, and period of diagnosis.

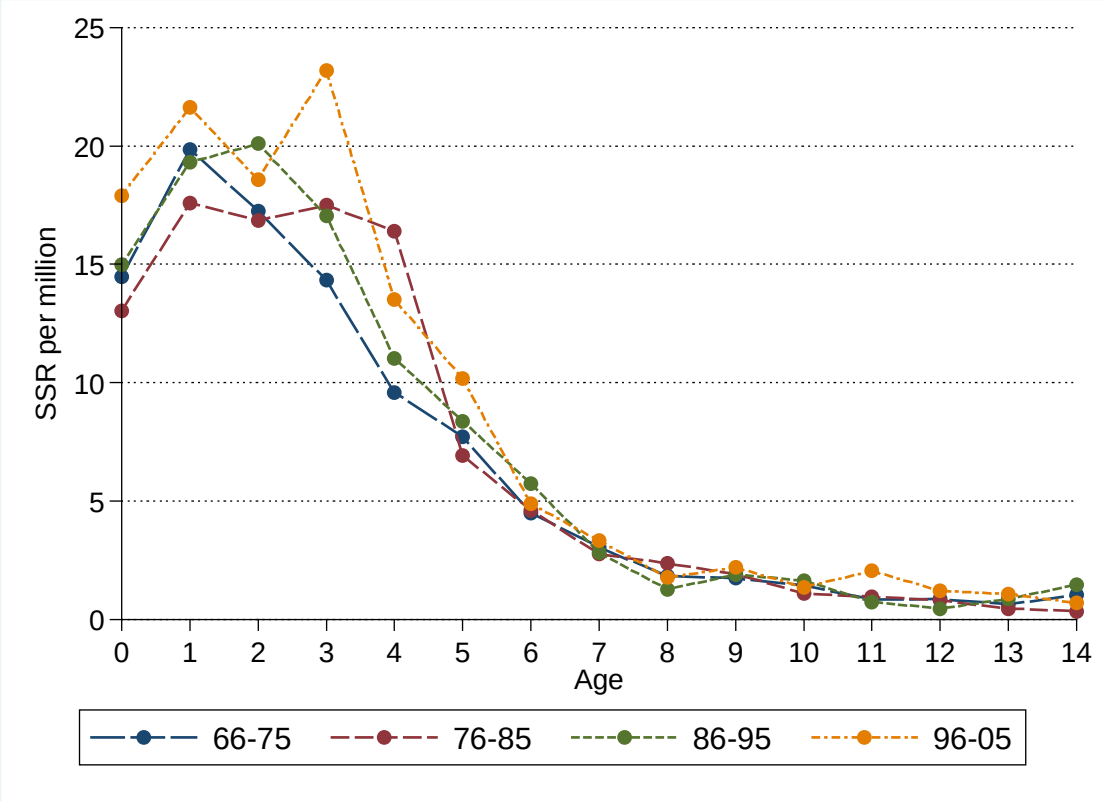
Age/sex	0		1-4		5-9		10-14		ASR	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	16.6	11.8	14.5	16.0	2.9	4.3	0.9	1.0	6.2	6.8
1971-75	16.8	12.9	14.8	15.6	4.2	3.8	0.8	1.1	6.7	6.7
1976-80	8.3	18.1	17.5	18.0	4.0	3.2	1.0	0.8	6.9	7.4
1981-85	14.6	11.2	15.3	17.5	3.4	4.0	0.7	0.4	6.4	6.9
1986-90	16.4	14.4	16.5	17.6	3.2	5.1	0.6	0.7	6.8	7.6
1991-95	16.9	12.2	15.7	17.8	4.5	3.4	1.0	1.8	7.2	7.3
1996-00	17.0	16.7	18.1	18.2	3.8	4.1	1.2	1.2	7.6	7.7
2001-05	20.0	17.9	19.2	21.4	3.1	6.9	1.0	1.6	7.8	9.7

b) Incidence rate per million by age group, sex and period of diagnosis.

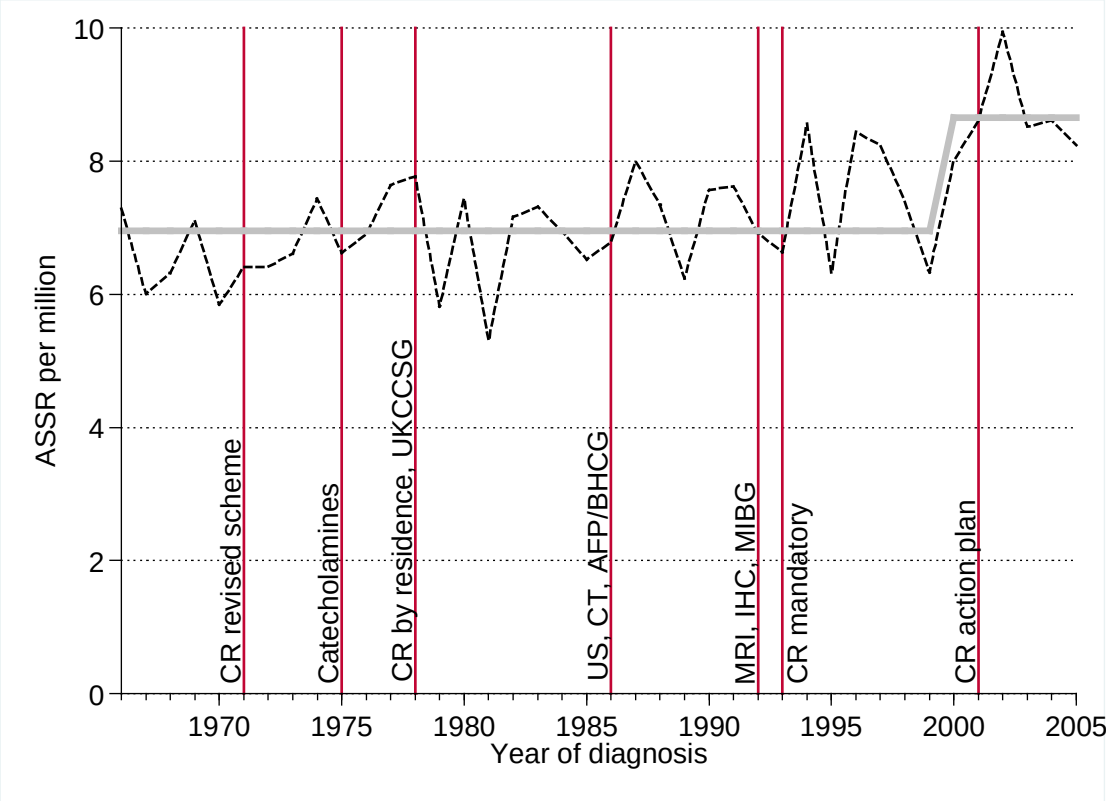
Age	0	1-4	5-9	10-14	ASSR
Diagnosed					
1966-70	14.2	15.2	3.6	0.9	6.5
1971-75	14.8	15.2	4.0	1.0	6.7
1976-80	13.2	17.8	3.6	0.9	7.1
1981-85	12.9	16.4	3.7	0.5	6.6
1986-90	15.4	17.1	4.2	0.7	7.2
1991-95	14.5	16.7	4.0	1.4	7.2
1996-00	16.9	18.2	3.9	1.2	7.7
2001-05	19	20.3	5	1.3	8.8
Trend	-	**	-	*	***
AAPC	0.70	0.65	0.56	1.40	0.68
CI	-0.10 to 1.50	0.28 to 1.03	-0.12 to 1.24	0.01 to 2.81	0.38 to 0.97
Fit	-	-	-	-	-

c) Sex-standardised incidence rate per million by age group and period of diagnosis.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.759.
- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Renal cancer: by year of diagnosis 1966-2005, Britain
Figures 5.3.6.2 (a) and (b).



a) Standardised rate by single year of age at diagnosis, for successive diagnosis periods.



b) Standardised rate by year of diagnosis: actual (dotted), step model (solid) line.

5.3.7 Hepatic cancer

5.3.7.1 Year of birth

See Tables 5.3.7.1 (a) to (c), and Figures 5.3.7.1 (a) and (b).

By year of birth, there was an overall increase of 1.8% per year, with evidence for lack of fit of the time trend model ($p<0.01$). In age groups 0 and 5-9 there were non-significant increases of 2.4% (-0.8 to 5.6) and 1.9% (-2.8 to 6.8). In age groups 1-4 and 10-14 there were increases of 1.6% and 1.2% per year on average, but there was evidence that the Poisson model did not fit ($p<0.05$) (Table 5.3.7.1(c)).

Figure 5.3.7.1(a) suggests that there was an increase in rate at ages 1 and 2 between the first and the second 8-year period of birth, followed by a decrease in rate at age 2 and an increase at age 1 between the second and third periods.

The step model indicates a near-doubling of the overall rate at the birth cohort of 1971-72 (Figure 5.3.7.1(b)).

5.3.6.2 Year of diagnosis

See Tables 5.3.7.2 (a) to (c), and Figures 5.3.7.2 (a) and (b)

By year of diagnosis, there was an overall time trend of 2.5% (1.7 to 3.3) per year. In age groups 0 and 1-4, there were increasing time trends of 2.4% (1.0 to 3.8) and 2.8% (1.6 to 4.0). In age groups 5-9 and 10-14 there were non-significant increases of 2.0% (-0.4 to 4.4) and 2.0% (-0.1 to 4.1) per year, respectively. The differences in trend between age groups were not statistically significant ($p=0.879$) (Table 5.3.7.2(c)).

Figure 5.3.7.2(a) shows increases from the first decade to the second, a decrease at age 2 and increases at ages 0 and 1 from the second decade to the third, and a large increase from the third decade to the fourth, mainly at ages 0 and 1.

The step model indicates increases at 1984 and 2001 (Figure 5.3.7.2(b)).

5.3.6.3 Discussion

Because of the small numbers of cases, there are large fluctuations in the annual rates.

By year of birth and by year of diagnosis the rates increased by 1.8% and 2.5% per year respectively, on average. The difference between these trends is the effect of the large increase in the most recent five-year period of diagnosis.

The step model by year of birth indicates a large increase in rate at the cohort of 1971-72. Neuroblastoma can cause liver abnormalities, and one possible explanation of this increase is diagnostic transfer due to the introduction of the catecholamine test for neuroblastoma, following the suggestion of Marsden and Steward. [34] that neuroblastoma might previously have been over-diagnosed. The transfer would not be noticeable in the neuroblastoma rate, because the neuroblastoma rate is ten times larger than the hepatoblastoma rate.

The step model by year of diagnosis indicates increases in 1984 and 2001. The obvious explanation for the increase in 1984 is diagnostic transfer due to the introduction of serum hormone testing (AFP/BHCG) for hepatic cancers, in about 1986. The extra cases might previously have been diagnosed as liver metastases of other cancers, or perhaps as non-malignant disease.

The increase in 2001 is harder to explain, and looks too large to be due to chance. One possible explanation is the Action Plan of 2001; similar increases are seen in other diagnostic groups at about the same time (see Section 5.3.13). Another possibility is that the population of susceptible children may have increased as advances in paediatric intensive care have allowed more babies with low birthweight to survive: the increase was mainly in infants, and there is a well-established association between hepatoblastoma and low birthweight [120-122].

Hepatic cancer: by 12-month birth cohort 1966-67 to 1989-90, Britain
Tables 5.3.7.1 (a) to (c).

Time trend analysis. 66-70 is the 48-month birth cohort from 1 July 1966 to 30 June 1970, etc.

Age	0		1-4		5-9		10-14		0-14	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	6	4	8	3	1	3	5	1	20	11
70-74	10	6	12	7	4	3	5	4	31	20
74-78	4	4	3	16	0	2	3	3	10	25
78-82	6	8	7	7	5	5	6	3	24	23
82-86	5	7	14	3	3	4	5	1	27	15
86-90	12	5	13	4	2	2	1	8	28	19
Total	43	34	57	40	15	19	25	20	140	113

a) Number of cases by age, sex and grouped birth cohort.

Age	0		1-4		5-9		10-14		ASR	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	3.3	2.3	1.1	0.4	0.1	0.4	0.6	0.1	0.7	0.4
70-74	6.2	3.9	1.9	1.2	0.5	0.4	0.6	0.5	1.3	0.9
74-78	3.0	3.2	0.6	3.2	0.0	0.3	0.5	0.5	0.5	1.3
78-82	4.2	5.9	1.2	1.3	0.7	0.7	0.8	0.4	1.1	1.1
82-86	3.5	5.1	2.4	0.5	0.4	0.6	0.7	0.1	1.2	0.7
86-90	7.9	3.4	2.1	0.7	0.3	0.3	0.1	1.1	1.2	0.9

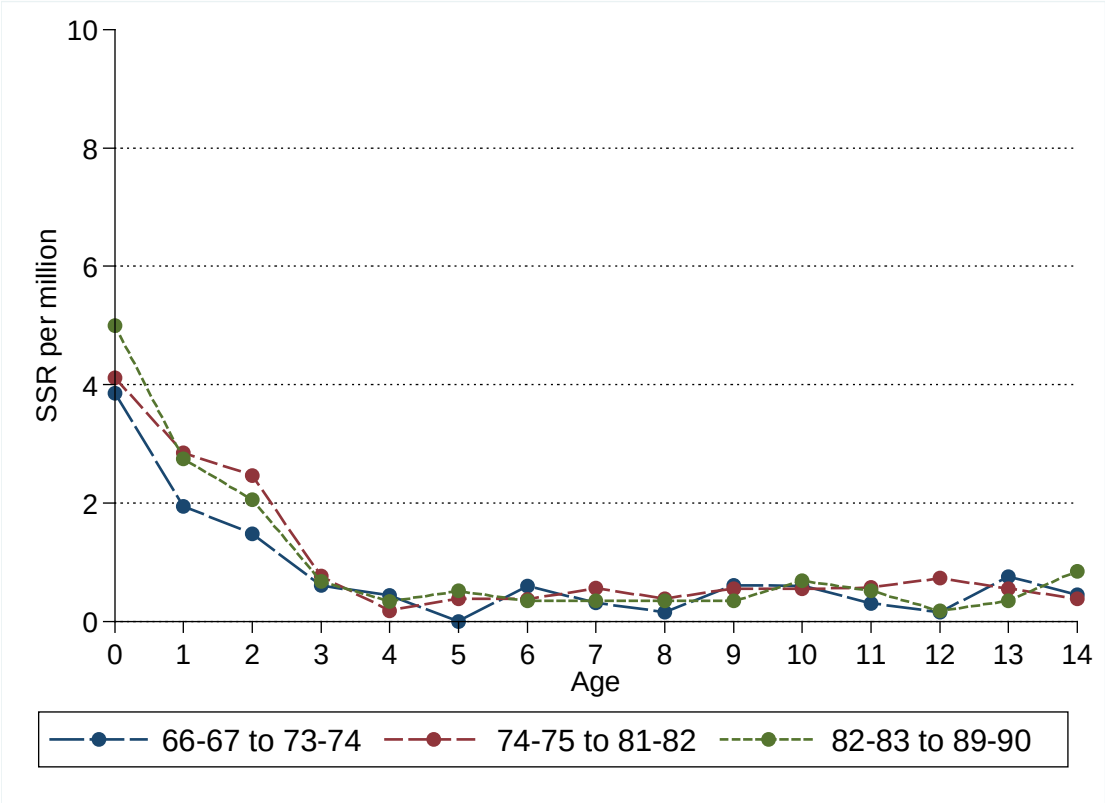
b) Incidence rate per million by age group, sex and grouped birth cohort.

Age	0	1-4	5-9	10-14	ASSR
Born					
66-70	2.8	0.8	0.2	0.3	0.6
70-74	5.0	1.5	0.5	0.6	1.1
74-78	3.1	1.9	0.2	0.5	0.9
78-82	5.1	1.3	0.7	0.6	1.1
82-86	4.3	1.5	0.5	0.4	1.0
86-90	5.7	1.4	0.3	0.6	1.0
Trend	-	-	-	-	*
AAPC	2.35	1.60	1.88	1.22	1.80
CI	-0.80 to 5.61	*-1.19 to 4.46*	-2.80 to 6.79	*-2.83 to 5.44*	*0.06 to 3.57*
Fit	-	*	-	*	**

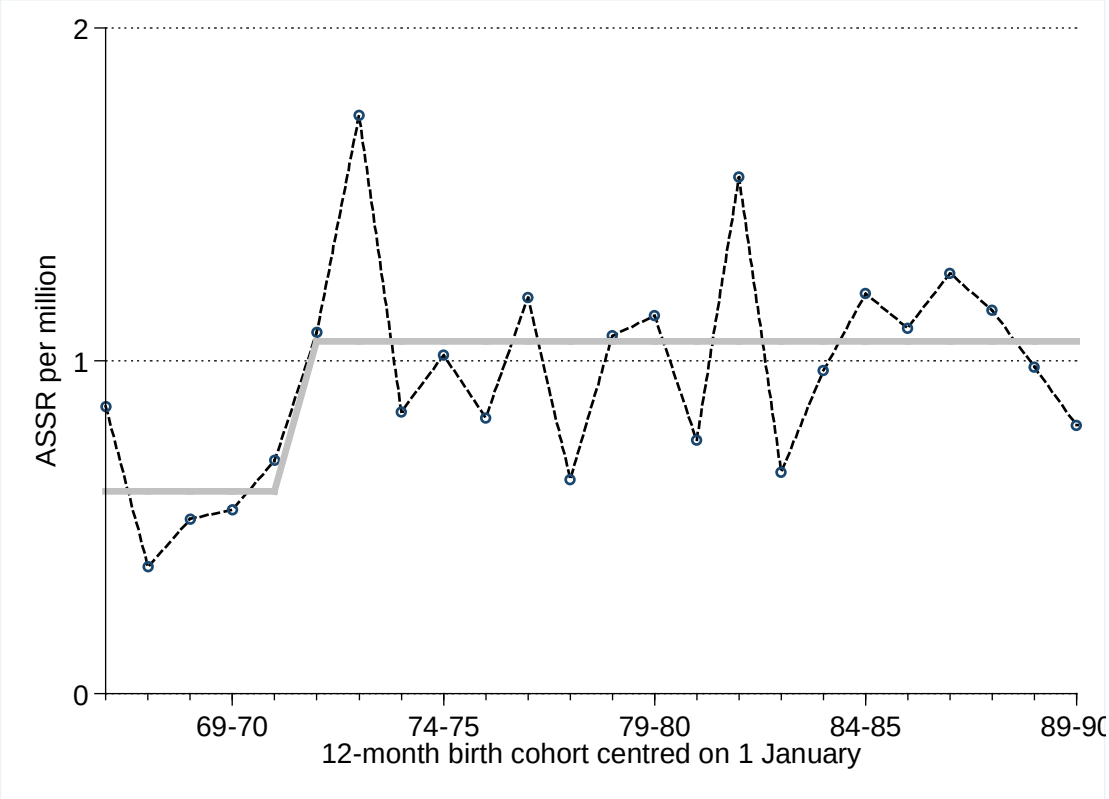
c) Sex-standardised incidence rate per million by age group and grouped birth cohort.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.976.

- = not significant; * p<0.05, ** p<0.01, *** p<0.001.

Hepatic cancer: by 12-month birth cohort 1966-67 to 1989-90, Britain
Figures 5.3.7.1 (a) and (b).



a) Standardised rate by single year of age at diagnosis, for successive birth periods.



b) Standardised rate by 12-month birth cohort: actual (dotted), step model (solid) line.

Hepatic cancer: by year of diagnosis 1966-2005, Britain
Tables 5.3.7.2 (a) to (c).

Time trend analysis.

Age/sex	0		1-4		5-9		10-14		0-14	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	9	6	14	7	2	1	5	3	30	17
1971-75	10	7	10	9	2	4	3	0	25	20
1976-80	5	7	9	15	2	4	4	4	20	30
1981-85	9	10	11	7	2	4	4	4	26	25
1986-90	13	6	17	4	5	5	8	4	43	19
1991-95	10	10	20	9	4	4	6	2	40	25
1996-00	14	8	23	12	3	1	4	8	44	29
2001-05	19	12	25	18	6	2	3	5	53	37
Total	89	66	129	81	26	25	37	30	281	202

a) Number of cases by age group, sex, and period of diagnosis.

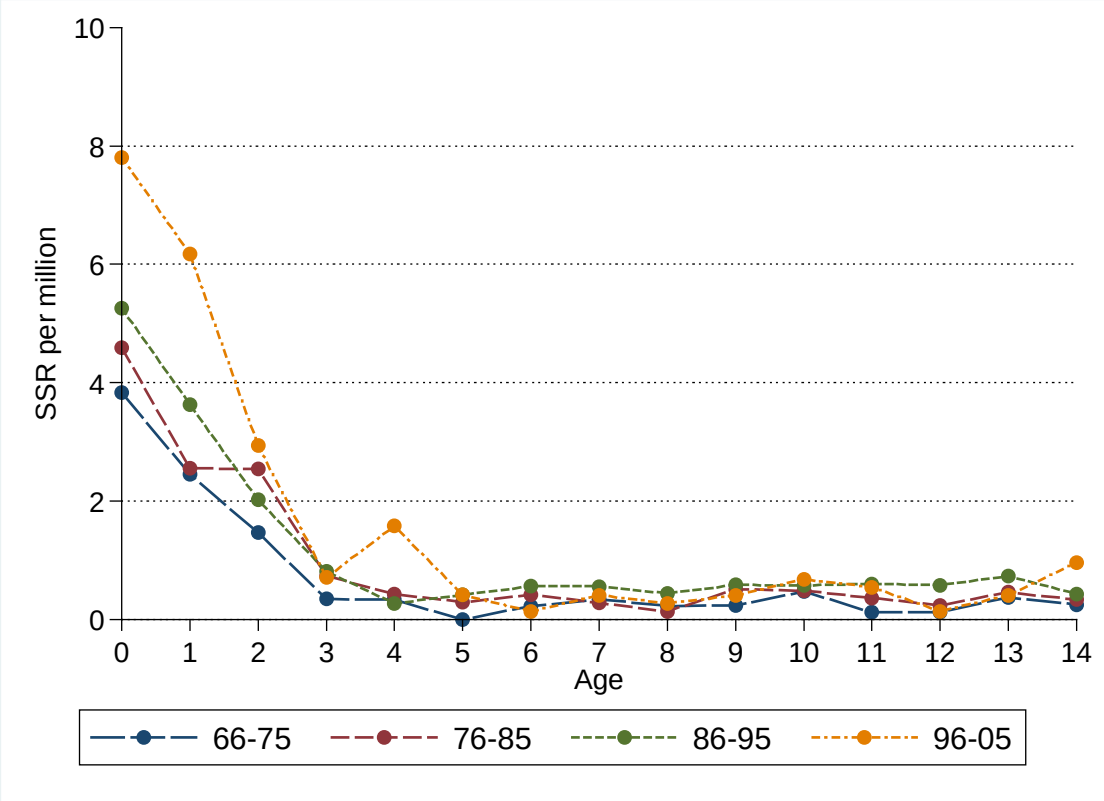
Age/sex	0		1-4		5-9		10-14		ASR	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	3.9	2.7	1.5	0.8	0.2	0.1	0.5	0.3	0.9	0.5
1971-75	5.1	3.8	1.2	1.1	0.2	0.4	0.3	0.0	0.8	0.7
1976-80	3.0	4.4	1.3	2.3	0.2	0.4	0.3	0.4	0.7	1.2
1981-85	5.1	5.9	1.6	1.1	0.2	0.5	0.4	0.4	1.0	1.0
1986-90	6.9	3.3	2.3	0.6	0.6	0.6	0.9	0.5	1.6	0.7
1991-95	5.3	5.5	2.6	1.2	0.4	0.5	0.7	0.2	1.4	0.9
1996-00	8.0	4.8	3.2	1.7	0.3	0.1	0.4	0.9	1.6	1.1
2001-05	11.2	7.4	3.7	2.8	0.7	0.2	0.3	0.5	2.1	1.5

b) Incidence rate per million by age group, sex and period of diagnosis.

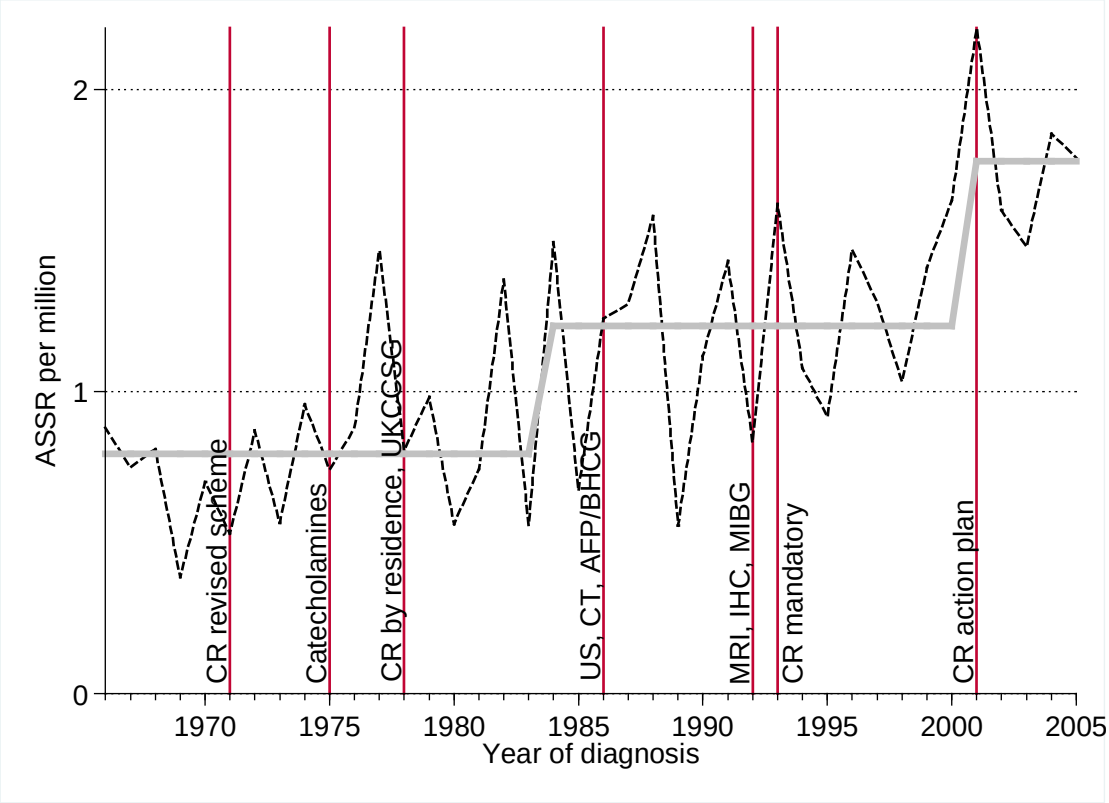
Age	0	1-4	5-9	10-14	ASSR
Diagnosed					
1966-70	3.3	1.1	0.1	0.4	0.7
1971-75	4.4	1.1	0.3	0.1	0.7
1976-80	3.7	1.8	0.3	0.4	0.9
1981-85	5.5	1.3	0.4	0.4	1.0
1986-90	5.1	1.4	0.6	0.7	1.2
1991-95	5.4	1.9	0.4	0.5	1.2
1996-00	6.4	2.4	0.2	0.7	1.4
2001-05	9.3	3.2	0.4	0.4	1.8
Trend	**	***	-	-	***
AAPC	2.39	2.80	1.99	1.96	2.47
CI	1.00 to 3.80	1.60 to 4.02	-0.38 to 4.42	-0.14 to 4.11	1.68 to 3.26
Fit	-	-	-	-	-

c) Sex-standardised incidence rate per million by age group and period of diagnosis.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.879.
- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Hepatic cancer: by year of diagnosis 1966-2005, Britain
Figures 5.3.7.2 (a) and (b).



a) Standardised rate by single year of age at diagnosis, for successive diagnosis periods.



b) Standardised rate by year of diagnosis: actual (dotted), step model (solid) line.

5.3.8 Bone cancer

5.3.8.1 Year of birth

See Tables 5.3.8.1 (a) to (c), and Figures 5.3.8.1 (a) and (b).

By year of birth, there was no overall time trend: the estimated average change was 0.0% (-0.72 to 0.72) per year. In age groups 0-4 and 5-9 there were non-significant decreases of -0.10% (-3.2 to 3.1) and -1.0% (-2.4 to 0.4). In age group 10-14 there was a non-significant increase of 0.4% (-0.5 to 1.3) per year (Table 5.3.8.1(c)). The differences in trend between age groups were not statistically significant (p=0.274).

The step model indicates no change in rate (Figure 5.3.8.1(b)).

5.3.8.2 Year of diagnosis

See Tables 5.3.8.2 (a) to (c), Figures 5.3.8.2 (a) to (e), and Figures 5.3.13.2 (c) to (f).

By year of diagnosis, there was an overall time trend of 0.5% (0.2 to 0.9) per year. In age group 5-9 there was an increasing time trend of 0.9% (0.3 to 1.6) per year. In both age groups 0-4 and 10-14 there was a non-significant increase of 0.4%, with confidence intervals (-1.1 to 1.9) and (-0.05 to 0.8), respectively. The differences in trend between age groups were not statistically significant (p=0.350). (Table 5.3.8.2(c)).

Table (c), Figures 5.3.8.2 (a) (c) (d) and (e), and Figures 5.3.13.2 (c) to (f) show fairly large increases from the first decade to the second. These increases were restricted to age groups 5-9 and 10-14, with much less change in the following decades and in younger children. The increases were almost entirely in cases diagnosed as Ewing sarcoma. At age 5-9, after the first decade, Ewing sarcoma and osteosarcoma exchanged places: Ewing was more frequent during 1976-85, there was a cross-over point in 1986-90, and osteosarcoma was more frequent during 1991-2000. There was a further increase in Ewing sarcoma in 2001-05.

The step model indicates an increase at 1972, and a large fluctuation during 2001-2005 (Figure 5.3.8.2(b)).

5.3.8.3 Discussion

By year of birth, this is the only diagnostic group that had no suggestion of an overall increasing time trend. By year of diagnosis there was a statistically significant time trend of 0.5% per year, but this derived mainly from increases that occurred during the first decade of the study period, in older children who were born before the start of the period covered by the birth analysis.

By year of diagnosis, the step model increase at 1972 might simply represent effects of the revised scheme for cancer registration that was introduced in 1971. However, for the following reasons, it seems more likely to be related to diagnostic transfer from 'neuroblastoma of bone'. Until the introduction of catecholamine testing around 1975, 'neuroblastoma' was apparently used as a default diagnosis for unspecified embryonal tumours of many sites, including bone (see Section 5.3.13.2). Without IHC, the distinction between osteosarcoma and Ewing sarcoma depended on morphology, and the term 'Ewing sarcoma' was used for apparently non-osseous tumours sited within the bone. The increase in bone cancer between 1966-70 and 1976-80 was restricted to cases called 'Ewing sarcoma'. There is no obvious reason why the earlier cancer registration system should have registered osseous but not non-osseous tumours of bone. So the increase may well be due to transfer to 'Ewing sarcoma' from 'neuroblastoma'. The actual number of cases affected is very small.

In age group 5-9, the striking transfer from Ewing sarcoma to osteosarcoma between 1981-85 and 1991-95, and the decrease in the proportion of unspecified cancers at the same time, almost certainly represents the introduction of IHC around 1992. There were analogous changes in the proportions of the subgroups of soft-tissue sarcoma (see section 5.3.9.2).

The initial detection of bone cancer is usually made by plain X-ray imaging, following clinical signs of pain, swelling or fracture [123], a procedure that hardly changed during the

study period. This might explain why the increase in recorded incidence was less for bone cancer than for any of the other main diagnostic groups.

The fluctuation in rate during 2001-2005 is hard to explain, except perhaps as an effect of additional funding for cancer registration (see Section 5.1.13).

Bone cancer: by 12-month birth cohort 1966-67 to 1989-90, Britain
Tables 5.3.8.1 (a) to (c).

Time trend analysis. 66-70 is the 48-month birth cohort from 1 July 1966 to 30 June 1970, etc.

Age	0		1-4		5-9		10-14		0-14	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	0	0	6	10	36	36	92	84	134	130
70-74	1	0	8	2	40	50	90	88	139	140
74-78	1	0	3	9	21	32	80	74	105	115
78-82	0	0	5	3	32	22	79	70	116	95
82-86	0	0	8	5	30	21	76	79	114	105
86-90	0	1	4	9	25	35	93	84	122	129
Total	2	1	34	38	184	196	510	479	730	714

a) Number of cases by age, sex and grouped birth cohort.

Age	0		1-4		5-9		10-14		ASR	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	0.0	0.0	0.8	1.5	4.0	4.2	10.3	9.9	5.0	5.1
70-74	0.6	0.0	1.2	0.3	5.0	6.7	11.4	11.8	5.9	6.2
74-78	0.8	0.0	0.6	1.8	3.2	5.2	12.1	11.8	5.3	6.1
78-82	0.0	0.0	0.9	0.6	4.5	3.2	11.1	10.3	5.4	4.7
82-86	0.0	0.0	1.4	0.9	4.1	3.0	10.5	11.4	5.2	5.0
86-90										

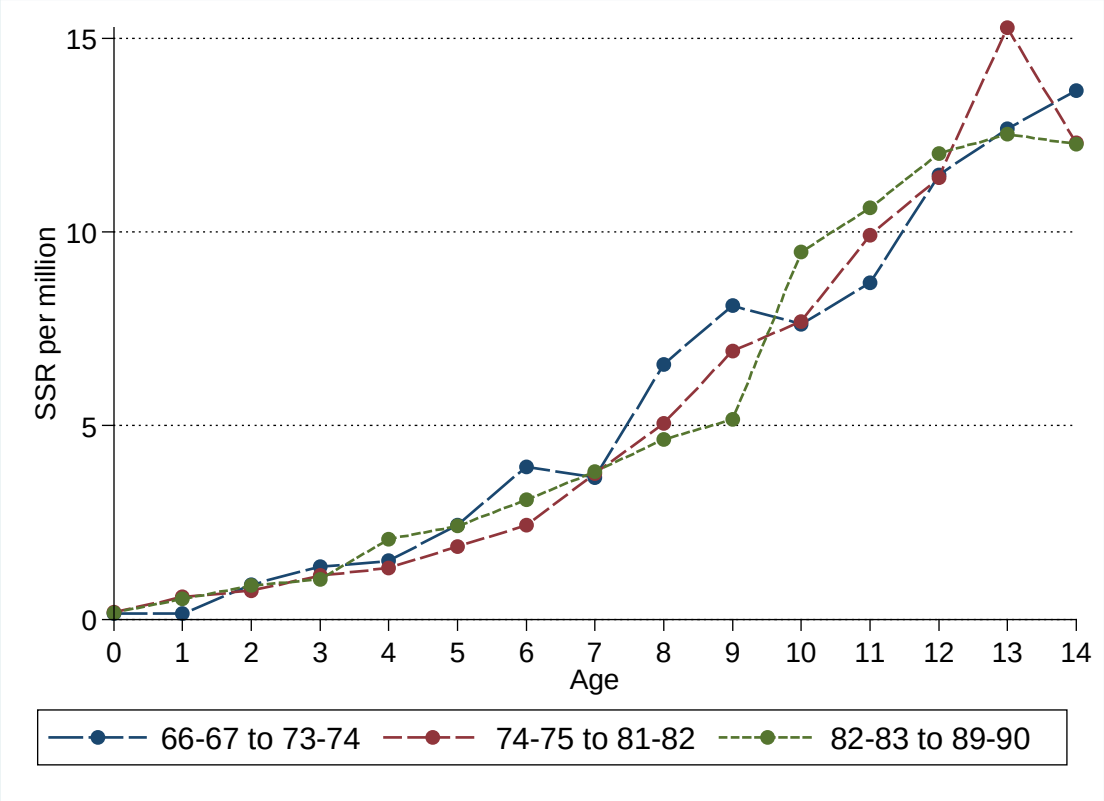
b) Incidence rate per million by age group, sex and grouped birth cohort.

Age	0	1-4	5-9	10-14	ASSR
Born					
66-70	0.0	1.1	4.1	10.1	5.1
70-74	0.3	0.8	5.9	11.6	6.0
74-78	0.4	1.2	4.2	12.0	5.7
78-82	0.0	0.7	3.9	10.7	5.0
82-86	0.0	1.1	3.6	10.9	5.1
86-90	0.3	1.1	4.0	11.8	5.6
Trend	-		-	-	-
AAPC	-0.10		-0.97	0.38	0.00
CI	-3.21 to 3.11		-2.36 to 0.44	-0.49 to 1.26	-0.72 to 0.72
Fit	-		-	-	-

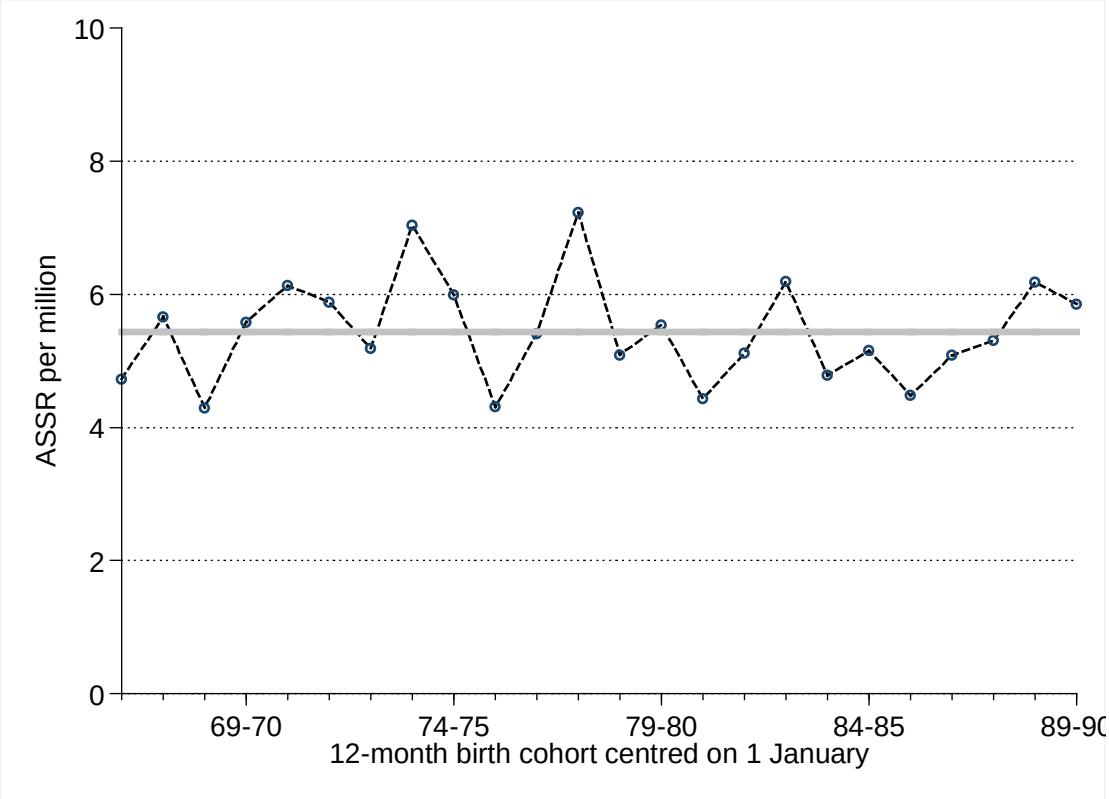
c) Sex-standardised incidence rate per million by age group and grouped birth cohort.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.274.

- = not significant; * p<0.05, ** p<0.01, *** p<0.001.

Bone cancer: by 12-month birth cohort 1966-67 to 1989-90, Britain
Figures 5.3.8.1 (a) and (b).



a) Standardised rate by single year of age at diagnosis, for successive birth periods.



b) Standardised rate by 12-month birth cohort: actual (dotted), step model (solid) line.

Bone cancer: by year of diagnosis 1966-2005, Britain
Tables 5.3.8.2 (a) to (c).

Time trend analysis.

Age/sex	0		1-4		5-9		10-14		0-14	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	0	0	5	10	25	43	83	90	113	143
1971-75	1	0	11	8	37	39	132	89	181	136
1976-80	1	0	6	7	49	52	125	117	181	176
1981-85	0	0	4	8	29	44	116	122	149	174
1986-90	0	1	9	5	40	34	105	96	154	136
1991-95	1	4	5	7	41	32	95	97	142	140
1996-00	0	0	6	8	32	45	103	88	141	141
2001-05	1	0	9	5	47	48	109	101	166	154
Total	4	5	55	58	300	337	868	800	1227	1200

a) Number of cases by age group, sex, and period of diagnosis.

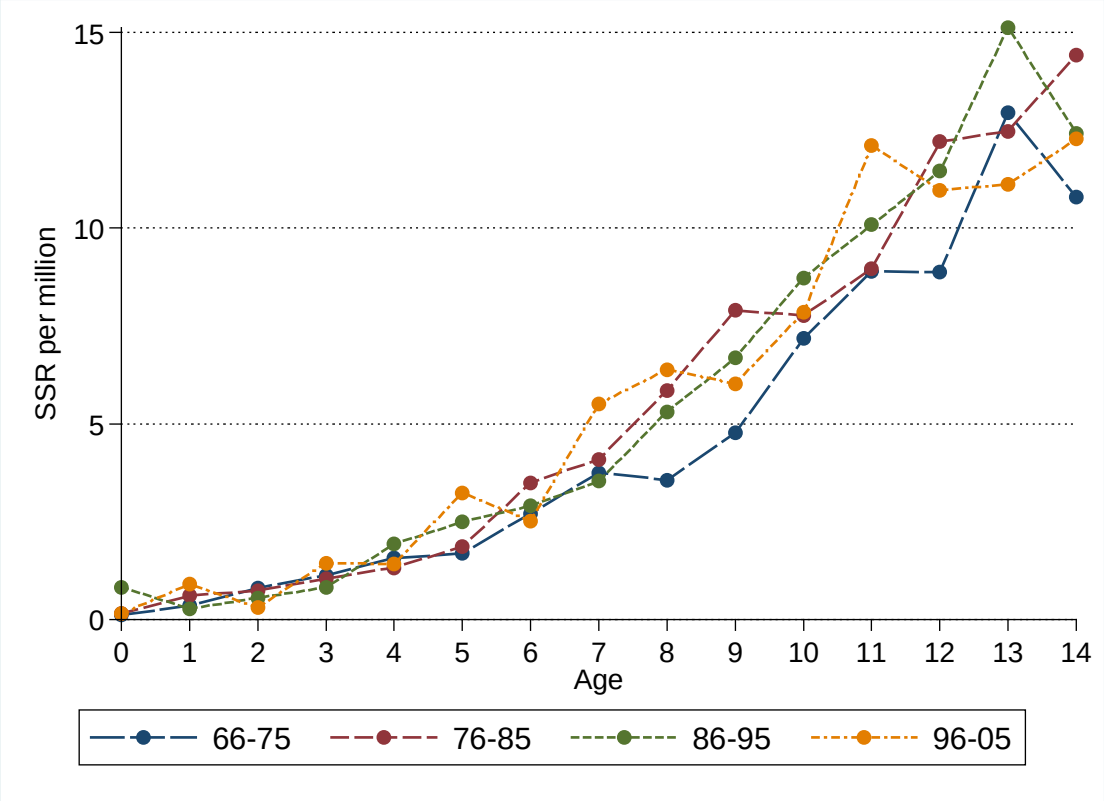
Age/sex	0		1-4		5-9		10-14		ASR	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	0.0	0.0	0.5	1.1	2.3	4.1	8.4	9.8	3.7	4.9
1971-75	0.5	0.0	1.3	1.0	3.2	3.6	12.0	8.5	5.4	4.3
1976-80	0.6	0.0	0.9	1.1	4.7	5.3	10.8	10.7	5.4	5.6
1981-85	0.0	0.0	0.6	1.2	3.4	5.4	11.2	12.4	5.0	6.3
1986-90	0.0	0.6	1.2	0.7	4.5	4.1	12.2	11.8	5.9	5.5
1991-95	0.5	2.2	0.7	1.0	4.4	3.6	10.8	11.5	5.3	5.4
1996-00	0.0	0.0	0.8	1.2	3.3	4.9	11.1	9.9	5.0	5.3
2001-05	0.6	0.0	1.3	0.8	5.2	5.6	11.3	11.1	5.9	5.8

b) Incidence rate per million by age group, sex and period of diagnosis.

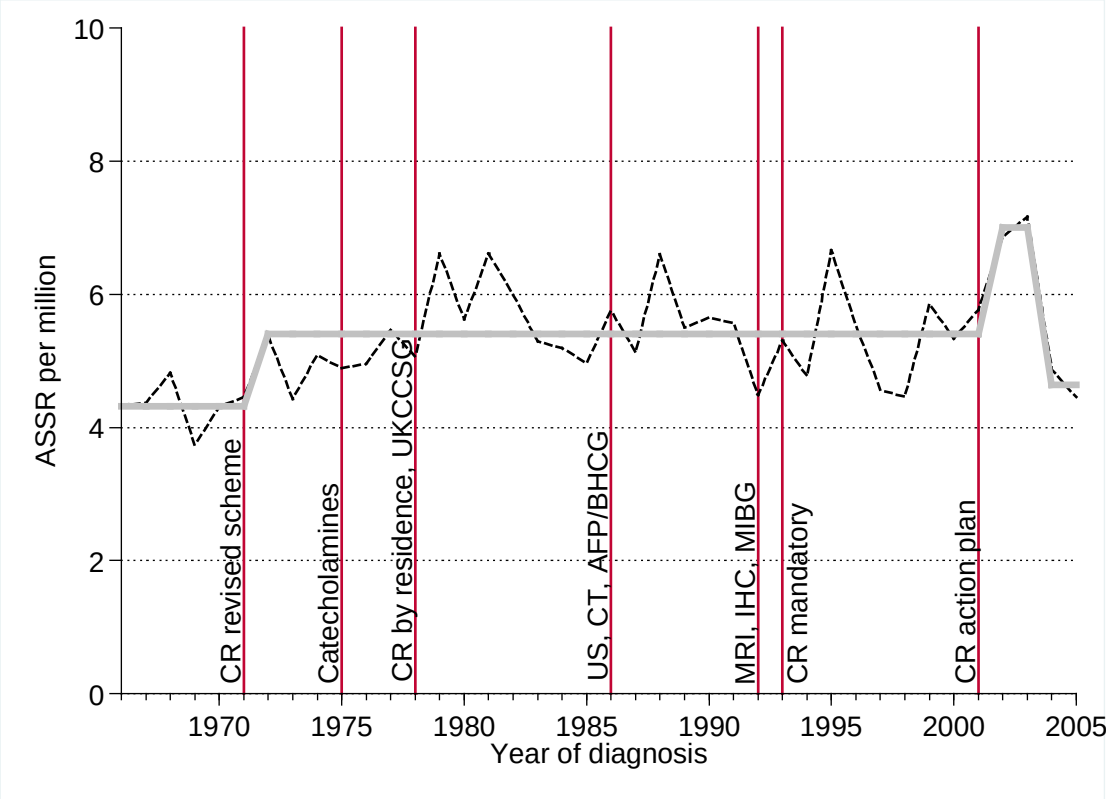
Age	0	1-4	5-9	10-14	ASSR
Diagnosed					
1966-70	0.0	0.8	3.2	9.1	4.3
1971-75	0.3	1.1	3.4	10.2	4.9
1976-80	0.3	1.0	5.0	10.8	5.5
1981-85	0.0	0.9	4.4	11.8	5.6
1986-90	0.3	1.0	4.3	12.0	5.7
1991-95	1.4	0.8	4.0	11.1	5.4
1996-00	0.0	1.0	4.1	10.5	5.1
2001-05	0.3	1.1	5.4	11.2	5.8
Trend	-		**	-	**
AAPC	0.39		0.94	0.37	0.52
CI	-1.11 to 1.92		0.28 to 1.61	-0.05 to 0.78	0.18 to 0.87
Fit	-		-	-	-

c) Sex-standardised incidence rate per million by age group and period of diagnosis.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.350.
- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Bone cancer: by year of diagnosis 1966-2005, Britain
Figures 5.3.8.2 (a) and (b).

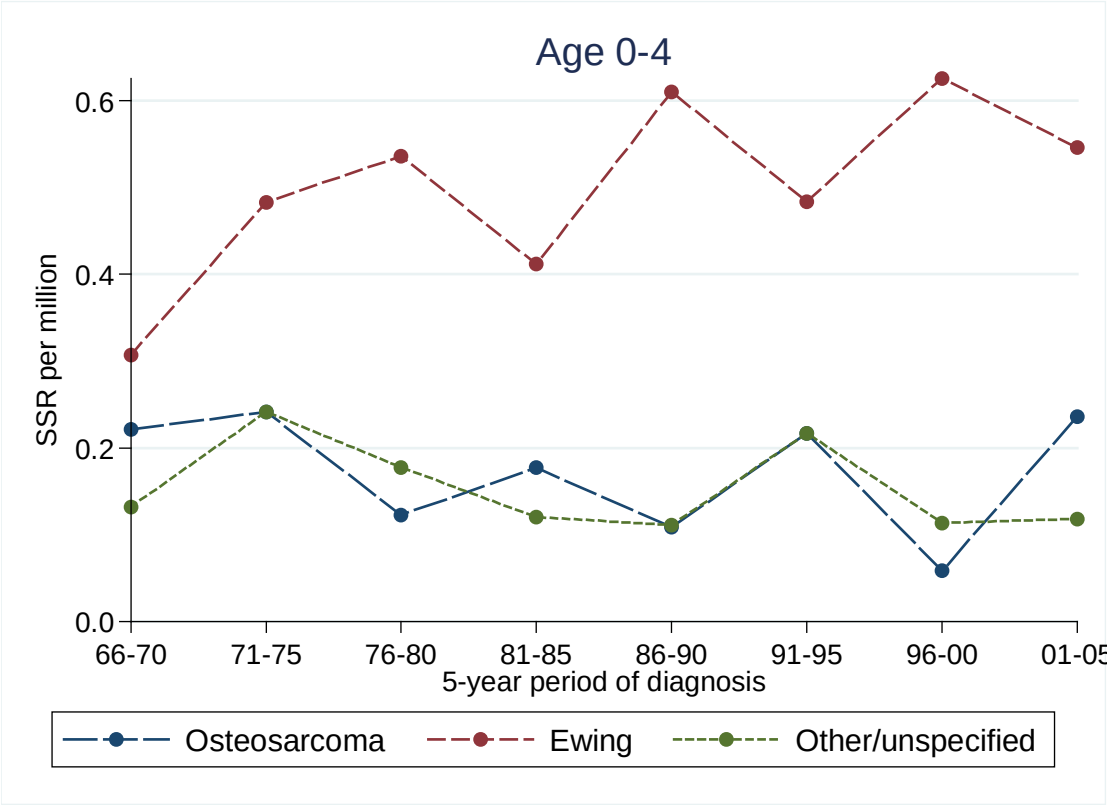


a) Standardised rate by single year of age at diagnosis, for successive diagnosis periods.



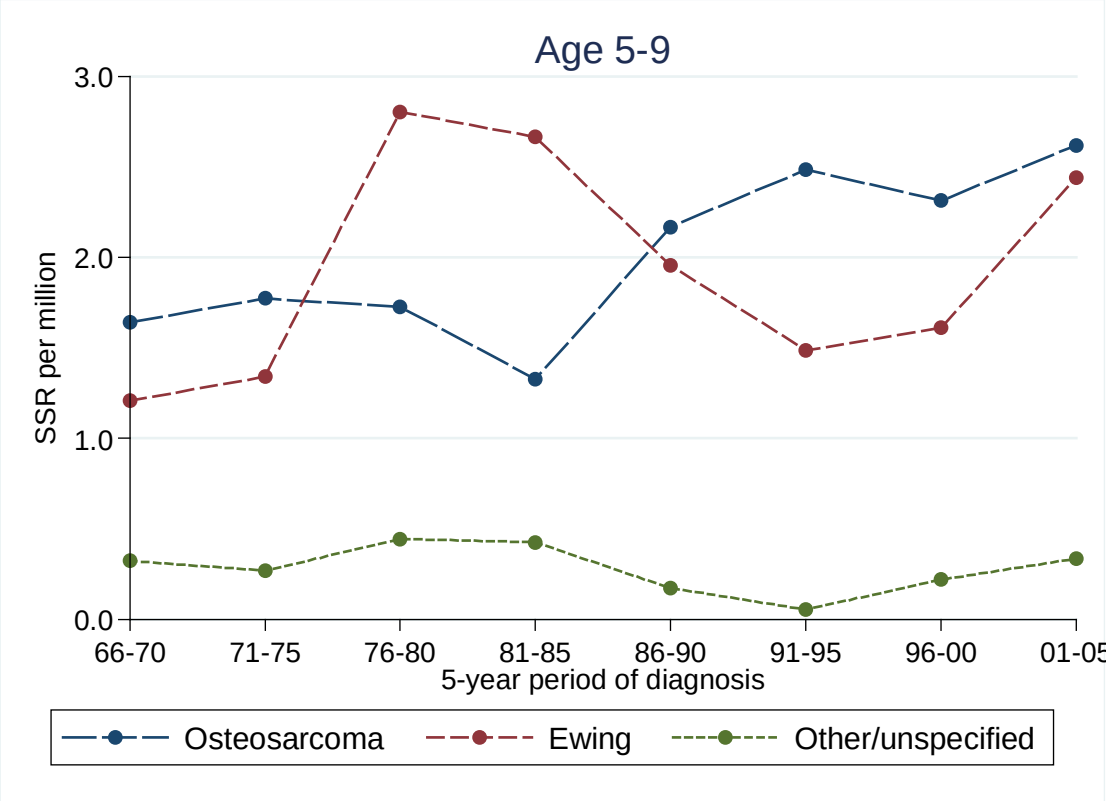
b) Standardised rate by year of diagnosis: actual (dotted), step model (solid) line.

Bone cancer: by year of diagnosis 1966-2005, Britain
Figure 5.3.8.2 (c).

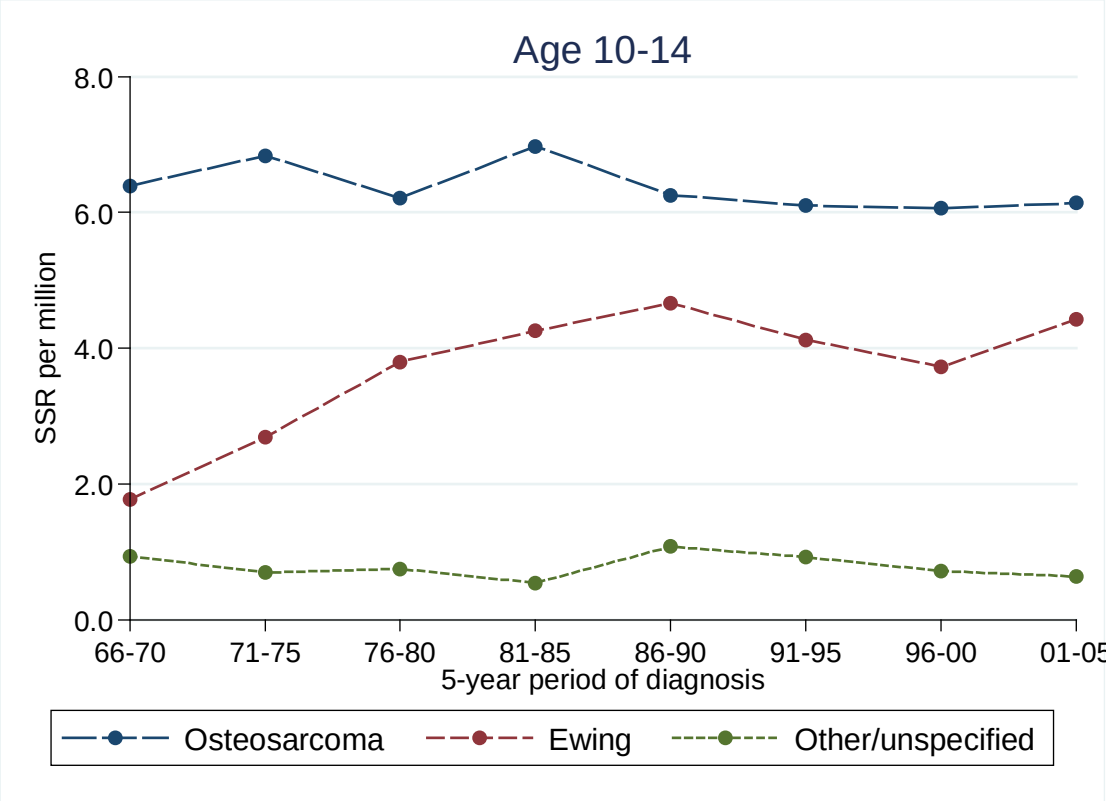


c) Standardised rate at age 0-4, by subtype and 5-year period of diagnosis.

Bone cancer: by year of diagnosis 1966-2005, Britain
Figures 5.3.8.2 (d) and (e).



d) Standardised rate at age 5-9, by subtype and 5-year period of diagnosis.



e) Standardised rate at age 10-14, by subtype and 5-year period of diagnosis.

5.3.9 Soft-tissue sarcoma

5.3.9.1 Year of birth

See Tables 5.3.9.1 (a) to (c), and Figures 5.3.9.1 (a) and (b).

By year of birth, there was an overall time trend of 2.2% (1.6 to 2.8) per year. In age groups 1-4, 5-9 and 10-14 there were increasing time trends of 2.1% (1.1 to 3.2), 2.2% (1.1 to 3.4) and 2.5% (1.4 to 3.6) per year, respectively. In age group 0, there was a non-significant increase of 1.3% (-0.6 to 3.2). The differences in trend between age groups were not statistically significant (p=0.755). (Table 5.3.9.1(c)).

The step model indicates increases at 1967-68 and 1981-82 (Figure 5.3.9.1(b)).

5.3.9.2 Year of diagnosis

See Tables 5.3.9.2 (a) to (c), Figures 5.3.9.2 (a) to (f), and Figures 5.3.13.2 (c) to (f).

By year of diagnosis, there was an overall increase of 1.6% per year on average, and evidence that the Poisson model did not fit ($p<0.05$). In age groups 1-4, 5-9 and 10-14, there were increasing time trends of 1.1% (0.6 to 1.6), 1.8% (1.2 to 2.3) and 2.3% (1.8 to 2.9) per year, respectively. In age group 0, there was an increase of 0.7% per year, on average, and the Poisson model did not fit ($p<0.01$) (Table 5.3.9.2(c)).

Table 5.3.9.2(c), Figure 5.3.9.2 (a) and Figures 5.3.13.2 (c) to (f) show small increases from the first decade to the second decade, and fairly large increases from the second decade to the third, in all age groups. At ages 5-9 and 10-14 there were relatively large increases in the ‘other specified’ subtype between 1986-90 and 1991-95, while the rhabdomyosarcoma subtype remained stable or decreased (Figures 5.3.9.2 (e) and (f)).

The step model indicates increases at 1971 and 1984.

5.3.9.3 Discussion

By year of birth and by year of diagnosis there were increases of 2.2% and 1.6% per year on average, respectively. The steeper trend by year of birth reflects a particularly low rate for children born in 1966-67.

By year of diagnosis, the large suggested increase at 1984 probably represents diagnosis of soft-tissue cancer at an earlier stage of disease, due to the introduction of US and CT scanning around 1986; there is scope for transfer of cases from beyond the upper age limit, because this diagnostic group is as common in adolescence as in later childhood [123]. As expected, the increasing time trend was larger in the older age groups, and most of the increase occurred between 1976-85 and 1986-95. The smaller increase in 1972 might be due to changes in the registration system in 1971.

There is fairly clear evidence for diagnostic transfer between subtypes around the time of the introduction of IHC in about 1992. The diagnosis of ‘rhabdomyosarcoma’ became less common, whereas the ‘other specified’ group became much more common, particularly at ages 10-14. This group consists mainly of tumours of the Ewing family, which were diagnosed sometimes as ‘extra-osseous Ewing sarcoma’, and sometimes as ‘peripheral primitive neuroectodermal tumour’ (pPNET).

Figures 5.3.13.2 (c) to (f) suggest that there may also have been diagnostic transfer between soft-tissue sarcoma and other types of non-CNS solid cancer (see Section 5.3.13).

Soft tissue sarcoma: by 12-month birth cohort 1966-67 to 1989-90, Britain
Tables 5.3.9.1 (a) to (c).

Time trend analysis. 66-70 is the 48-month birth cohort from 1 July 1966 to 30 June 1970, etc.

Age	0		1-4		5-9		10-14		0-14	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	17	17	65	42	54	39	48	37	184	135
70-74	19	25	73	43	57	37	56	55	205	160
74-78	22	10	39	36	43	31	58	42	162	119
78-82	16	10	64	43	50	44	60	63	190	160
82-86	22	17	67	54	58	56	67	50	214	177
86-90	23	18	82	58	70	48	78	64	253	188
Total	119	97	390	276	332	255	367	311	1208	939

a) Number of cases by age, sex and grouped birth cohort.

Age	0		1-4		5-9		10-14		ASR	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	9.3	9.8	9.0	6.1	6.0	4.6	5.4	4.4	6.8	5.3
70-74	11.7	16.3	11.4	7.1	7.2	4.9	7.1	7.3	8.6	7.1
74-78	16.6	8.0	7.4	7.2	6.6	5.0	8.8	6.7	8.2	6.4
78-82	11.2	7.4	11.3	8.0	7.0	6.5	8.4	9.2	8.9	7.9
82-86	15.3	12.4	11.6	9.8	8.0	8.1	9.2	7.2	9.9	8.6
86-90	15.1	12.4	13.5	10.0	9.2	6.6	10.2	8.8	11.1	8.6

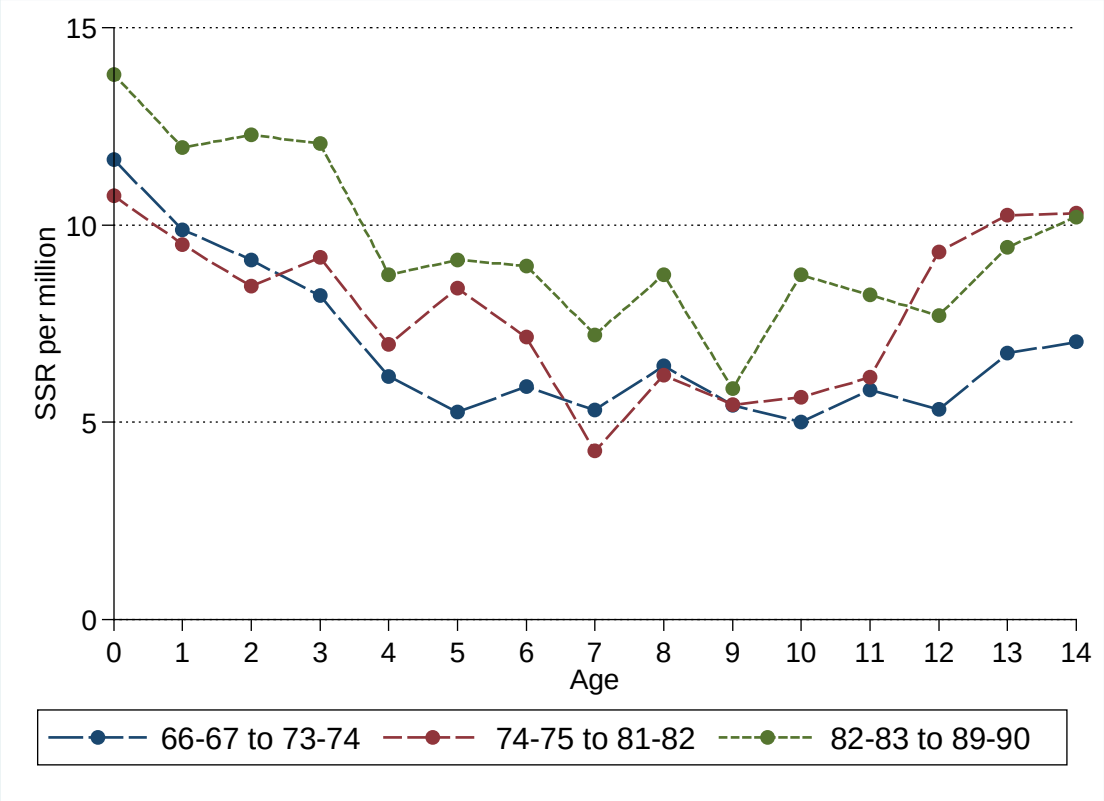
b) Incidence rate per million by age group, sex and grouped birth cohort.

Age	0	1-4	5-9	10-14	ASSR
Born					
66-70	9.6	7.6	5.3	4.9	6.0
70-74	14.0	9.2	6.1	7.2	7.8
74-78	12.3	7.3	5.8	7.8	7.3
78-82	9.3	9.6	6.8	8.8	8.4
82-86	13.9	10.7	8.1	8.2	9.2
86-90	13.8	11.8	7.9	9.5	9.8
Trend	-	***	***	***	***
AAPC	1.29	2.13	2.24	2.49	2.19
CI	-0.58 to 3.19	1.05 to 3.22	1.09 to 3.41	1.42 to 3.58	1.59 to 2.80
Fit	-	-	-	-	-

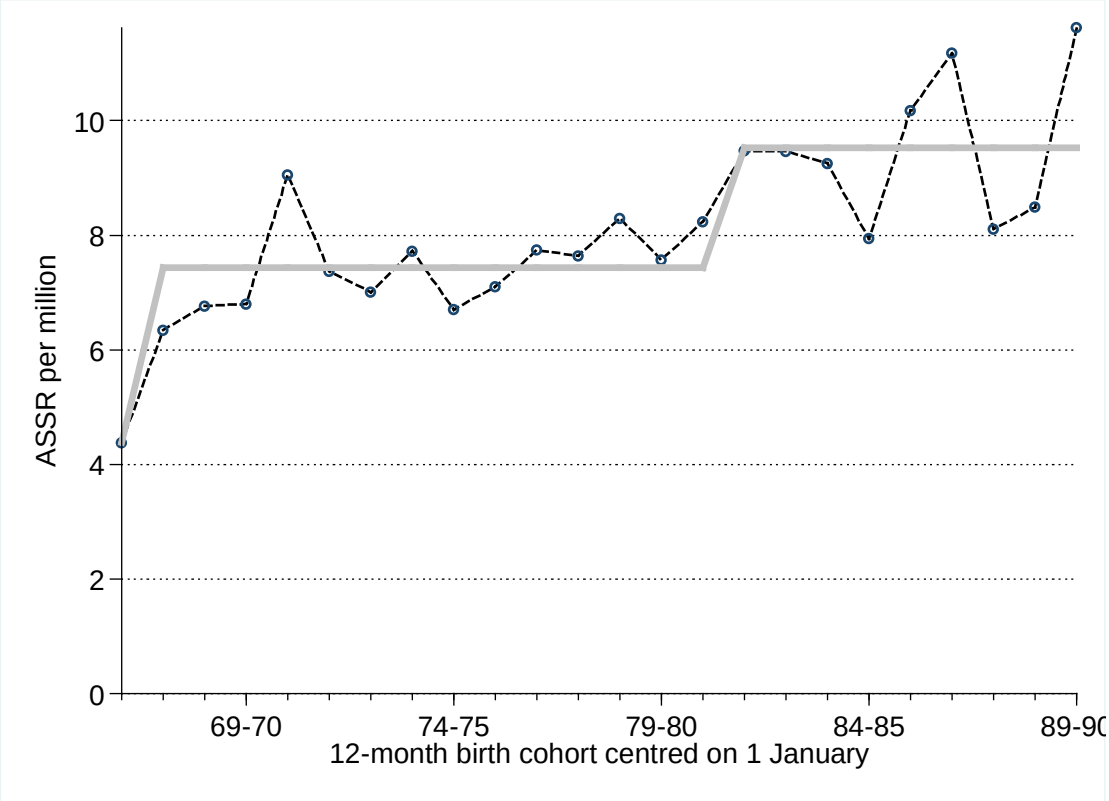
c) Sex-standardised incidence rate per million by age group and grouped birth cohort.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.755.

- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Soft tissue sarcoma: by 12-month birth cohort 1966-67 to 1989-90, Britain
Figures 5.3.9.1 (a) and (b).



a) Standardised rate by single year of age at diagnosis, for successive birth periods.



b) Standardised rate by 12-month birth cohort: actual (dotted), step model (solid) line.

Soft tissue sarcoma: by year of diagnosis 1966-2005, Britain
Tables 5.3.9.2 (a) to (c).

Time trend analysis.

Age/sex	0		1-4		5-9		10-14		0-14	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	19	28	82	58	55	48	48	26	204	160
1971-75	26	23	85	60	56	52	63	46	230	181
1976-80	24	15	64	40	80	44	70	53	238	152
1981-85	26	18	70	55	59	45	64	61	219	179
1986-90	27	22	95	69	56	53	69	59	247	203
1991-95	25	30	104	73	79	71	83	74	291	248
1996-00	32	19	84	60	93	54	73	72	282	205
2001-05	28	15	76	65	76	75	104	71	284	226
Total	207	170	660	480	554	442	574	462	1995	1554

a) Number of cases by age group, sex, and period of diagnosis.

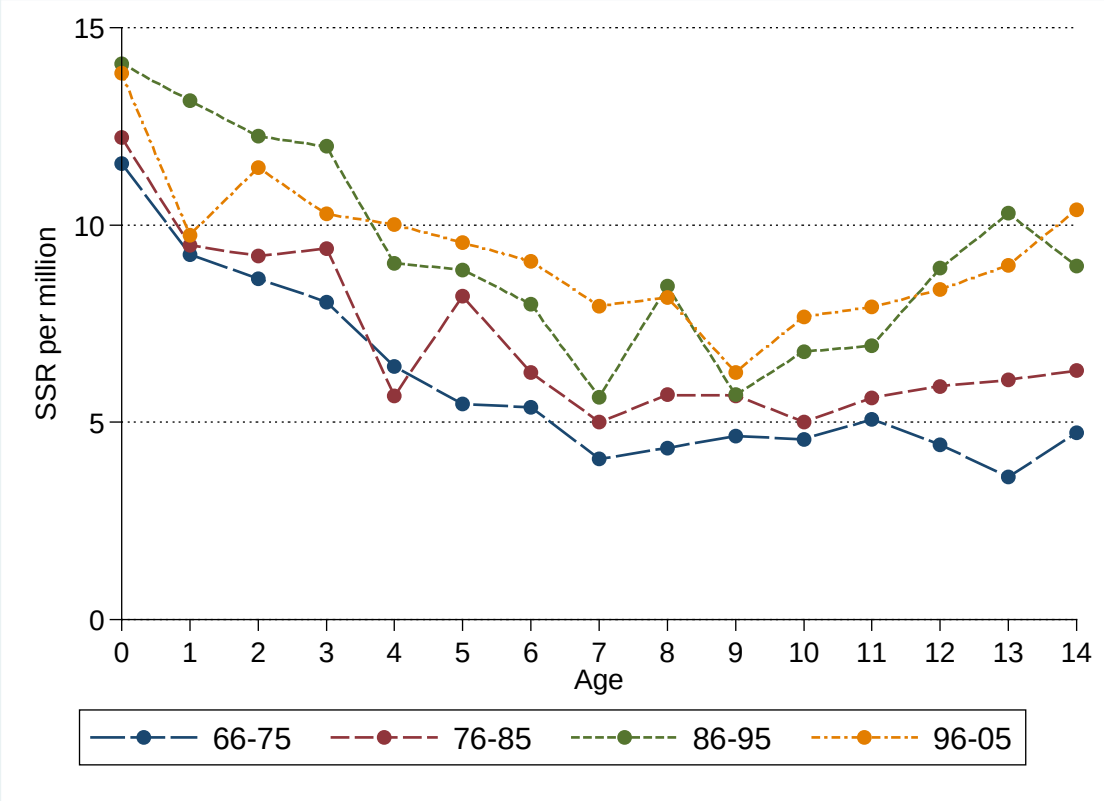
Age/sex	0		1-4		5-9		10-14		ASR	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	8.3	12.8	8.7	6.4	5.0	4.6	4.9	2.8	6.2	5.0
1971-75	13.2	12.3	9.9	7.4	4.9	4.7	5.7	4.4	7.0	5.8
1976-80	14.2	9.4	9.3	6.1	7.7	4.4	6.1	4.8	8.0	5.4
1981-85	14.6	10.6	10.0	8.3	6.9	5.6	6.2	6.2	8.0	6.8
1986-90	14.3	12.2	13.0	9.9	6.4	6.3	8.0	7.2	9.2	8.0
1991-95	13.2	16.6	13.6	10.0	8.5	8.0	9.4	8.8	10.5	9.4
1996-00	18.2	11.4	11.5	8.7	9.7	5.9	7.9	8.1	10.2	7.7
2001-05	16.5	9.3	11.2	10.1	8.4	8.7	10.8	7.8	10.5	8.8

b) Incidence rate per million by age group, sex and period of diagnosis.

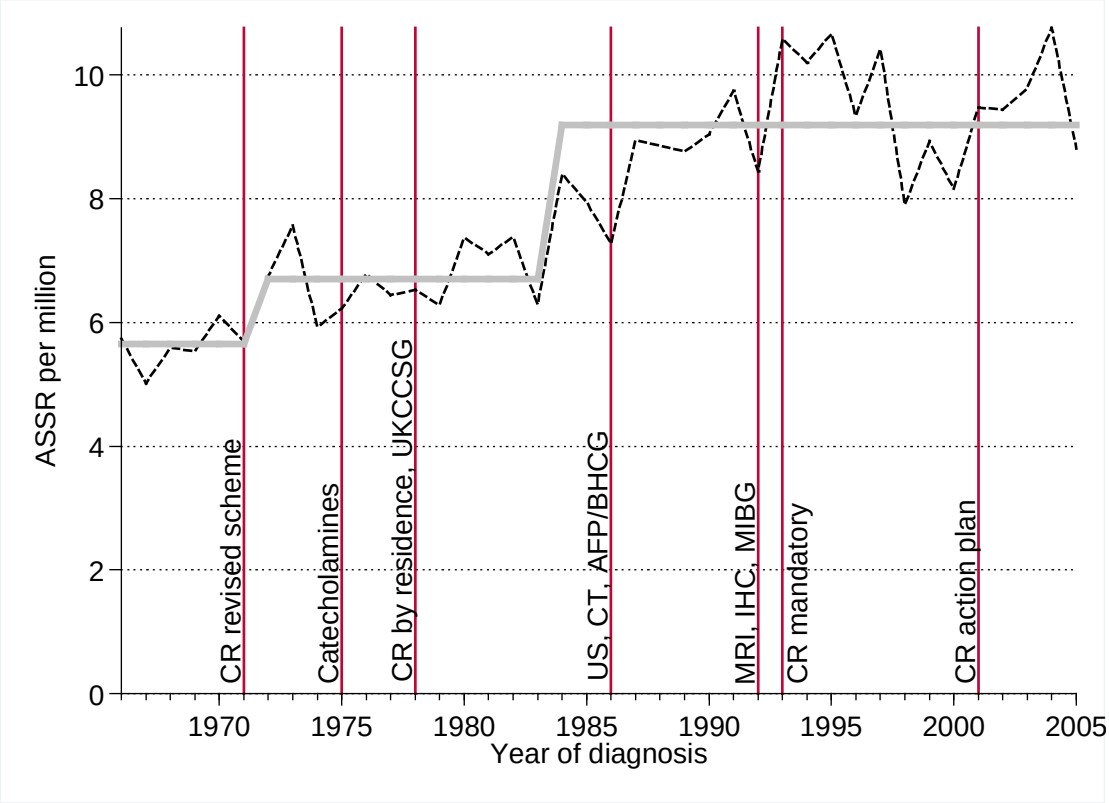
Age	0	1-4	5-9	10-14	ASSR
Diagnosed					
1966-70	10.5	7.6	4.8	3.9	5.6
1971-75	12.8	8.6	4.8	5.0	6.4
1976-80	11.8	7.7	6.1	5.5	6.7
1981-85	12.6	9.2	6.2	6.2	7.4
1986-90	13.3	11.4	6.3	7.6	8.6
1991-95	14.9	11.8	8.3	9.1	9.9
1996-00	14.8	10.1	7.8	8.0	9.0
2001-05	12.9	10.6	8.6	9.3	9.7
Trend	-	***	***	***	***
AAPC	0.68	1.14	1.75	2.33	1.60
CI	*-0.18 to 1.55*	0.64 to 1.64	1.21 to 2.29	1.79 to 2.88	*1.31 to 1.89*
Fit	**	-	-	-	*

c) Sex-standardised incidence rate per million by age group and period of diagnosis.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.002.
- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Soft tissue sarcoma: by year of diagnosis 1966-2005, Britain
Figures 5.3.9.2 (a) and (b).

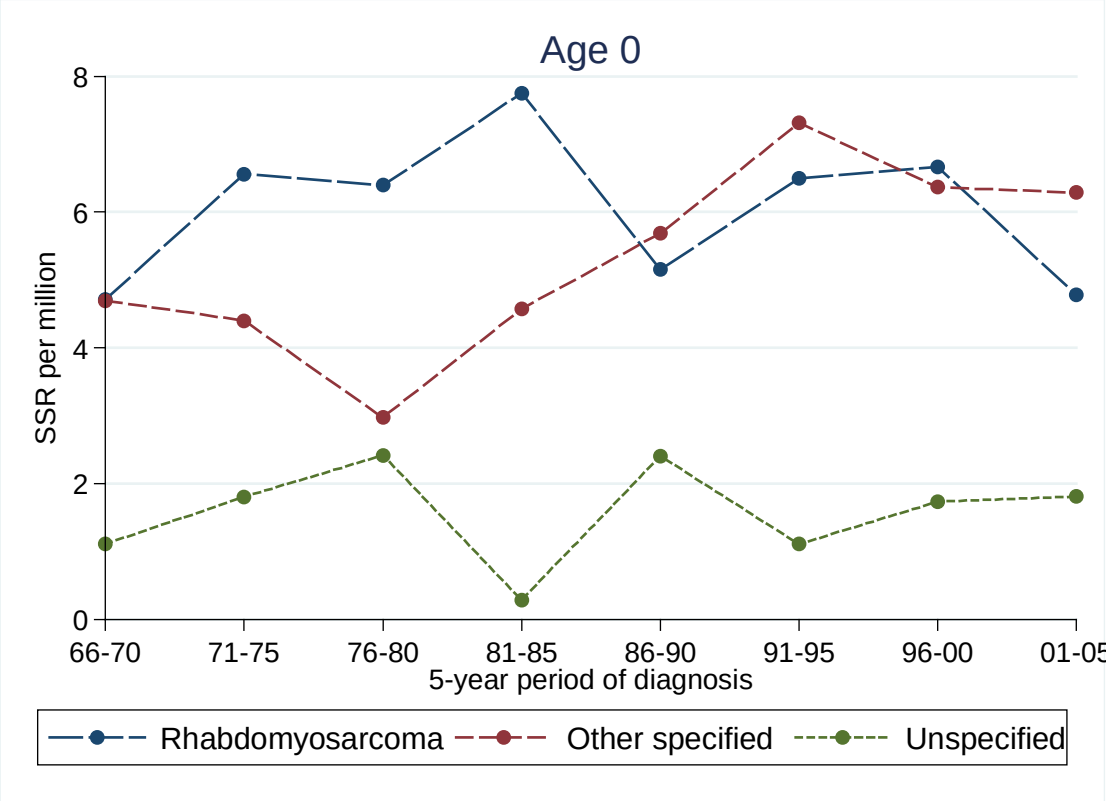


a) Standardised rate by single year of age at diagnosis, for successive diagnosis periods.

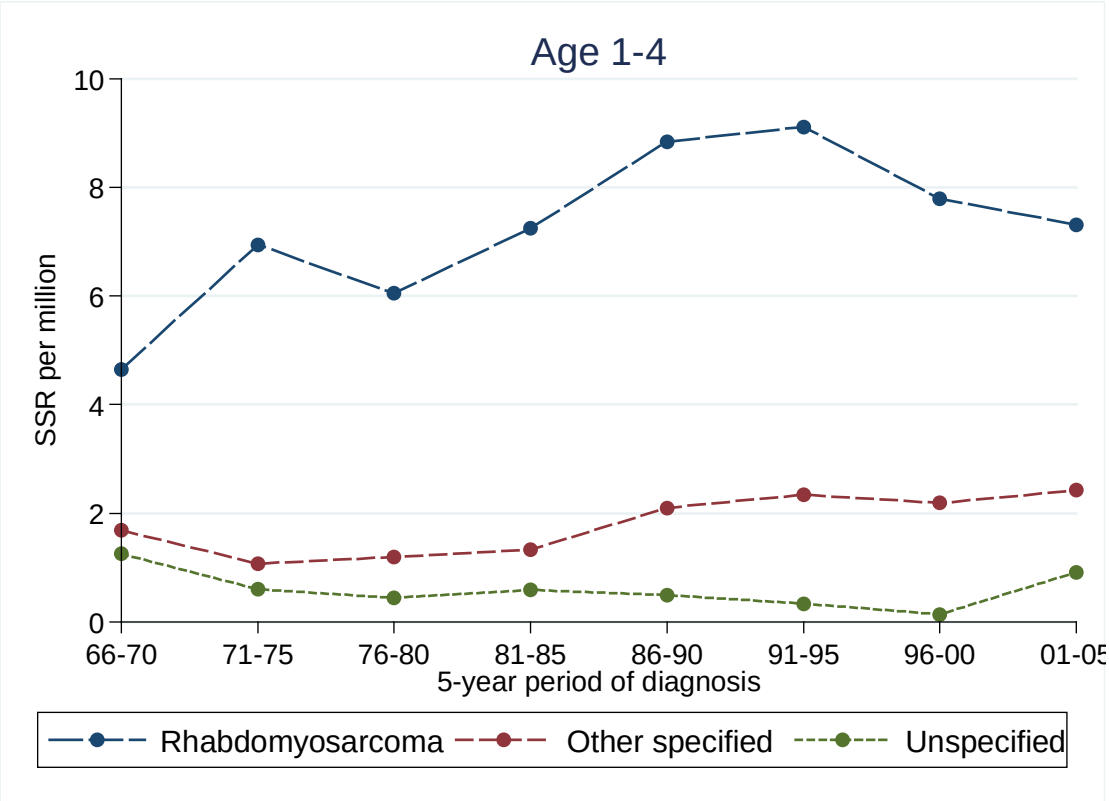


b) Standardised rate by year of diagnosis: actual (dotted), step model (solid) line.

Soft tissue sarcoma: by year of diagnosis 1966-2005, Britain
Figures 5.3.9.2 (c) and (d).

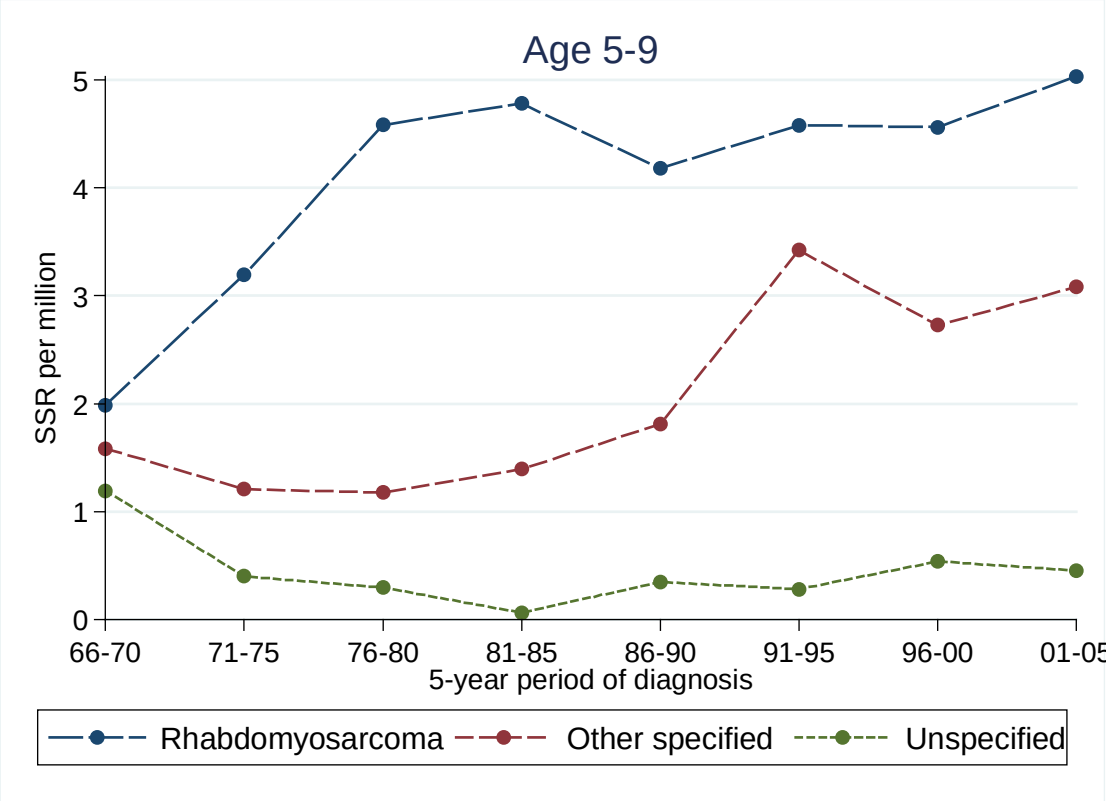


c) Standardised rate at age 0, by subtype and 5-year period of diagnosis.

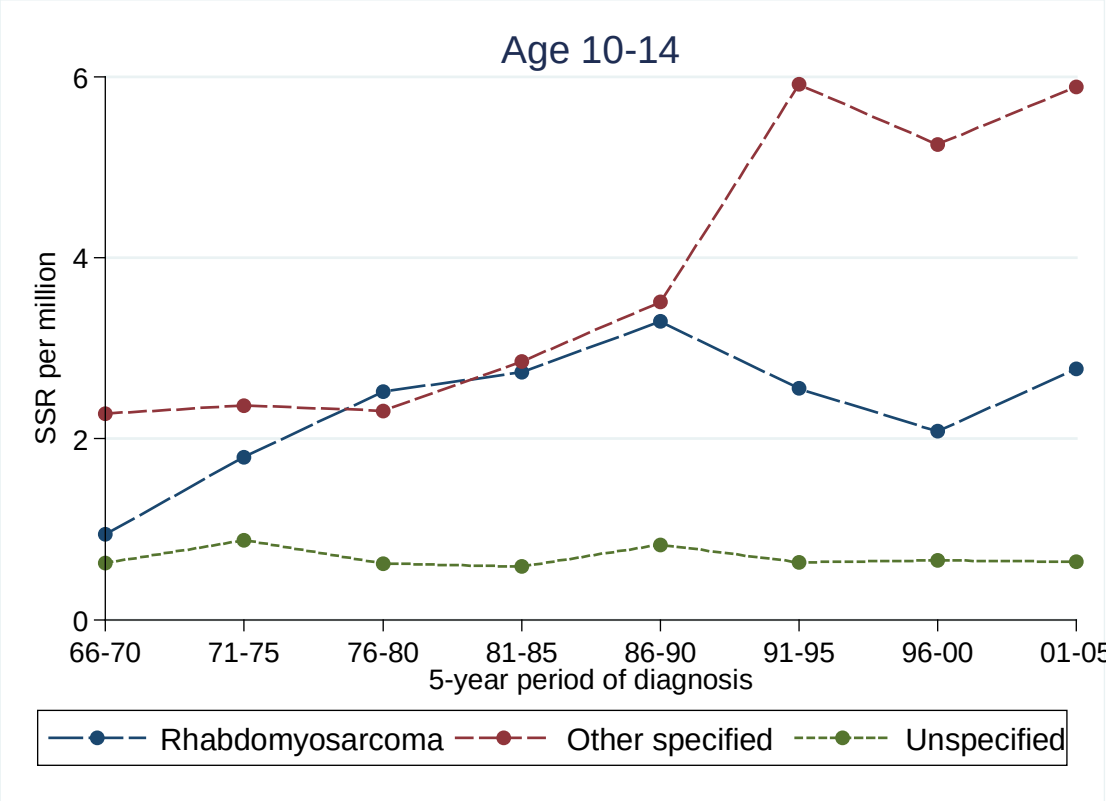


d) Standardised rate at age 1-4, by subtype and 5-year period of diagnosis.

Soft tissue sarcoma: by year of diagnosis 1966-2005, Britain
Figures 5.3.9.2 (e) and (f).



e) Standardised rate at age 5-9, by subtype and 5-year period of diagnosis.



f) Standardised rate at age 10-14, by subtype and 5-year period of diagnosis.

5.3.10 Gonadal/germ-cell cancer NOS

5.3.10.1 Year of birth

See Tables 5.3.10.1 (a) to (c), and Figures 5.3.10.1 (a) and (b).

By year of birth, there was an overall increase of 1.3% per year, and evidence that the Poisson model did not fit ($p<0.01$). In age group 1-4, there was an increasing time trend of 1.7% (0.1 to 3.4) per year. In age group 10-14, there was a non-significant increase of 0.9% (-0.8 to 2.6) per year. In age groups 0 and 5-9, there were increases of 1.4% and 1.3% per year, on average, and evidence that the Poisson models did not fit ($p<0.05$) (Table 5.3.10.1(c)).

The step model suggests an increase in 1981-82 (Figure 5.3.10.1(b)).

5.3.10.2 Year of diagnosis

See Tables 5.3.10.2 (a) to (c), Figures 5.3.10.2 (a) to (f), and Figures 5.3.13.2 (c) to (f).

By year of diagnosis, there was an overall increase of 1.1% per year, and the Poisson model did not fit ($p<0.001$). In age group 10-14, there was an increasing time trend of 1.0% (0.2 to 1.8) per year. In age groups 1-4 and 5-9 there were non-significant increases of 0.2% (-0.6 to 1.0) and 1.2% (-0.3 to 2.6), respectively. In age group 0, there was an increase of 2.9% per year, on average, and the Poisson model did not fit ($p<0.001$) (Table 5.3.10.2(c)).

Table 5.3.10.2(c), Figures 5.3.10.2(a) and 5.3.13.2 (c) to (f) show that, up to 1986-90, there was a fairly large increase in rate in age groups 0, 1-4 and 10-14. The largest increase appeared to be in female non-gonadal (non-CNS) germ-cell tumours diagnosed at age 0, particularly in the most recent period; there was a suggestion of a corresponding decrease at ages 1-4 (Figures 5.3.10.2 (c) and (d)). The highest age-specific rate moved from age 1 (in the first three decades) to age 0 (in the most recent decade) (Figure 5.3.10.2 (a)).

The step model indicates an increase at 1981.

5.3.10.3 Discussion

By year of birth and by year of diagnosis there were increases of 1.3% and 1.1% per year on average, respectively. There was evidence of lack of fit to the Poisson trend model.

Children were more likely to be registered with gonadal/germ-cell cancer if they were born in the 1980s than if they were born in the 1970s. The obvious explanation is the introduction of serum hormone testing for germ-cell cancer. The timing indicated by the step function by year of diagnosis (around 1981) is slightly earlier than the timing predicted in Chapter 2 (around 1986), but it fits quite well with the start of the UKCCSG's first malignant germ-cell tumour study (in 1979, see Chapter 2). The existence of the trial protocol would have been an incentive to diagnose germ-cell cancer, and the availability of (experimental) AFP and HCG measurement would have made definite diagnosis possible. Some of the cases may have transferred from soft-tissue sarcoma, which decreased at ages 0 and 1-4 from 1971-75 to 1976-80 (Table 5.3.9.2(c) and Figure 5.3.13.2(d)).

There is clear evidence that young children were diagnosed at an earlier stage of disease in more recent years: the peak age at diagnosis moved from age 1 to age 0 in the most recent decade, and the rates at ages 1 and 2 decreased (Figure 5.3.10.2 (a)). This change appears to have occurred almost entirely in non-gonadal (non-CNS) germ-cell cancer. Male gonadal tumours may be easier to detect clinically than other germ-cell and gonadal tumours, and therefore less subject to delay in diagnosis, while female gonadal cancer is very rarely diagnosed in infants and very young children.

In older children, female gonadal cancer was by far the commonest subgroup (Table 5.3.10.2(b)). The increase from the 1970s to the 1990s at age 5-9 was confined to this subgroup (Table 5.2(d) and Figure 5.3.10.2 9(e)).

Gonadal/germ-cell cancer NOS: by birth cohort 1966-67 to 1989-90, Britain

Tables 5.3.10.1 (a) to (c).

Time trend analysis. 66-70 is the 48-month birth cohort from 1 July 1966 to 30 June 1970, etc.

Age	0		1-4		5-9		10-14		0-14	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	12	10	34	17	0	13	11	36	57	76
70-74	10	2	19	20	5	11	7	33	41	66
74-78	15	7	33	9	3	10	8	31	59	57
78-82	11	4	25	16	2	11	14	26	52	57
82-86	13	4	32	22	0	10	7	45	52	81
86-90	11	10	33	22	2	19	9	35	55	86
Total	72	37	176	106	12	74	56	206	316	423

a) Number of cases by age, sex and grouped birth cohort.

Age	0		1-4		5-9		10-14		ASR	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	6.6	5.7	4.7	2.5	0.0	1.5	1.2	4.3	2.1	3.0
70-74	6.2	1.3	3.0	3.3	0.6	1.5	0.9	4.4	1.7	2.9
74-78	11.3	5.6	6.3	1.8	0.5	1.6	1.2	5.0	3.0	3.0
78-82	7.7	3.0	4.4	3.0	0.3	1.6	2.0	3.8	2.4	2.8
82-86	9.0	2.9	5.6	4.0	0.0	1.4	1.0	6.5	2.4	3.9
86-90	7.2	6.9	5.4	3.8	0.3	2.6	1.2	4.8	2.4	3.9

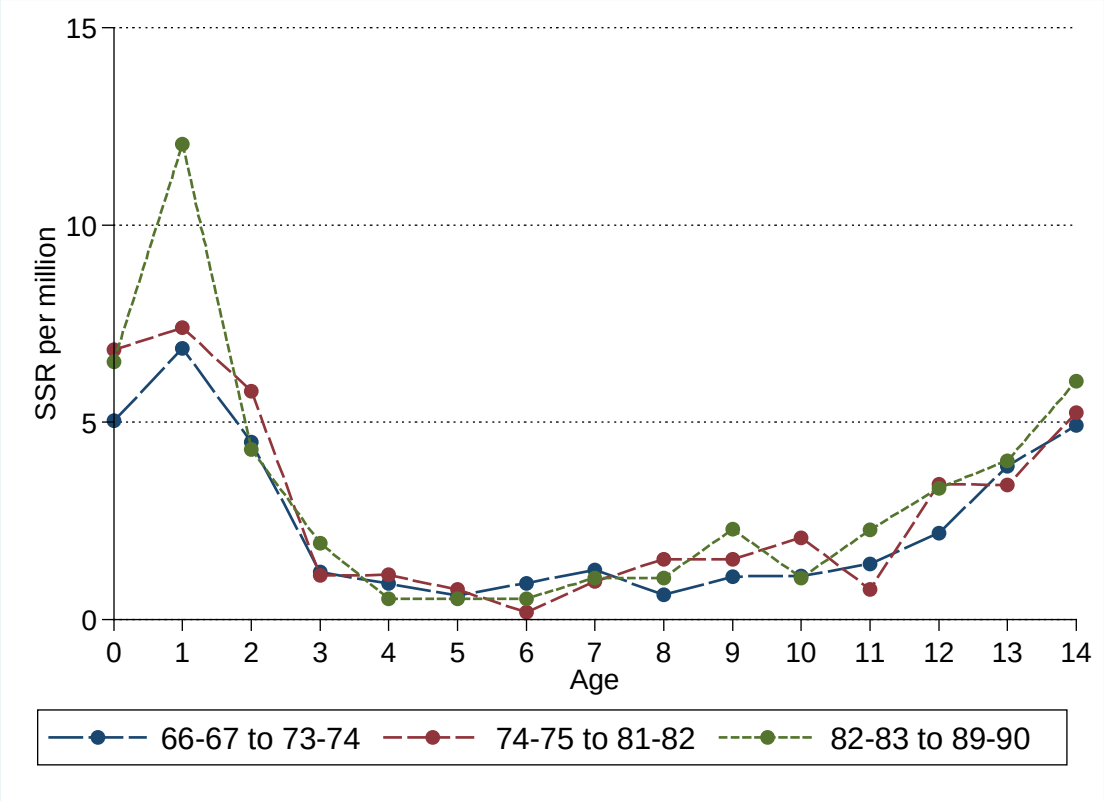
b) Incidence rate per million by age group, sex and grouped birth cohort.

Age	0	1-4	5-9	10-14	ASSR
Born					
66-70	6.2	3.6	0.8	2.7	2.5
70-74	3.7	3.1	1.0	2.6	2.3
74-78	8.4	4.0	1.0	3.1	3.0
78-82	5.3	3.7	1.0	2.9	2.6
82-86	6.0	4.8	0.7	3.7	3.2
86-90	7.1	4.6	1.4	3.0	3.2
Trend	-	*	-	-	*
AAPC	1.35	1.74	1.32	0.89	1.33
CI	*-1.27 to 4.04*	0.09 to 3.41	*-1.63 to 4.36*	-0.81 to 2.61	*0.31 to 2.36*
Fit	*	-	*	-	**

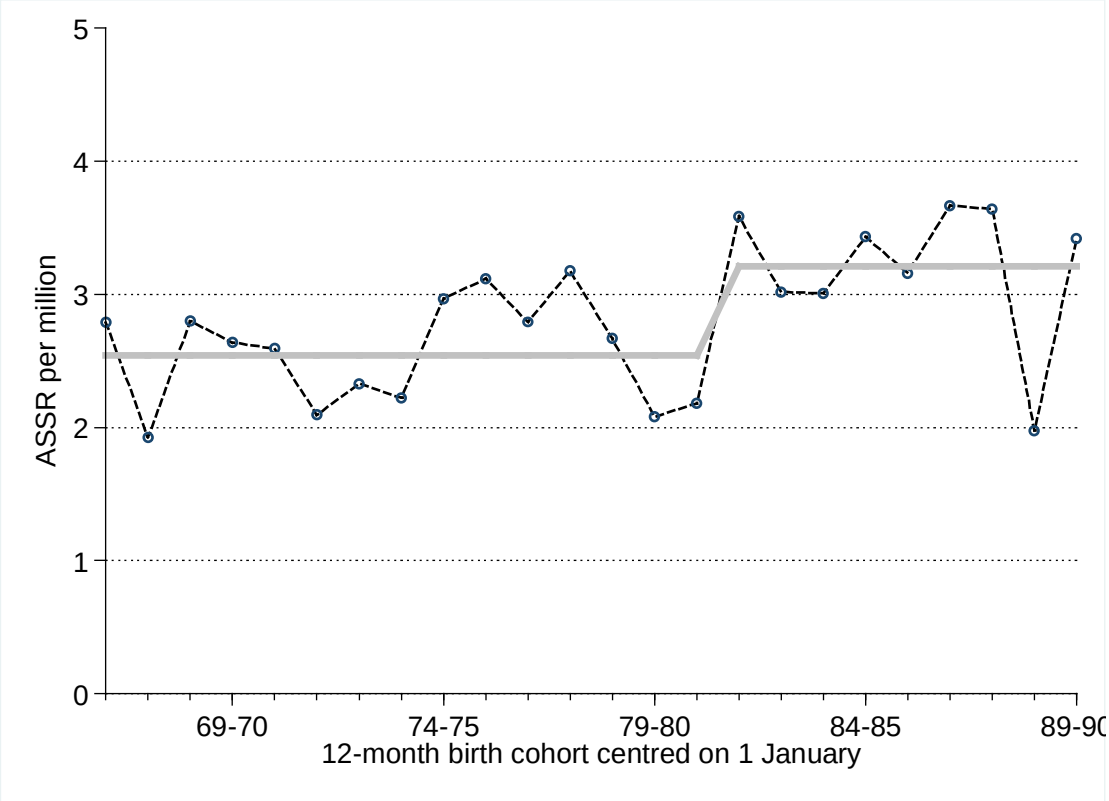
c) Sex-standardised incidence rate per million by age group and grouped birth cohort.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.922.

- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Gonadal/germ-cell cancer NOS: by birth cohort 1966-67 to 1989-90, Britain
Figures 5.3.10.1 (a) and (b).



a) Standardised rate by single year of age at diagnosis, for successive birth periods.



b) Standardised rate by 12-month birth cohort: actual (dotted), step model (solid) line.

Gonadal/germ-cell cancer NOS: by year of diagnosis 1966-2005, Britain
Tables 5.3.10.2 (a) to (c).

Time trend analysis.

Age/sex	0		1-4		5-9		10-14		0-14	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	15	16	36	21	2	8	5	43	58	88
1971-75	15	3	28	22	4	16	9	33	56	74
1976-80	10	7	39	14	5	11	6	45	60	77
1981-85	17	7	36	19	3	13	15	46	71	85
1986-90	20	11	39	32	2	12	9	45	70	100
1991-95	18	12	29	24	2	18	13	31	62	85
1996-00	23	14	31	21	0	19	13	53	67	107
2001-05	21	35	19	19	1	16	11	42	52	112
Total	139	105	257	172	19	113	81	338	496	728

a) Number of cases by age group, sex, and period of diagnosis.

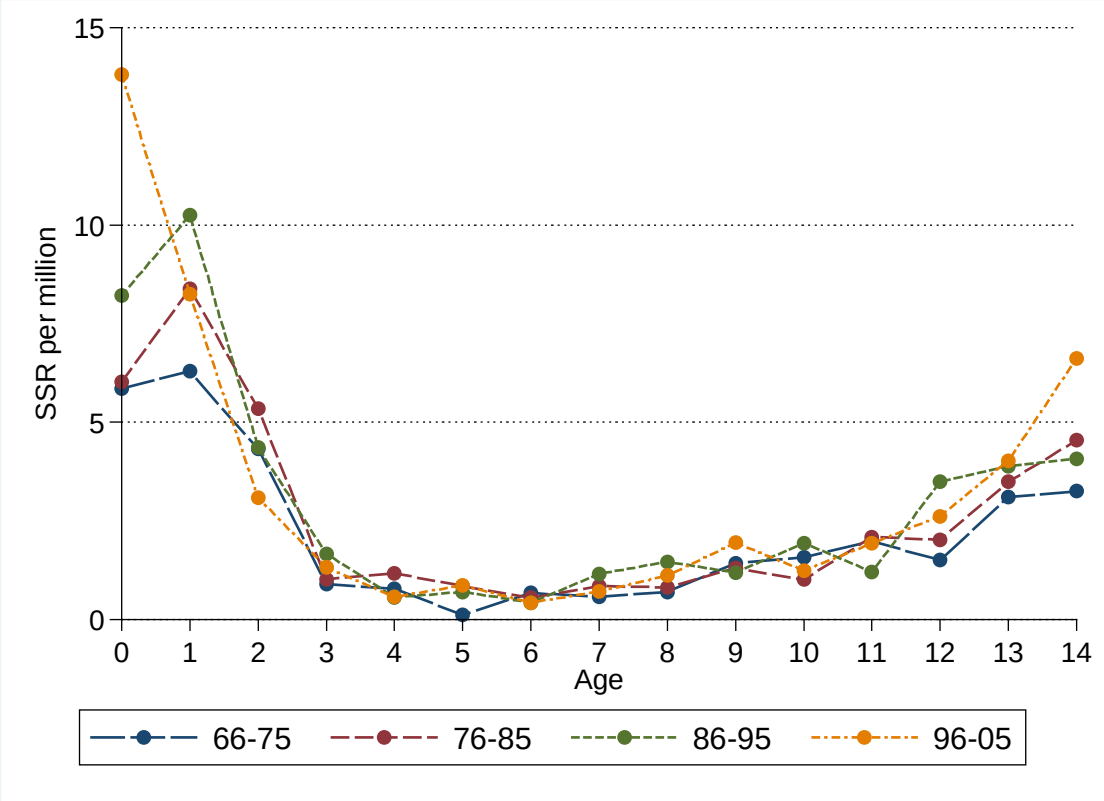
Age/sex	0		1-4		5-9		10-14		ASR	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	6.5	7.3	3.8	2.3	0.2	0.8	0.5	4.7	1.7	2.9
1971-75	7.6	1.6	3.3	2.7	0.3	1.5	0.8	3.1	1.8	2.4
1976-80	5.9	4.4	5.6	2.1	0.5	1.1	0.5	4.1	2.2	2.6
1981-85	9.5	4.1	5.2	2.9	0.4	1.6	1.4	4.7	2.6	3.1
1986-90	10.6	6.1	5.3	4.6	0.2	1.4	1.0	5.5	2.6	3.9
1991-95	9.5	6.7	3.8	3.3	0.2	2.0	1.5	3.7	2.2	3.2
1996-00	13.1	8.4	4.3	3.0	0.0	2.1	1.4	6.0	2.5	4.1
2001-05	12.4	21.6	2.8	2.9	0.1	1.9	1.1	4.6	2.0	4.4

b) Incidence rate per million by age group, sex and period of diagnosis.

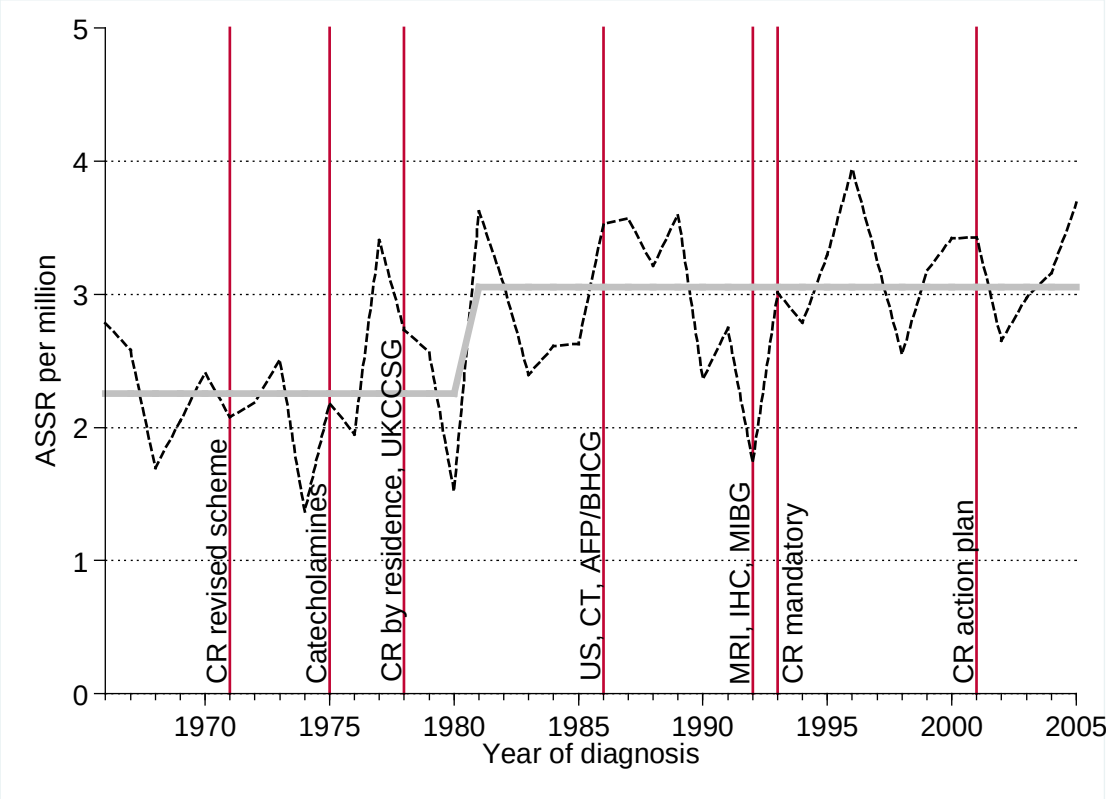
Age	0	1-4	5-9	10-14	ASSR
Diagnosed					
1966-70	6.9	3.1	0.5	2.6	2.3
1971-75	4.6	3.0	0.9	2.0	2.1
1976-80	5.1	3.9	0.8	2.3	2.4
1981-85	6.8	4.0	1.0	3.1	2.9
1986-90	8.3	5.0	0.8	3.3	3.2
1991-95	8.1	3.5	1.1	2.6	2.7
1996-00	10.7	3.6	1.0	3.7	3.3
2001-05	17.0	2.9	1.0	2.9	3.2
Trend	***	-	-	*	***
AAPC	2.93	0.23	1.15	1.00	1.12
CI	*1.81 to 4.07*	-0.57 to 1.04	-0.31 to 2.63	0.16 to 1.84	*0.63 to 1.60*
Fit	***	-	-	-	***

c) Sex-standardised incidence rate per million by age group and period of diagnosis.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.002.
- = not significant; * p<0.05, ** p<0.01, *** p<0.001.

Gonadal/germ-cell cancer NOS: by year of diagnosis 1966-2005, Britain
Figures 5.3.10.2 (a) and (b).

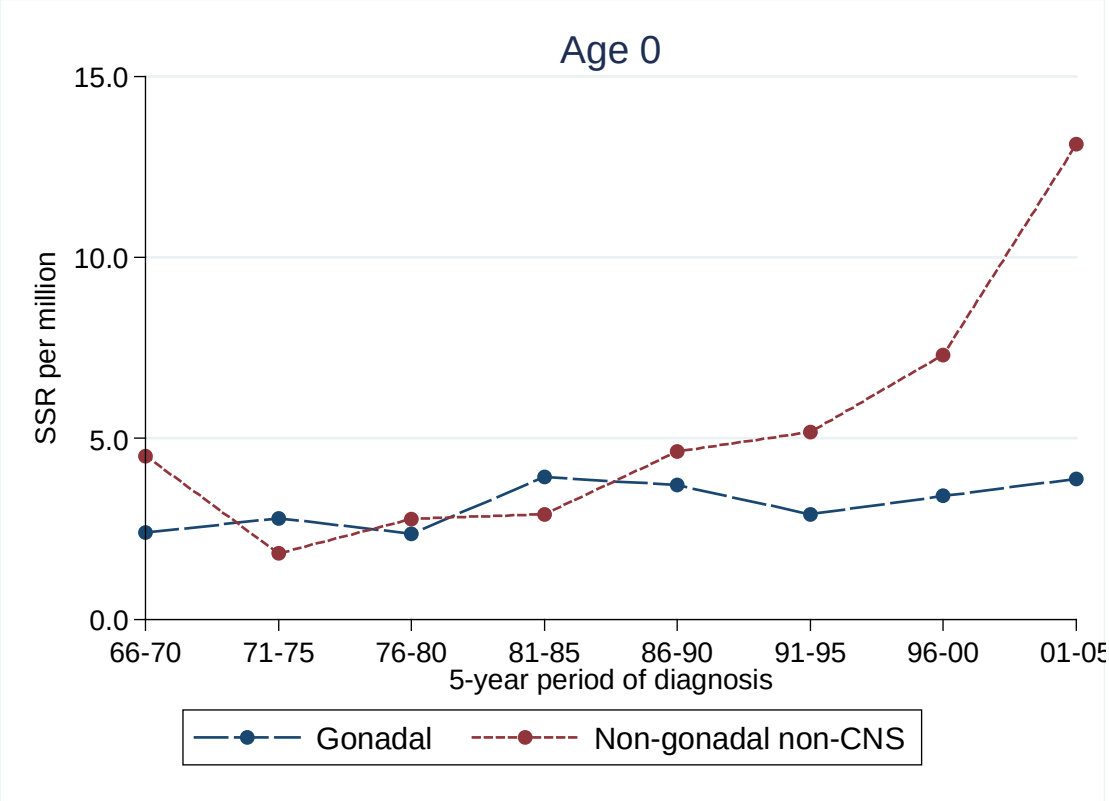


a) Standardised rate by single year of age at diagnosis, for successive diagnosis periods.

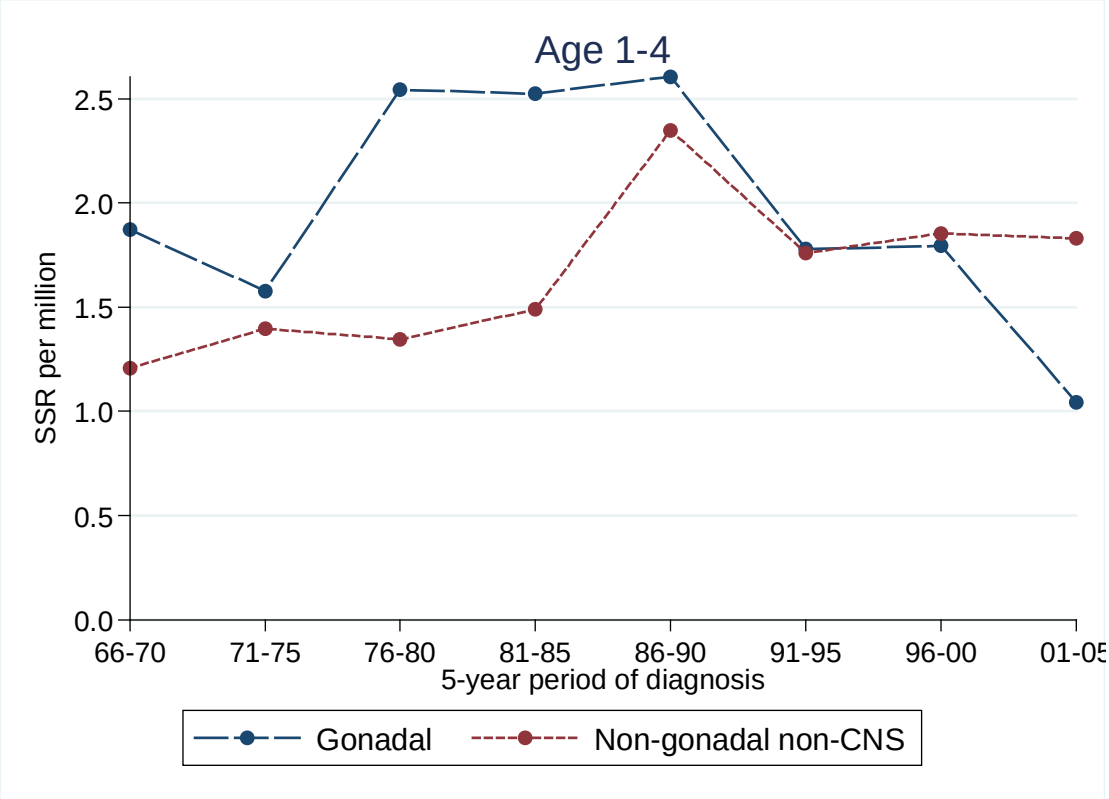


b) Standardised rate by year of diagnosis: actual (dotted), step model (solid) line.

Gonadal/germ-cell cancer NOS: by year of diagnosis 1966-2005, Britain
Figures 5.3.10.2 (c) and (d).

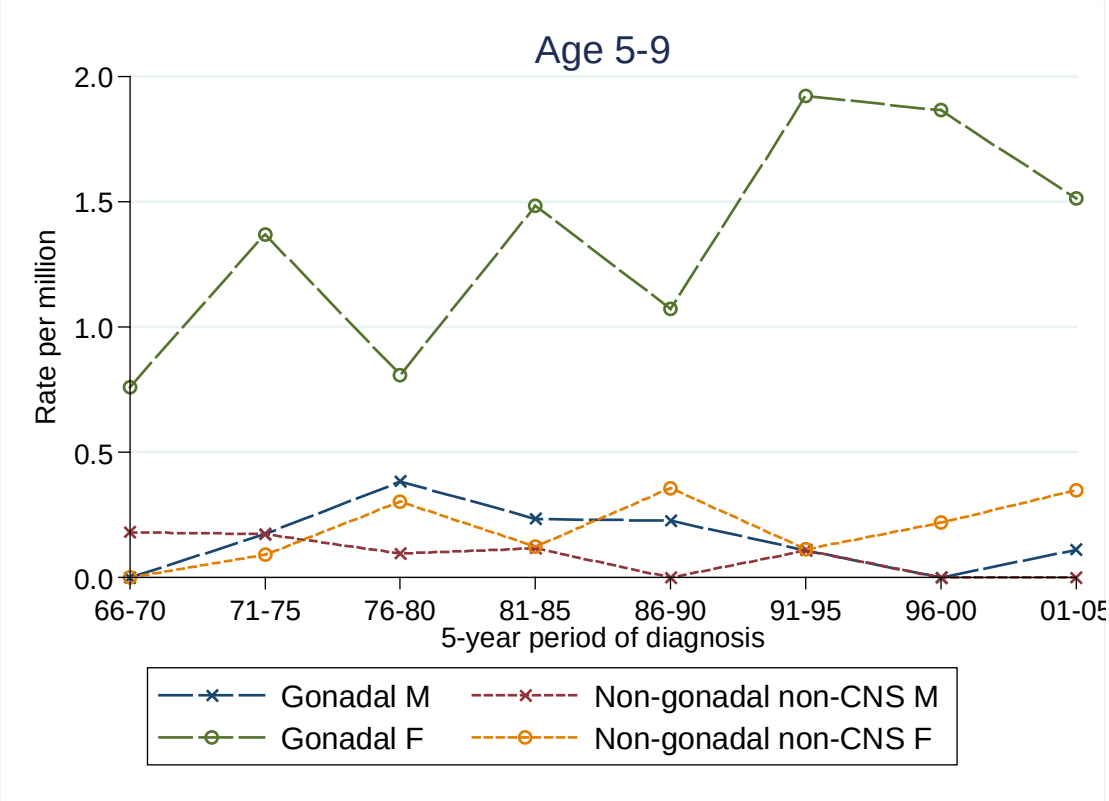


c) Standardised rate at age 0, by subtype and 5-year period of diagnosis.

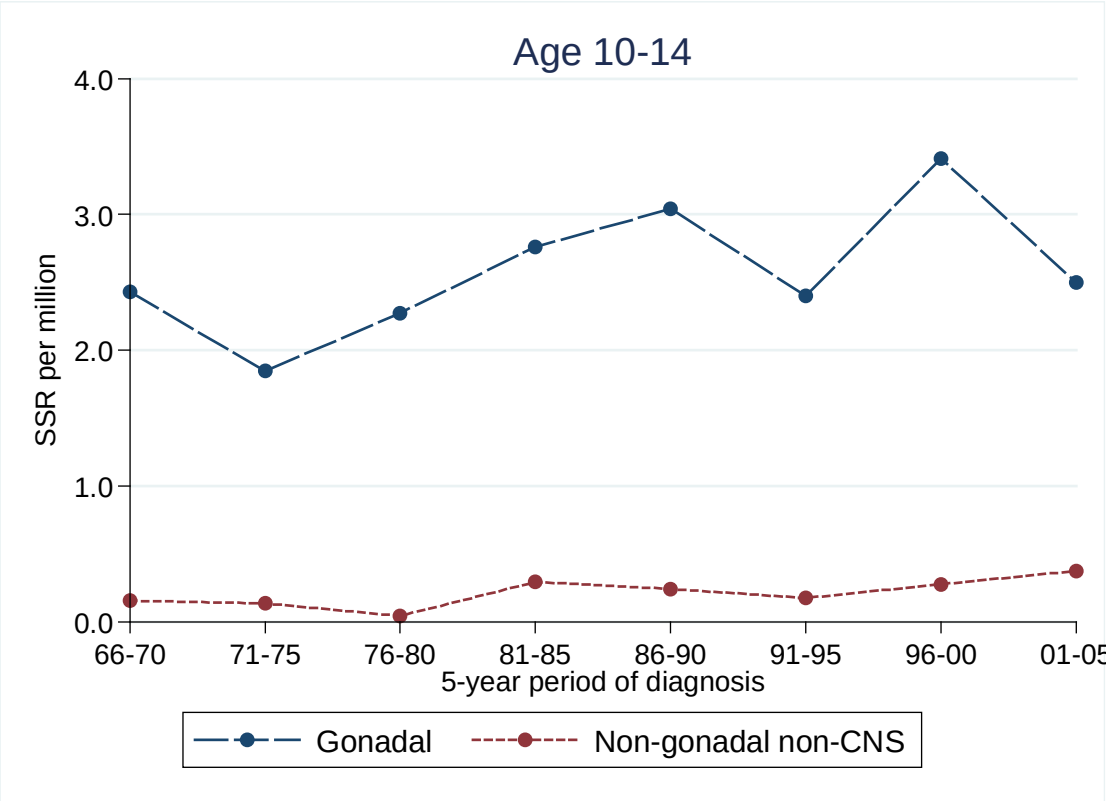


d) Standardised rate at age 1-4, by subtype and 5-year period of diagnosis.

Gonadal/germ-cell cancer NOS: by year of diagnosis 1966-2005, Britain
Figures 5.3.10.2 (e) and (f).



e) Rate at age 5-9, by subtype and sex, and 5-year period of diagnosis.



f) Standardised rate at age 10-14, by subtype and 5-year period of diagnosis.

5.3.11 Melanoma/carcinoma NOS

5.3.11.1 Year of birth

See Tables 5.3.11.1 (a) to (c), Figures 5.3.11.1 (a) and (b), and Figures 5.3.13.2 (c) to (f).

By year of birth, there was an overall increasing time trend of 1.5% (0.5 to 2.5) per year. In age groups 5-9 and 10-14, there were increasing time trends of 2.1% (0.04 to 4.3) and 2.0% (0.8 to 3.2) per year, respectively. In age group 0-4, there was a non-significant decrease of -2.2% (-5.0 to 0.6) (Table 5.3.11.1(c)). The time trends differed significantly between age groups (p=0.021).

The step model indicates increases at 1971-72 and 1981-82, with a trough at 1980-81.

5.3.11.2 Year of diagnosis

See Tables 5.3.11.2 (a) to (c), Figures 5.3.11.2 (a) and (b), and Figures 5.3.13.2 (c) to (f).

By year of diagnosis, there was an overall increasing time trend of 1.8% (1.3 to 2.3) per year. In age groups 5-9 and 10-14, there were increasing time trends of 2.0% (1.0 to 3.1) and 2.0% (1.4 to 2.6) per year, respectively. In age group 0, there was a non-significant decrease of -1.0% (-4.0 to 2.1) per year. In age group 1-4, there was a non-significant increase of 0.7% (-0.7 to 2.1) (Table 5.3.11.2(c)). The time trends did not differ significantly between age groups (p=0.104).

The step function suggests increases at 1975 and 1992.

Figures 5.3.11.2 (c) to (f) show increases in melanoma and thyroid carcinoma in all age groups, except age 0. Melanoma rates appeared to level out from the early or mid-1980s onwards, but thyroid cancer rates continued to increase up to the most recent five-year period. In the ‘carcinoma NOS’ group there was a steady increase in rates for the 10-14 age group from the early 1970s to the mid-1980s, followed by a plateau, and no apparent trend in the other age groups.

5.3.11.3 Discussion

By year of birth and by year of diagnosis there were increases of 1.5% and 1.8% per year on average, respectively.

It is possible that some of the apparent increase in melanoma and thyroid carcinoma might represent real increases in incidence, caused by increases in exposure to sunlight and radiation, respectively. There seems to have been relatively little change in the rate for the group consisting of 'carcinoma not otherwise specified', but the constituents of this group may well have varied over time.

The timing indicated by the step functions is not easy to explain. The increase at 1975 might be partly due to transfer from neuroblastoma (see Figures 5.3.13.2 (e) and (f)). Mandatory registration in 1993 is a possible explanation of the step at the diagnosis year 1992, since some of these cancers might be seen and treated by non-cancer specialists (dermatologists, endocrinologists, oral surgeons etc.).

Otherwise, the trends probably represent diagnosis at an earlier stage of disease: there was a greater increase at older ages, consistent with the fact that recorded incidence is higher in the 15-19 age group than in the 10-14 group [119].

Melanoma/carcinoma NOS: by 12-month birth cohort 1966-67 to 1989-90, Britain

Tables 5.3.11.1 (a) to (c).

Time trend analysis. 66-70 is the 48-month birth cohort from 1 July 1966 to 30 June 1970, etc.

Age	0		1-4		5-9		10-14		0-14	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	2	3	5	10	12	11	32	40	51	64
70-74	1	4	5	12	12	19	40	44	58	79
74-78	1	4	3	5	16	9	34	46	54	64
78-82	0	3	6	8	11	19	39	52	56	82
82-86	0	0	6	6	12	15	49	53	67	74
86-90	0	0	1	10	17	23	31	63	49	96
Total	4	14	26	51	80	96	225	298	335	459

a) Number of cases by age, sex and grouped birth cohort.

Age	0		1-4		5-9		10-14		ASR	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	1.1	1.7	0.7	1.5	1.3	1.3	3.6	4.7	1.9	2.5
70-74	0.6	2.6	0.8	2.0	1.5	2.5	5.1	5.9	2.4	3.5
74-78	0.8	3.2	0.6	1.0	2.4	1.5	5.2	7.3	2.7	3.4
78-82	0.0	2.2	1.1	1.5	1.5	2.8	5.5	7.6	2.6	4.0
82-86	0.0	0.0	1.0	1.1	1.7	2.2	6.7	7.6	3.1	3.6
86-90	0.0	0.0	0.2	1.7	2.2	3.2	4.0	8.6	2.1	4.4

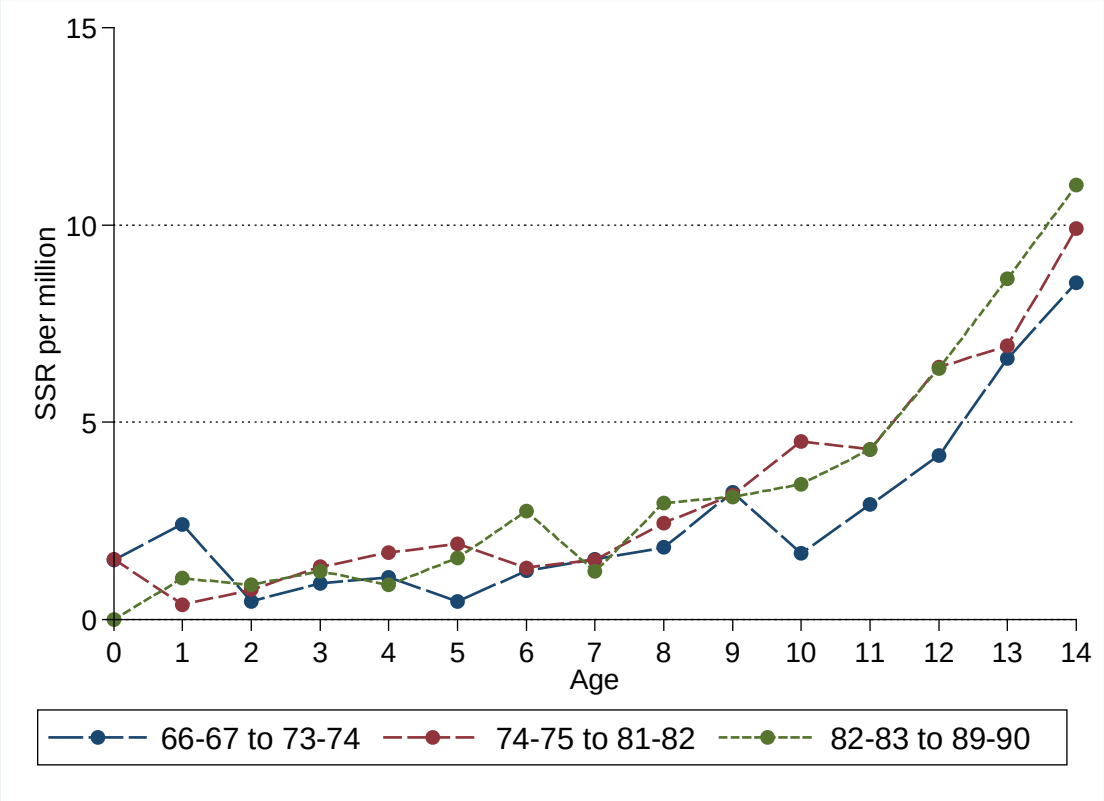
b) Incidence rate per million by age group, sex and grouped birth cohort.

Age	0	1-4	5-9	10-14	ASSR
Born					
66-70	1.4	1.1	1.3	4.2	2.2
70-74	1.6	1.4	2.0	5.5	3.0
74-78	2.0	0.8	1.9	6.3	3.1
78-82	1.1	1.3	2.2	6.6	3.3
82-86	0.0	1.1	1.9	7.2	3.3
86-90	0.0	0.9	2.7	6.3	3.3
Trend	-		*	**	**
AAPC	-2.21		2.14	2.01	1.52
CI	-4.95 to 0.62		0.04 to 4.27	0.79 to 3.24	0.54 to 2.51
Fit	-		-	-	-

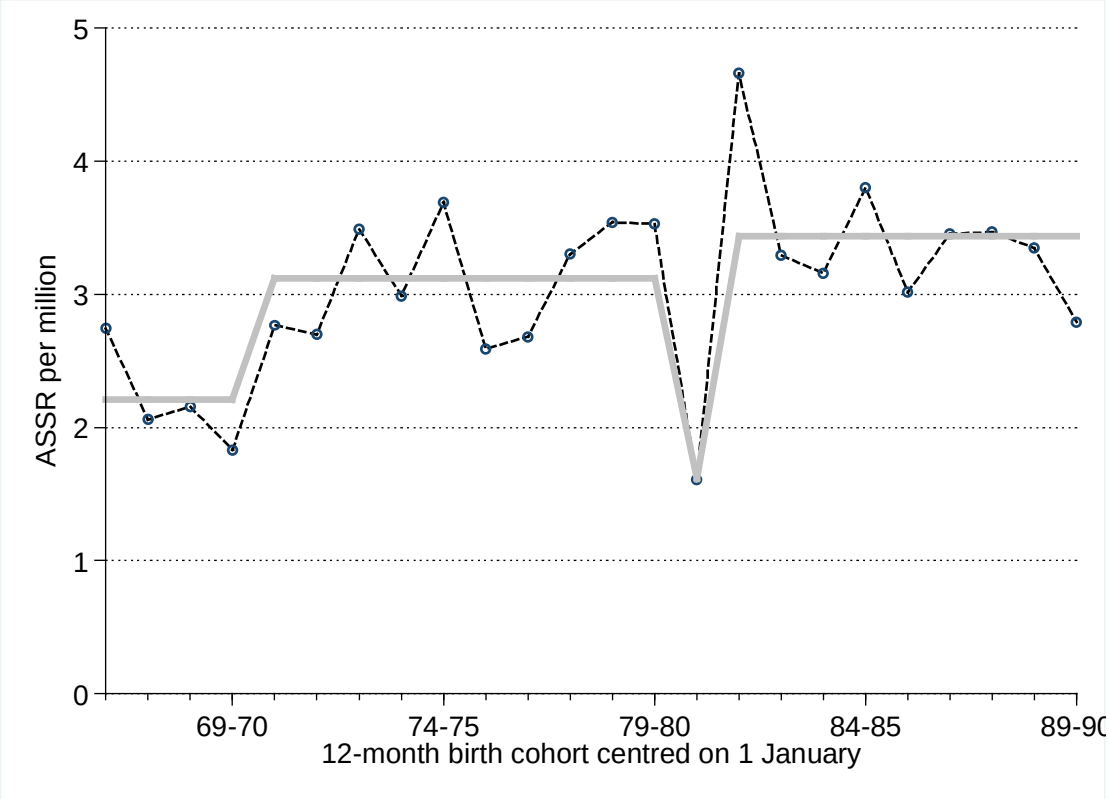
c) Sex-standardised incidence rate per million by age group and grouped birth cohort.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.021.

- = not significant; * p<0.05, ** p<0.01, *** p<0.001.

Melanoma/carcinoma NOS: by 12-month birth cohort 1966-67 to 1989-90, Britain
Figures 5.3.11.1 (a) and (b).



a) Standardised rate by single year of age at diagnosis, for successive birth periods.



b) Standardised rate by 12-month birth cohort: actual (dotted), step model (solid) line.

Melanoma/carcinoma NOS: by year of diagnosis 1966-2005, Britain
Tables 5.3.11.2 (a) to (c).

Time trend analysis.

Age/sex	0		1-4		5-9		10-14		0-14	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	2	3	13	14	16	10	29	46	60	73
1971-75	1	6	4	10	10	10	26	45	41	71
1976-80	1	4	3	11	13	23	44	53	61	91
1981-85	0	1	9	9	16	18	47	55	72	83
1986-90	0	0	5	7	16	15	45	63	66	85
1991-95	1	2	3	15	21	25	50	58	75	100
1996-00	2	4	11	10	13	25	57	61	83	100
2001-05	1	2	8	14	19	19	43	88	71	123
Total	8	22	56	90	124	145	341	469	529	726

a) Number of cases by age group, sex, and period of diagnosis.

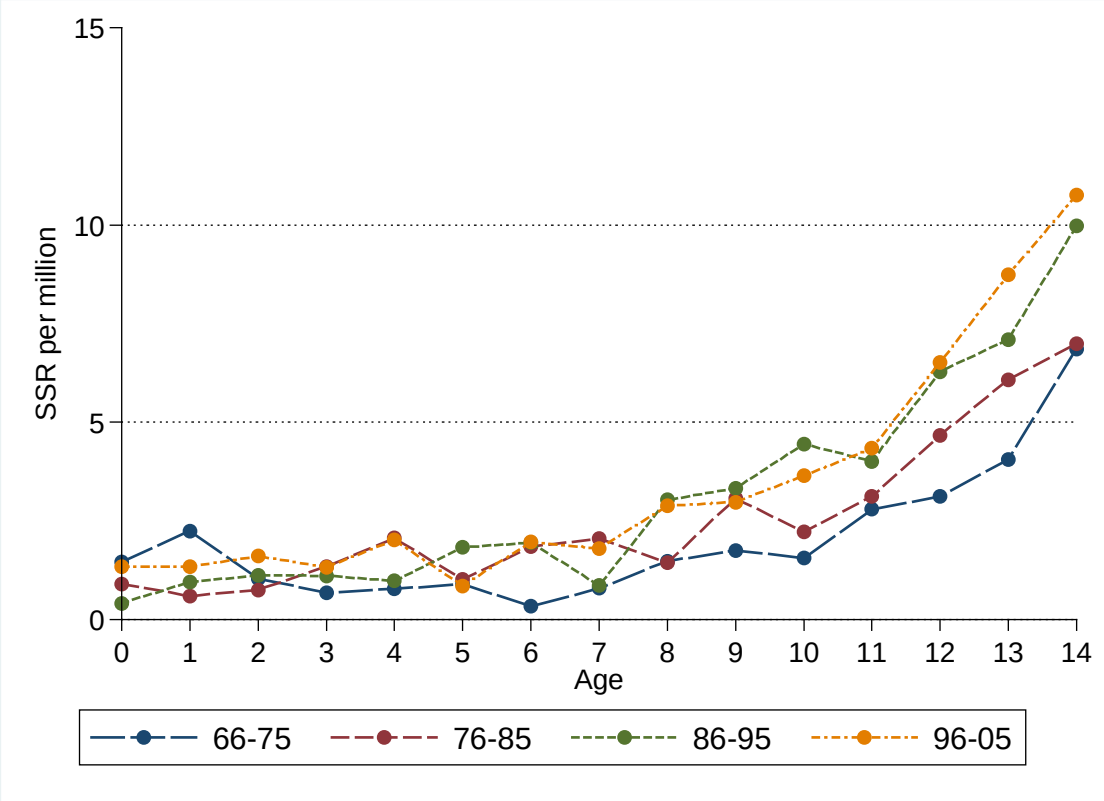
Age/sex	0		1-4		5-9		10-14		ASR	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	0.9	1.4	1.4	1.6	1.4	0.9	3.0	5.0	1.9	2.5
1971-75	0.5	3.2	0.5	1.2	0.9	0.9	2.4	4.3	1.2	2.3
1976-80	0.6	2.5	0.4	1.7	1.2	2.3	3.8	4.8	1.8	3.0
1981-85	0.0	0.6	1.3	1.4	1.9	2.2	4.5	5.6	2.5	3.0
1986-90	0.0	0.0	0.7	1.0	1.8	1.8	5.2	7.7	2.5	3.4
1991-95	0.5	1.1	0.4	2.1	2.3	2.8	5.7	6.9	2.8	3.9
1996-00	1.1	2.4	1.5	1.4	1.4	2.7	6.1	6.9	3.0	3.8
2001-05	0.6	1.2	1.2	2.2	2.1	2.2	4.5	9.6	2.5	4.6

b) Incidence rate per million by age group, sex and period of diagnosis.

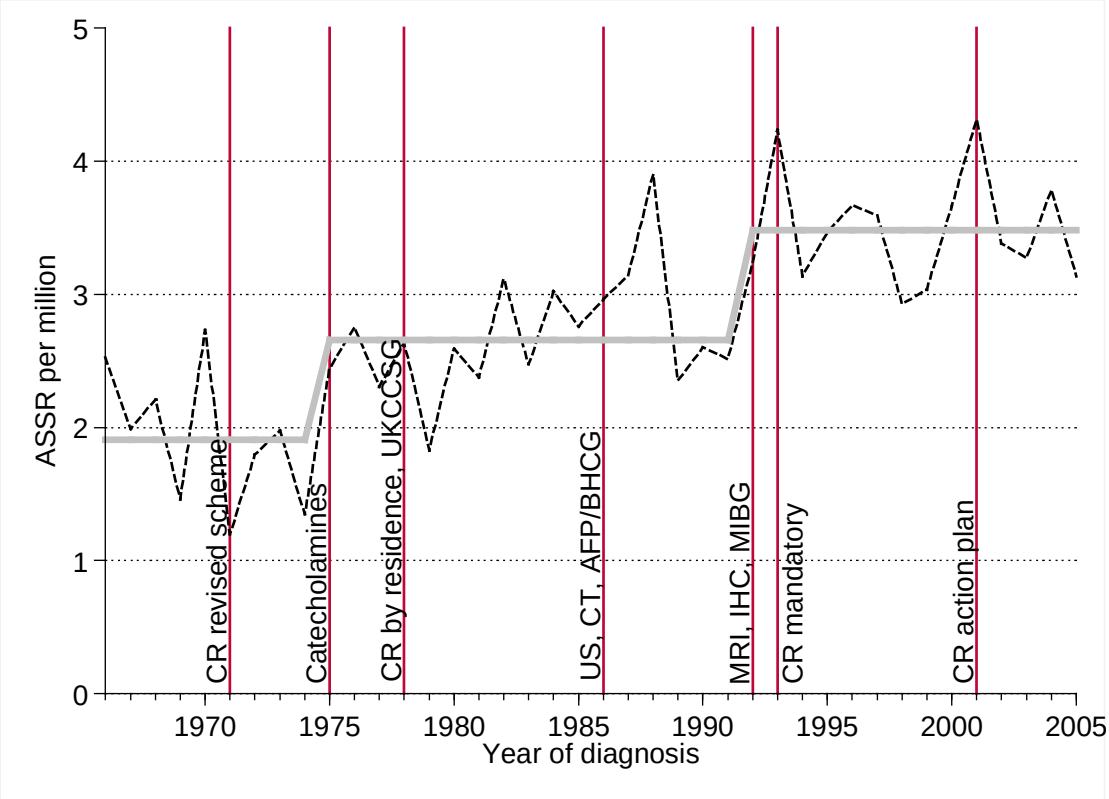
Age	0	1-4	5-9	10-14	ASSR
Diagnosed					
1966-70	1.1	1.5	1.2	4.0	2.2
1971-75	1.9	0.8	0.9	3.3	1.8
1976-80	1.5	1.1	1.8	4.3	2.4
1981-85	0.3	1.3	2.0	5.1	2.7
1986-90	0.0	0.8	1.8	6.5	3.0
1991-95	0.8	1.2	2.5	6.3	3.3
1996-00	1.8	1.5	2.1	6.5	3.4
2001-05	0.9	1.7	2.2	7.1	3.6
Trend	-	-	***	***	***
AAPC	-0.97	0.71	2.03	2.02	1.79
CI	-3.96 to 2.12	-0.67 to 2.10	0.99 to 3.08	1.41 to 2.64	1.31 to 2.28
Fit	-	-	-	-	-

c) Sex-standardised incidence rate per million by age group and period of diagnosis.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.104.
- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Melanoma/carcinoma NOS: by year of diagnosis 1966-2005, Britain
Figures 5.3.11.2 (a) and (b).

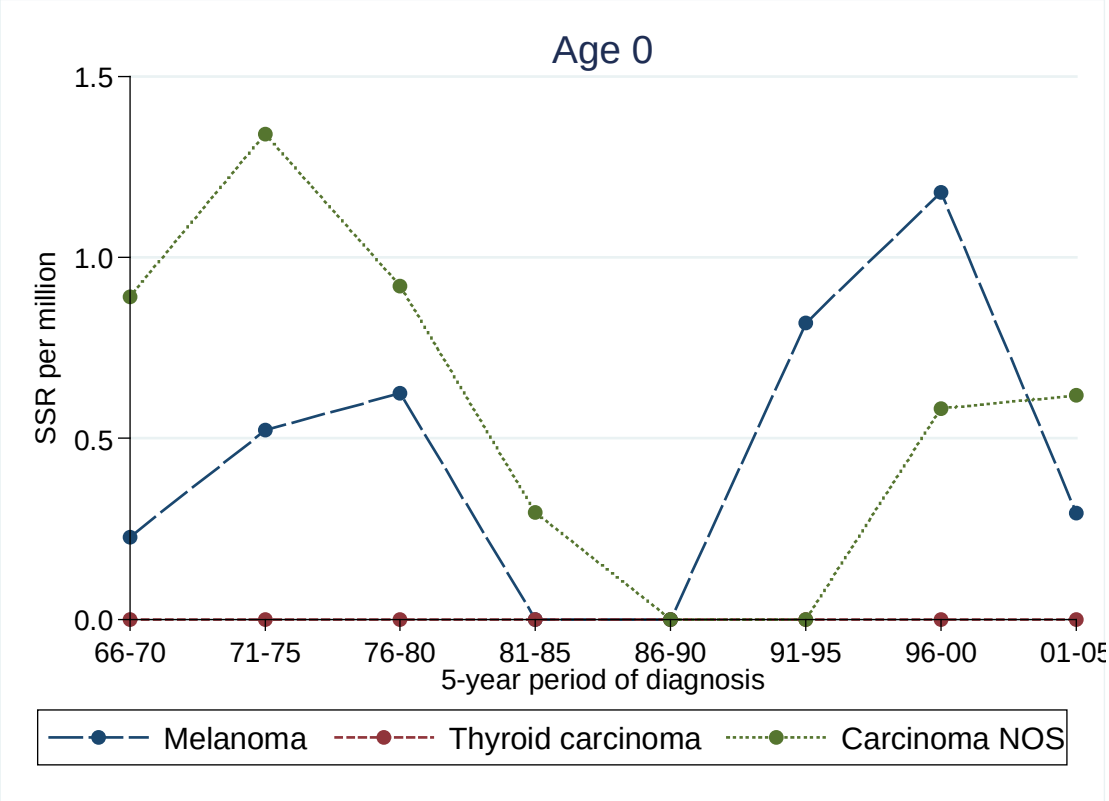


a) Standardised rate by single year of age at diagnosis, for successive diagnosis periods.

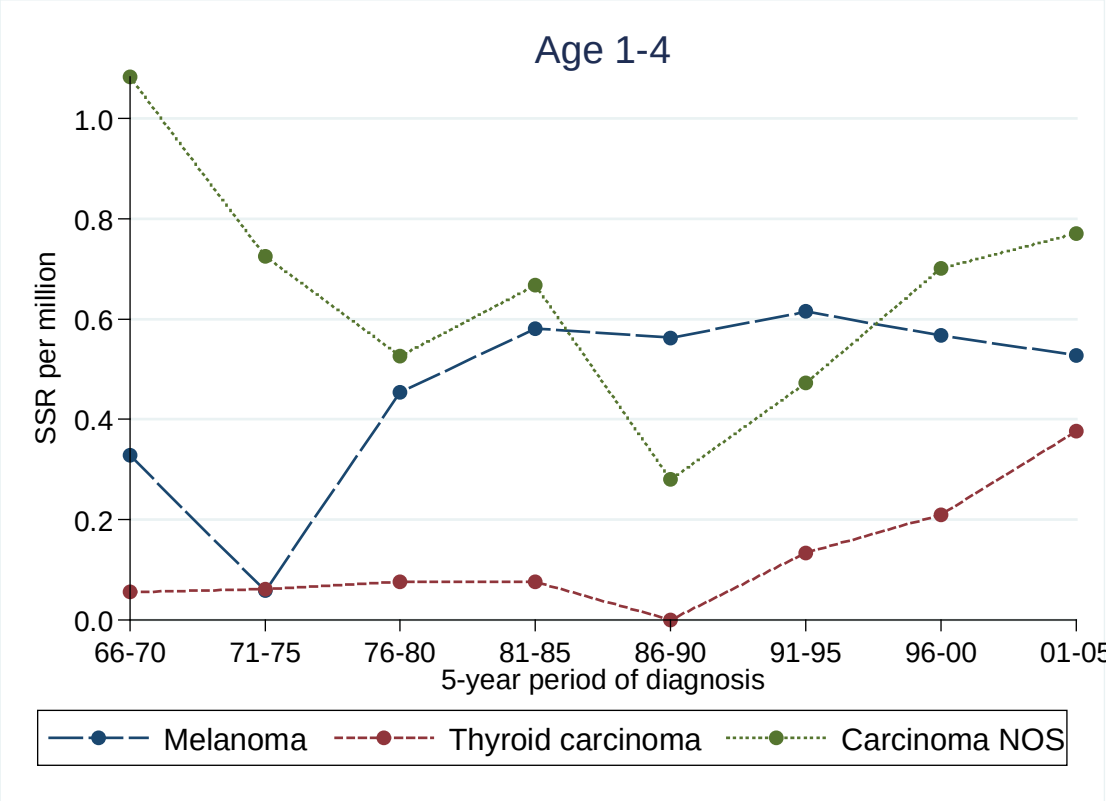


b) Standardised rate by year of diagnosis: actual (dotted), step model (solid) line.

Melanoma/carcinoma NOS: by year of diagnosis 1966-2005, Britain
Figures 5.3.11.2 (c) and (d).

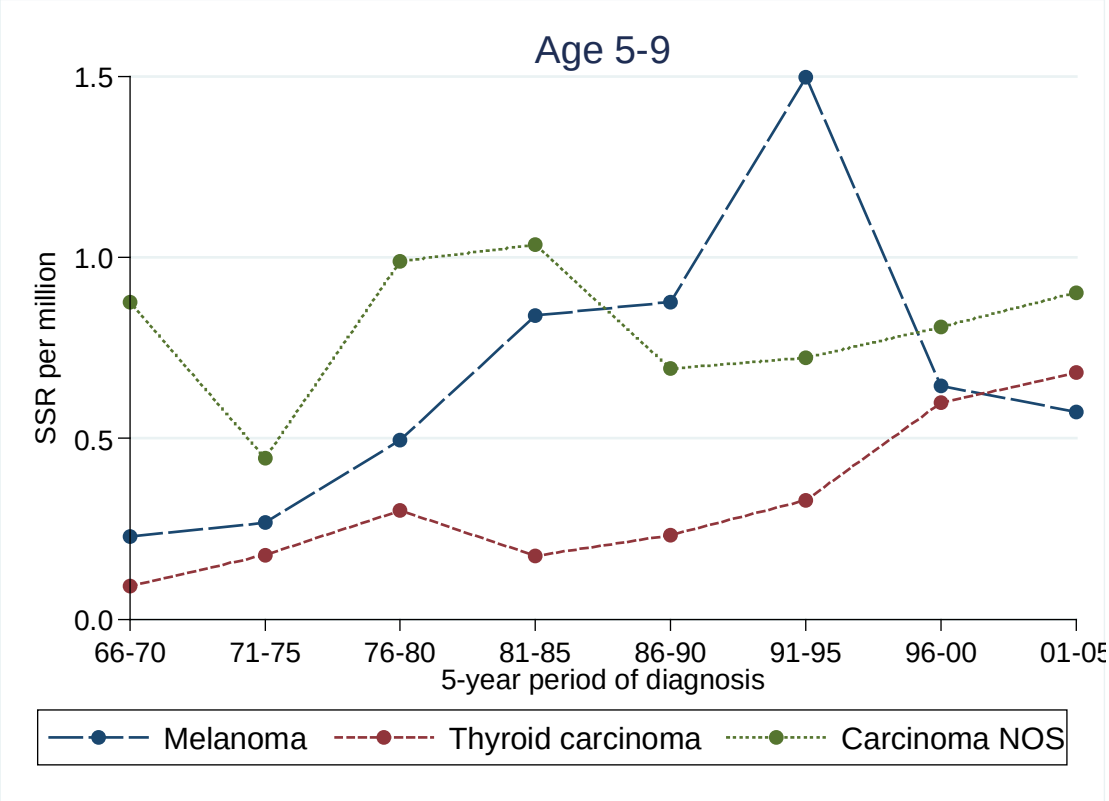


c) Standardised rate at age 0, by subtype and 5-year period of diagnosis.

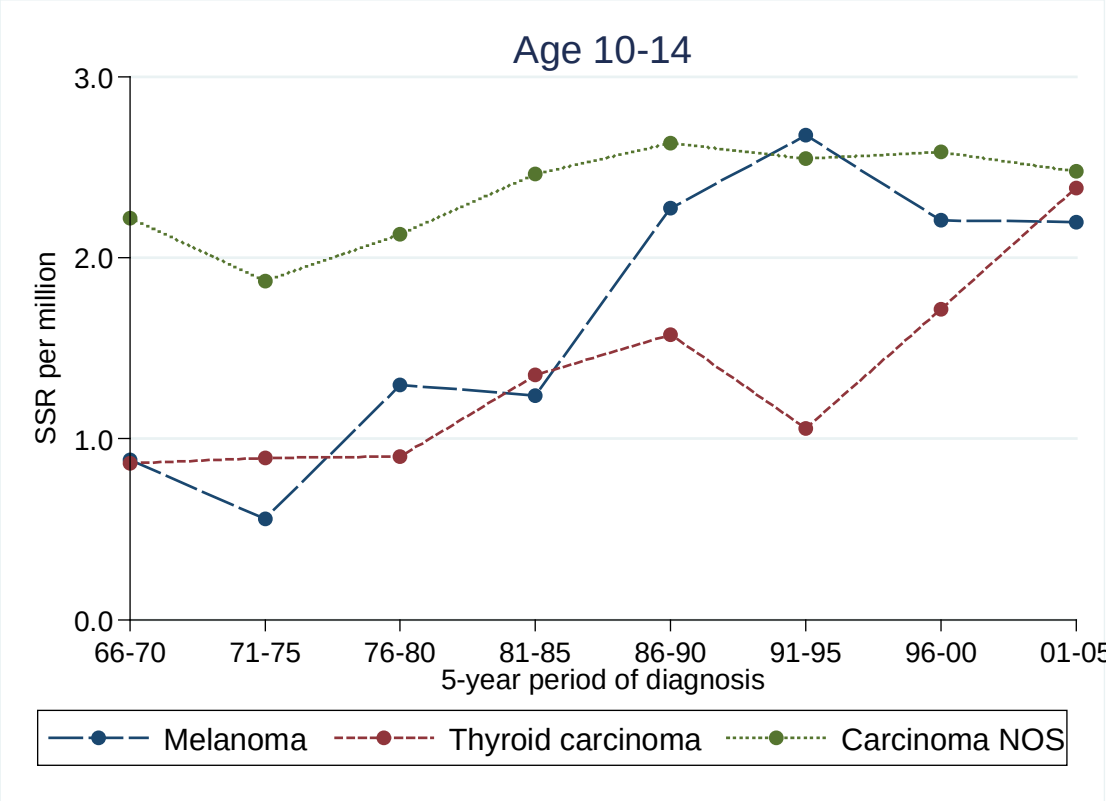


d) Standardised rate at age 1-4, by subtype and 5-year period of diagnosis.

Melanoma/carcinoma NOS: by year of diagnosis 1966-2005, Britain
Figures 5.3.11.2 (e) and (f).



e) Standardised rate at age 5-9, by subtype and 5-year period of diagnosis.



f) Standardised rate at age 10-14, by subtype and 5-year period of diagnosis.

5.3.12 Other/unspecified cancer

5.3.12.1 Year of birth

See Tables 5.3.12.1 (a) to (c), and Figures 5.3.12.1 (a) and (b).

The step model indicates an increase at 1985-86.

5.3.12.2 Year of diagnosis

See Tables 5.3.12.2 (a) to (c), Figures 5.3.12.2 (a) and (b).

The step model is confused, but the rates seem to be higher after 1990.

5.3.12.3 Discussion

This very small group is included for completeness. It consists mainly of unspecified malignant tumours (260 of 297), and the changes over time reflect changes in this subgroup. The apparently higher rates in recent years might possibly be an effect of mandatory registration from 1993 and the Action Plan from 2001, if these initiatives made poorly-documented cancers more likely to be registered.

Other/unspecified cancer: by 12-month birth cohort 1966-67 to 1989-90, Britain
Tables 5.3.12.1 (a) to (c).

Time trend analysis. 66-70 is the 48-month birth cohort from 1 July 1966 to 30 June 1970, etc.

Age	0		1-4		5-9		10-14		0-14	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	3	5	5	3	3	2	5	4	16	14
70-74	1	0	2	1	2	3	4	6	9	10
74-78	1	1	1	1	3	2	3	3	8	7
78-82	0	0	6	0	5	2	5	8	16	10
82-86	2	0	1	1	7	3	3	9	13	13
86-90	4	1	4	12	6	3	6	5	20	21
Total	11	7	19	18	26	15	26	35	82	75

a) Number of cases by age, sex and grouped birth cohort.

Age	0		1-4		5-9		10-14		ASR	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	1.6	2.9	0.7	0.4	0.3	0.2	0.6	0.5	0.6	0.5
70-74	0.6	0.0	0.3	0.2	0.3	0.4	0.5	0.8	0.4	0.4
74-78	0.8	0.8	0.2	0.2	0.5	0.3	0.5	0.5	0.4	0.4
78-82	0.0	0.0	1.1	0.0	0.7	0.3	0.7	1.2	0.8	0.5
82-86	1.4	0.0	0.2	0.2	1.0	0.4	0.4	1.3	0.6	0.6
86-90	2.6	0.7	0.7	2.1	0.8	0.4	0.8	0.7	0.9	1.0

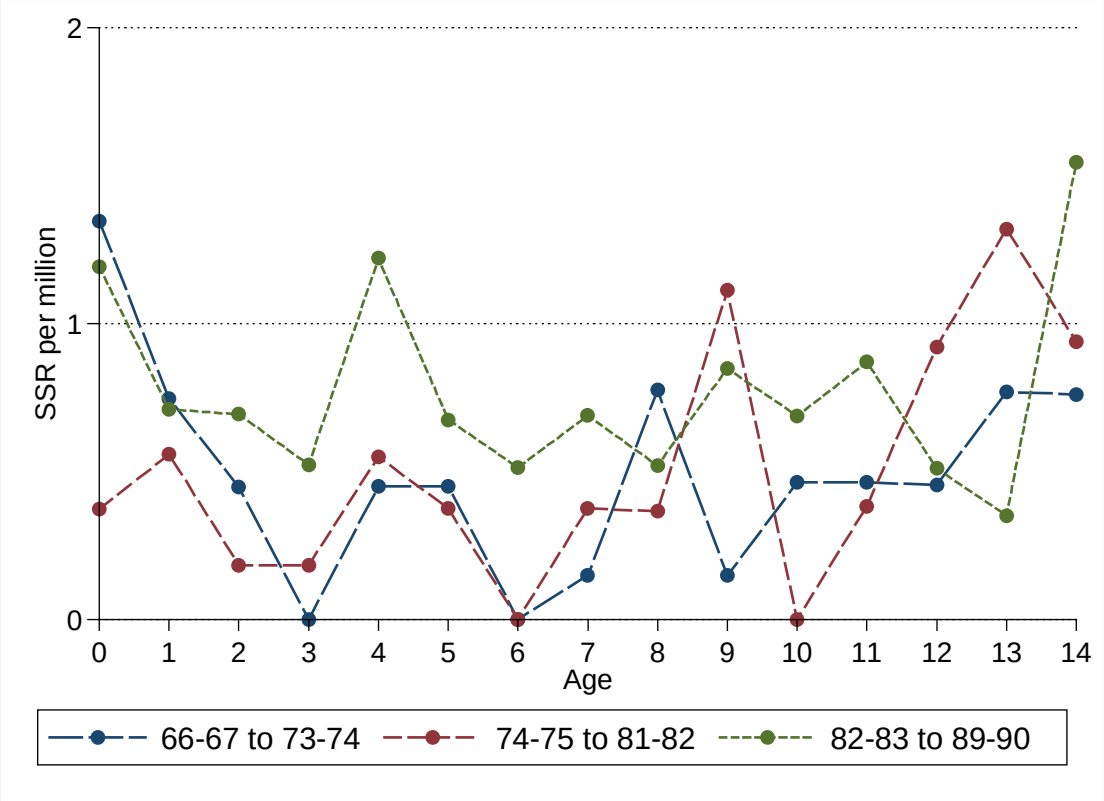
b) Incidence rate per million by age group, sex and grouped birth cohort.

Age	0	1-4	5-9	10-14	ASSR
Born					
66-70	2.3	0.6	0.3	0.5	0.6
70-74	0.3	0.2	0.3	0.7	0.4
74-78	0.8	0.2	0.4	0.5	0.4
78-82	0.0	0.5	0.5	0.9	0.6
82-86	0.7	0.2	0.7	0.9	0.6
86-90	1.7	1.4	0.6	0.7	0.9
Trend	-		-	-	*
AAPC	2.40		4.31	2.38	2.88
CI	*-1.33 to 6.26*		-0.14 to 8.97	-1.16 to 6.06	0.64 to 5.17
Fit	**		-	-	-

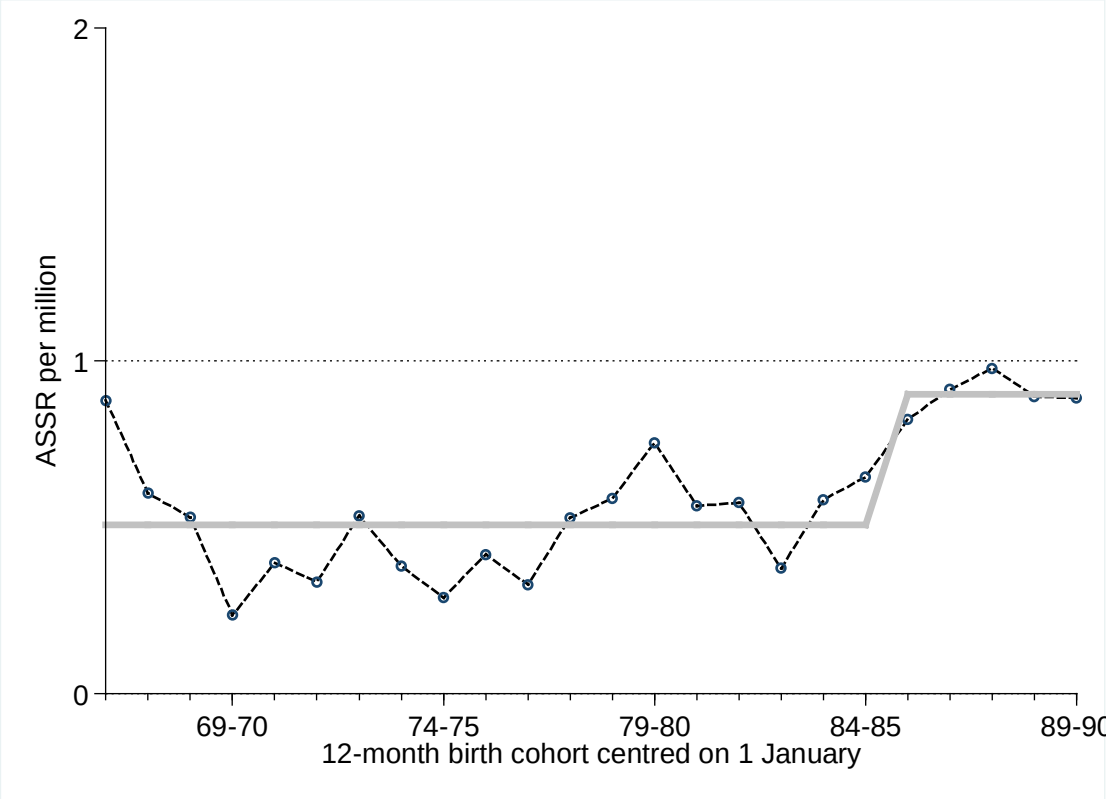
c) Sex-standardised incidence rate per million by age group and grouped birth cohort.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.769.

- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Other/unspecified cancer: by 12-month birth cohort 1966-67 to 1989-90, Britain
Figures 5.3.12.1 (a) and (b).



a) Standardised rate by single year of age at diagnosis, for successive birth periods.



b) Standardised rate by 12-month birth cohort: actual (dotted), step model (solid) line.

Other/unspecified cancer: by year of diagnosis 1966-2005, Britain
Tables 5.3.12.2 (a) to (c).

Time trend analysis.

Age/sex	0		1-4		5-9		10-14		0-14	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	6	5	9	8	6	4	10	6	31	23
1971-75	1	0	4	0	5	1	4	4	14	5
1976-80	0	1	1	2	2	4	3	3	6	10
1981-85	2	0	4	0	5	3	4	7	15	10
1986-90	4	1	4	4	5	2	4	6	17	13
1991-95	4	5	4	17	10	5	7	11	25	38
1996-00	3	3	6	5	2	3	7	7	18	18
2001-05	1	0	8	7	5	5	13	15	27	27
Total	21	15	40	43	40	27	52	59	153	144

a) Number of cases by age group, sex, and period of diagnosis.

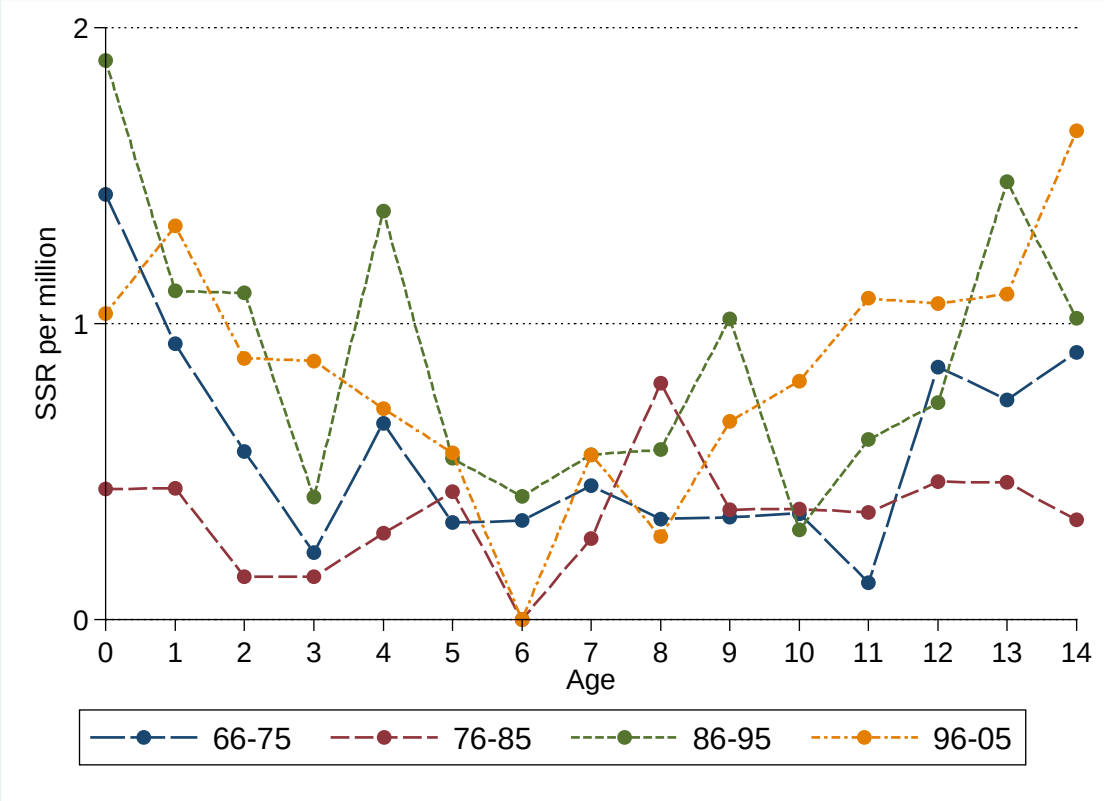
Age/sex	0		1-4		5-9		10-14		ASR	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	2.6	2.3	1.0	0.9	0.5	0.4	1.0	0.7	0.9	0.7
1971-75	0.5	0.0	0.5	0.0	0.4	0.1	0.4	0.4	0.4	0.2
1976-80	0.0	0.6	0.1	0.3	0.2	0.4	0.3	0.3	0.2	0.3
1981-85	1.1	0.0	0.6	0.0	0.6	0.4	0.4	0.7	0.6	0.4
1986-90	2.1	0.6	0.5	0.6	0.6	0.2	0.5	0.7	0.6	0.5
1991-95	2.1	2.8	0.5	2.3	1.1	0.6	0.8	1.3	0.9	1.4
1996-00	1.7	1.8	0.8	0.7	0.2	0.3	0.8	0.8	0.7	0.7
2001-05	0.6	0.0	1.2	1.1	0.6	0.6	1.4	1.6	1.0	1.0

b) Incidence rate per million by age group, sex and period of diagnosis.

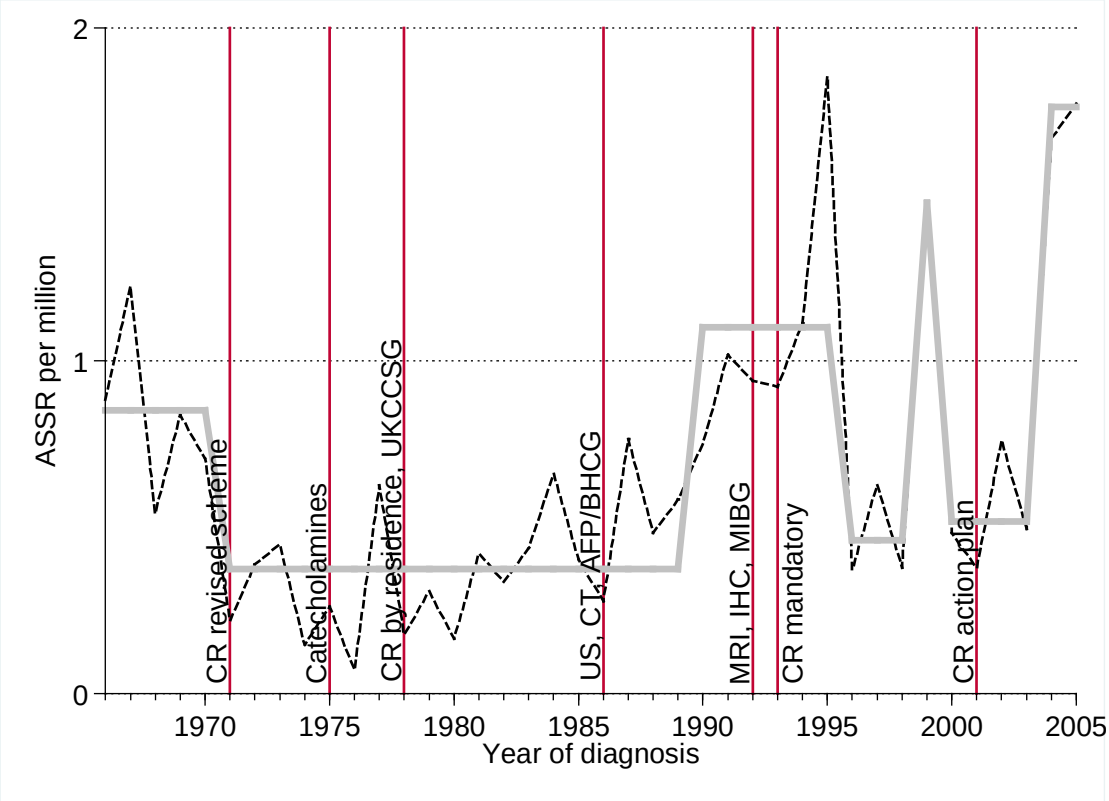
Age	0	1-4	5-9	10-14	ASSR
Diagnosed					
1966-70	2.4	0.9	0.5	0.8	0.8
1971-75	0.3	0.2	0.3	0.4	0.3
1976-80	0.3	0.2	0.3	0.3	0.3
1981-85	0.6	0.3	0.5	0.5	0.5
1986-90	1.3	0.6	0.4	0.6	0.6
1991-95	2.4	1.4	0.8	1.0	1.2
1996-00	1.7	0.8	0.3	0.8	0.7
2001-05	0.3	1.1	0.6	1.5	1.0
Trend	-	*	-	***	***
AAPC	0.03	2.36	1.44	3.31	2.20
CI	-2.71 to 2.86	*0.48 to 4.28*	*-0.61 to 3.54*	*1.62 to 5.03*	*1.20 to 3.21*
Fit	-	*	*	**	***

c) Sex-standardised incidence rate per million by age group and period of diagnosis.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.213.
- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Other/unspecified cancer: by year of diagnosis 1966-2005, Britain
Figures 5.3.12.2 (a) and (b).



a) Standardised rate by single year of age at diagnosis, for successive diagnosis periods.



b) Standardised rate by year of diagnosis: actual (dotted), step model (solid) line.

5.3.13 Non-CNS solid cancer

This is a sub-total category consisting of all diagnostic groups except leukaemia and CNS tumours. It is included firstly as a comparison group for leukaemia and CNS tumours, and secondly to assess the possibilities of diagnostic transfer between groups. Diagnostic transfer between this category, leukaemia and CNS tumours is unlikely (except perhaps between leukaemia and lymphoma in the early decades of the study period).

5.3.13.1 Year of birth

See Tables 5.3.13.1 (a) to (c), and Figures 5.3.13.1 (a) and (b).

By year of birth, there was an overall time trend of 1.0% (0.8 to 1.3) per year. In age groups 0, 1-4 and 5-9 there were increasing time trends of 1.0% (0.3 to 1.7), 1.1% (0.6 to 1.5) and 0.8% (0.3 to 1.3) per year, respectively. In age group 10-14 there was an increase of 1.3% per year on average, but the Poisson model did not fit (Table 5.3.13.1(c)).

The step model indicates a small increase at 1972-73 followed by a small decrease at 1975-76, and then further increases at 1977-78 and 1983-84 (Figure 5.3.13.1(b)).

5.3.13.2 Year of diagnosis

See Tables 5.3.13.2 (a) to (c), and Figures 5.3.13.2 (a) to (f).

By year of diagnosis, there was an overall increase of 1.0% per year, and the Poisson model did not fit ($p<0.05$). In age groups 0, 5-9 and 10-14, there were increasing time trends of 1.3% (0.9 to 1.6), 0.9% (0.6 to 1.1) and 1.2% (1.0 to 1.4) per year, respectively. In age group 1-4, there was an increase of 0.7% per year, on average, and the Poisson model did not fit ($p<0.05$) (Table 5.3.13.2(c)).

The step model suggests increases at 1971, 1984, 1987 and 2001 (Figure 5.3.13.2(b)).

5.3.13.3 Geographical analysis

See Tables 5.3.13.3 and Figures 5.3.13.3 (a) and (b). There was evidence for lack of fit of the Poisson model in the decade 1995-2005 ($p<0.05$).

In all regions, the SES-adjusted rate was higher in 1996-2005 than in 1976-85. (Figure 5.3.13.3(a)).

In 1976-85 there was statistically significant heterogeneity by region ($p<0.001$). The lowest SES-adjusted rates were in the North East and North West regions, with IRRs of 0.80 (0.69 to 0.93) and 0.80 (0.72 to 0.89) respectively, relative to the South East region. The highest rates were in the South East, and in Wales, with an IRR of 1.00 (0.88 to 1.15). In the other two census decades the rates did not differ significantly between regions. (Table and Figure 5.3.13.3(a)).

In all five SES categories, the region-adjusted rate was higher in 1996-2005 than in 1976-85. (Figure 5.3.13.3(b)).

Within each of the three census decades, after adjusting for regional differences, there was no statistically significant heterogeneity by SES category, or trend with SES. The IRR for each unit increase in SES score was 1.00 (0.98 to 1.02) in 1976-85, 0.99 (0.97 to 1.01) in 1986-95, and 1.01 (0.99 to 1.03) in 1996-2005. (Table 5.3.13.3 and Figure 5.3.13.3(b)).

5.3.13.4 Discussion

Both by year of birth and by year of diagnosis there were increases of 1.0% per year on average.

The time trends by year of diagnosis are consistent with a general effect of diagnosis at an earlier stage of disease. The largest increases were in age groups 0 and 10-14.

The step model suggests that increases in rates coincided with the revised scheme for cancer registration in 1971, the introduction of US, CT and AFP/BCHG around 1986, and the Action Plan that provided additional funding for cancer registration for three years from 2001. In this combined group the step model does not indicate any increase associated with the introduction of MRI, IHC and MIBG around 1992, or with mandatory cancer registration from 1993. This is reasonable, since MRI is used mainly for CNS tumours, while IHC and MIBG are used to refine the diagnosis after the cancer has been detected. The diagnostic groups that appeared to increase in 1992-93 (retinoblastoma, melanoma/carcinoma and other/unspecified cancer) are relatively rare and would have little effect on the overall rate for the combined group.

To investigate possible diagnostic transfer within this sub-total category, Figures 5.3.13.2 (c) to (f) compare the rates of most of its main components. Very small groups (hepatic cancer and other/unspecified cancer), and site-specific groups (renal cancer and retinoblastoma) are not shown. At age 0, the decrease in lymphoma from 1966-70 to 1981-85 closely matches the corresponding increase in neuroblastoma. In all age groups, there seem to be signs of exchange between PNS cancer, bone cancer, soft-tissue sarcoma, and gonadal/germ-cell cancer, particularly from 1966-70 to 1976-80, and from 1991-95 to 2001-05. This is consistent with the availability of specific tests for neuroblastoma and germ-cell cancer from the mid-1970s and early 1980s, and the introduction of immunohistochemistry from about 1992.

The strong heterogeneity by region during 1976-85 suggests that the relatively low rates for this period may be due to under-registration in some regions. The lack of statistically significant regional variation in the following decades suggests that the differences between the regions may have been reduced when the overall rate increased. There is no evidence for an effect of SES in any of the three decades.

The step model indicates an increase of about 10% in 2001. This is unlikely to be due to chance, and cannot be due to diagnostic transfer. Step-model discontinuities at 2001 or 2002 appear in renal, hepatic and bone cancer, and in lymphoma. The only known relevant event in the history of diagnosis and registration methods is the additional funding for cancer registration that was available from 2001.

Non-CNS solid cancer: by 12-month birth cohort 1966-67 to 1989-90, Britain
Tables 5.2.13.1 (a) to (c).

Time trend analysis. 66-70 is the 48-month birth cohort from 1 July 1966 to 30 June 1970, etc.

Age	0		1-4		5-9		10-14		0-14	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	155	146	475	362	348	208	412	313	1390	1029
70-74	143	125	442	323	323	209	406	334	1314	991
74-78	127	109	332	270	235	146	355	293	1049	818
78-82	137	117	382	337	311	198	391	323	1221	975
82-86	163	113	395	337	290	198	415	348	1263	996
86-90	158	142	486	400	316	241	424	410	1384	1193
Total	883	752	2512	2029	1823	1200	2403	2021	7621	6002

a) Number of cases by age, sex and grouped birth cohort.

Age	0		1-4		5-9		10-14		ASR	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	85.2	83.9	65.8	52.5	38.9	24.5	46.3	37.0	51.6	40.1
70-74	88.2	81.5	69.0	53.2	40.7	27.9	51.5	44.6	55.0	43.8
74-78	95.8	86.8	63.1	54.1	35.9	23.5	53.9	46.8	53.2	43.7
78-82	96.1	86.5	67.4	62.6	43.7	29.2	55.1	47.4	57.3	48.0
82-86	113.3	82.5	68.6	61.4	40.1	28.6	57.1	50.1	58.2	48.1
86-90	104.1	97.8	80.1	68.9	41.5	33.1	55.3	56.2	60.6	54.6

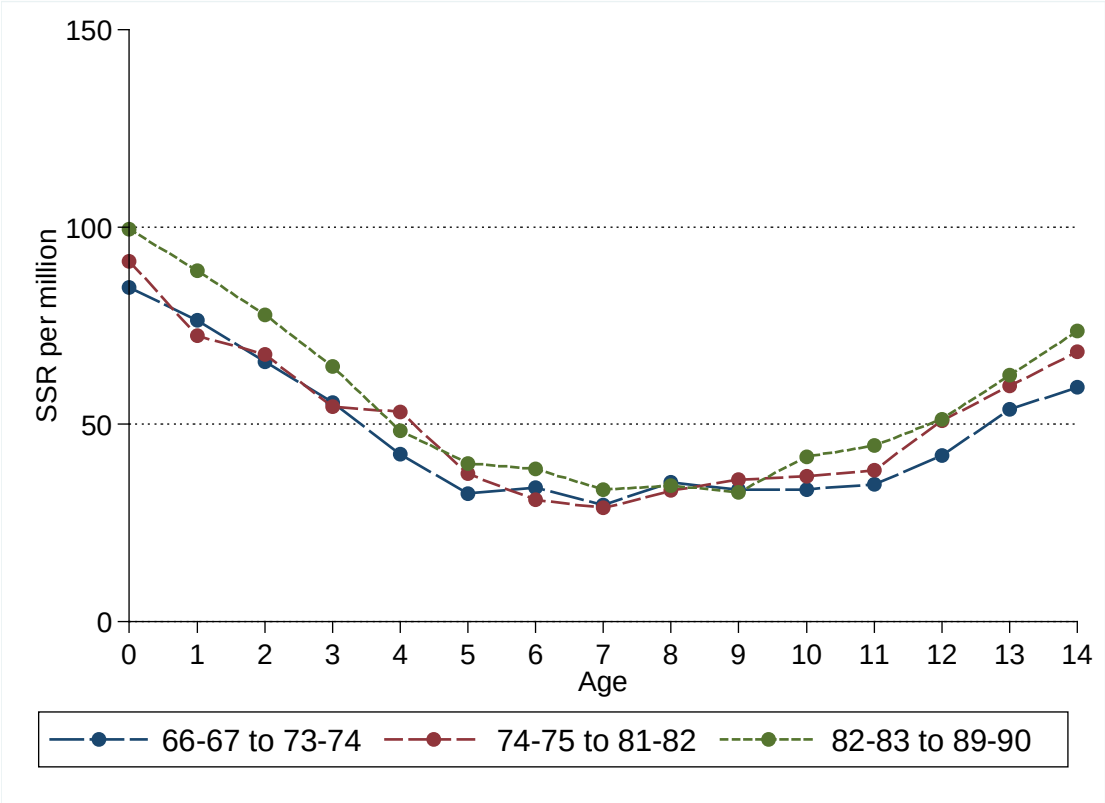
b) Incidence rate per million by age group, sex and grouped birth cohort.

Age	0	1-4	5-9	10-14	ASSR
Born					
66-70	84.6	59.2	31.7	41.6	45.9
70-74	84.9	61.1	34.3	48.0	49.4
74-78	91.3	58.6	29.7	50.3	48.4
78-82	91.3	65.0	36.4	51.2	52.6
82-86	97.9	65.0	34.4	53.6	53.2
86-90	100.9	74.5	37.3	55.8	57.6
Trend	**	***	**	***	***
AAPC	0.98	1.05	0.75	1.26	1.04
CI	0.30 to 1.67	0.64 to 1.46	0.25 to 1.25	*0.84 to 1.68*	0.81 to 1.28
Fit	-	-	-	*	-

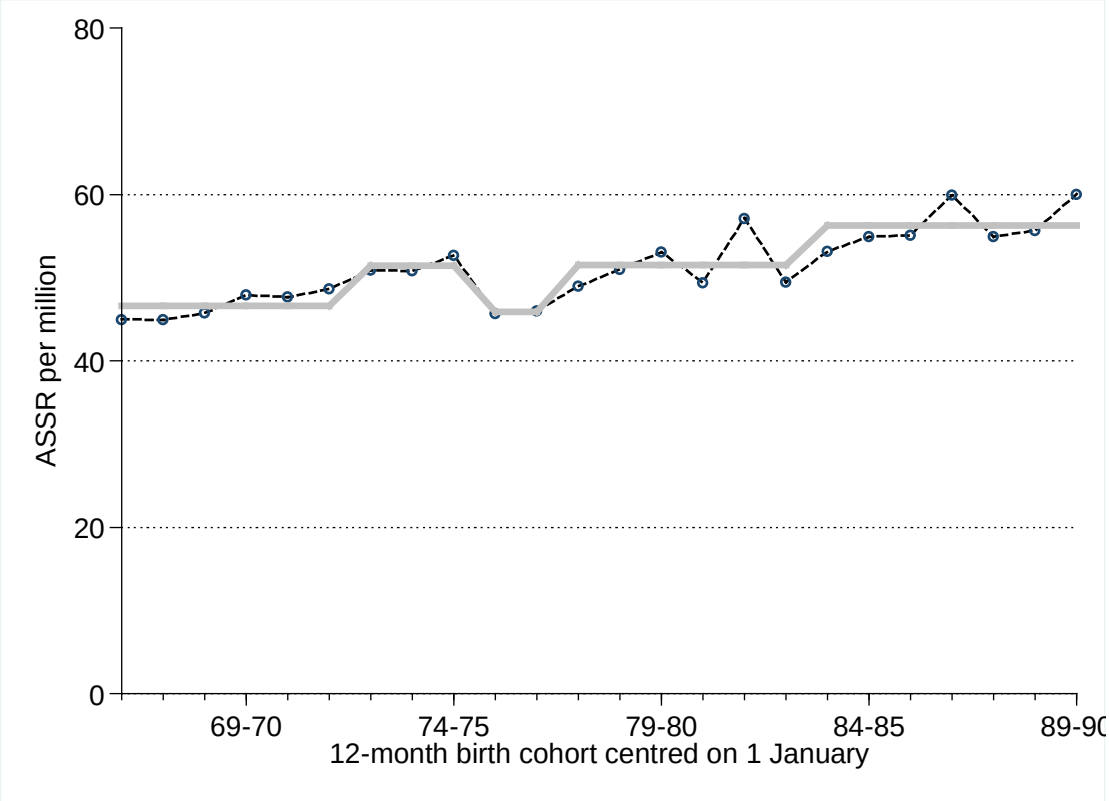
c) Sex-standardised incidence rate per million by age group and grouped birth cohort.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.496.

- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Non-CNS solid cancer: by 12-month birth cohort 1966-67 to 1989-90, Britain
Figures 5.3.13.1 (a) and (b).



a) Standardised rate by single year of age at diagnosis, for successive birth periods.



b) Standardised rate by 12-month birth cohort: actual (dotted), step model (solid) line.

Non-CNS solid cancer: by year of diagnosis 1966-2005, Britain
Tables 5.3.13.2 (a) to (c).

Time trend analysis.

Age/sex	0		1-4		5-9		10-14		0-14	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	192	200	612	487	365	263	415	333	1584	1283
1971-75	176	146	556	429	391	261	484	353	1607	1189
1976-80	157	144	458	356	429	254	526	420	1570	1174
1981-85	196	145	445	395	310	209	509	427	1460	1176
1986-90	203	171	566	455	354	251	453	386	1576	1263
1991-95	225	175	559	495	405	268	493	405	1682	1343
1996-00	217	186	578	429	393	284	519	433	1707	1332
2001-05	240	215	509	476	389	310	573	520	1711	1521
Total	1606	1382	4283	3522	3036	2100	3972	3277	12897	10281

a) Number of cases by age group, sex, and period of diagnosis.

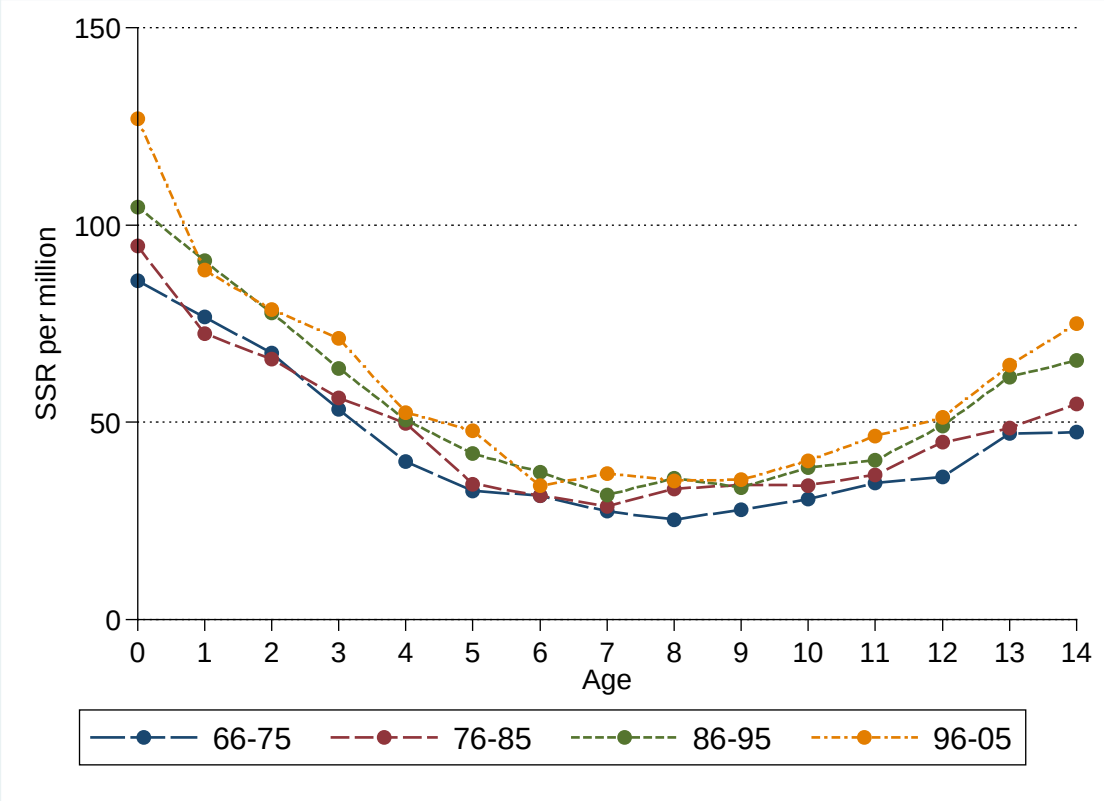
Age/sex	0		1-4		5-9		10-14		ASR	
Diagnosed	M	F	M	F	M	F	M	F	M	F
1966-70	83.7	91.1	65.1	54.0	33.0	25.0	42.2	36.1	48.0	40.8
1971-75	89.4	78.3	64.6	52.6	33.9	23.8	43.8	33.7	49.1	38.4
1976-80	92.9	89.9	66.2	54.4	41.1	25.7	45.6	38.4	52.7	41.9
1981-85	110.1	85.5	63.8	59.6	36.3	25.8	49.0	43.3	52.8	44.6
1986-90	107.5	94.8	77.3	65.1	40.2	29.9	52.8	47.3	58.8	49.4
1991-95	118.9	97.0	73.1	67.7	43.8	30.3	56.1	48.0	60.7	50.6
1996-00	123.3	111.1	79.4	62.0	41.1	31.1	55.9	48.8	61.7	50.6
2001-05	141.3	132.9	75.2	73.7	43.1	36.1	59.6	57.0	63.7	59.5

b) Incidence rate per million by age group, sex and period of diagnosis.

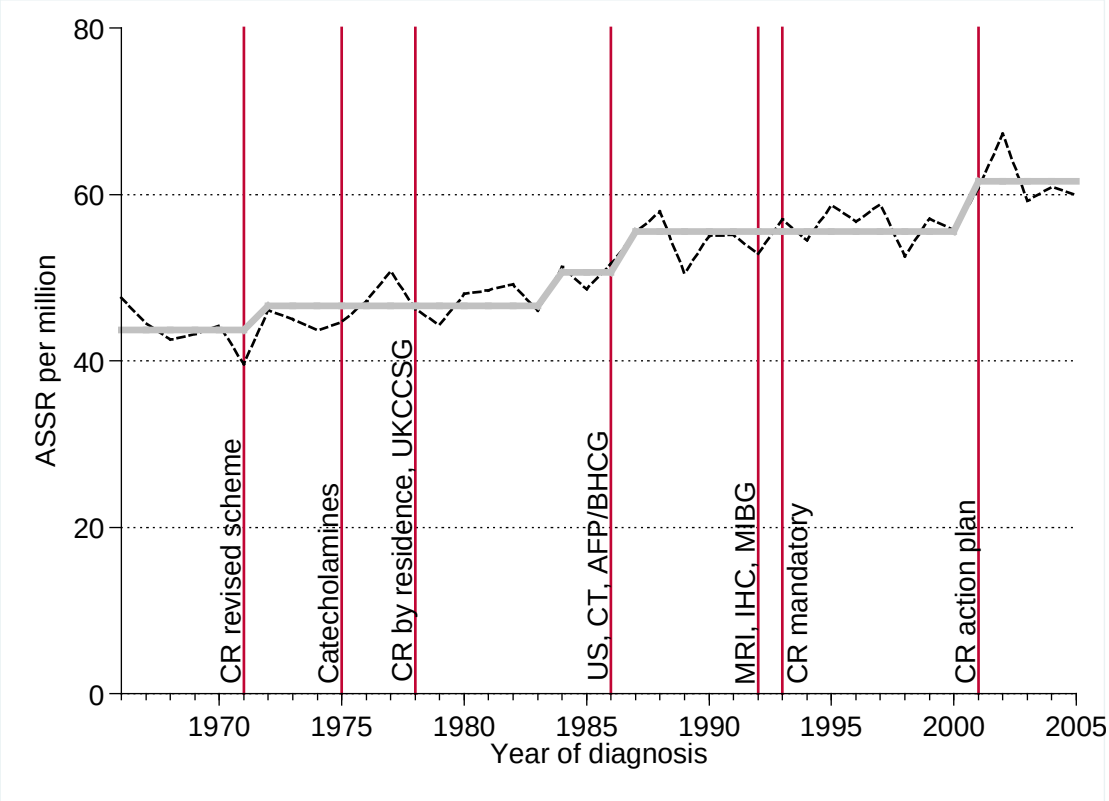
Age	0	1-4	5-9	10-14	ASSR
Diagnosed					
1966-70	87.4	59.5	29.0	39.2	44.4
1971-75	83.8	58.6	28.9	38.8	43.8
1976-80	91.4	60.3	33.4	42.0	47.3
1981-85	97.8	61.7	31.1	46.2	48.7
1986-90	101.2	71.2	35.1	50.0	54.1
1991-95	107.9	70.4	37.0	52.0	55.7
1996-00	117.2	70.7	36.1	52.4	56.2
2001-05	137.1	74.5	39.6	58.3	61.6
Trend	***	***	***	***	***
AAPC	1.25	0.73	0.86	1.19	0.97
CI	0.94 to 1.56	*0.54 to 0.92*	0.63 to 1.10	0.99 to 1.39	*0.86 to 1.08*
Fit	-	*	-	-	*

c) Sex-standardised incidence rate per million by age group and period of diagnosis.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.002.
- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Non-CNS solid cancer: by year of diagnosis 1966-2005, Britain
Figures 5.3.13.2 (a) and (b).

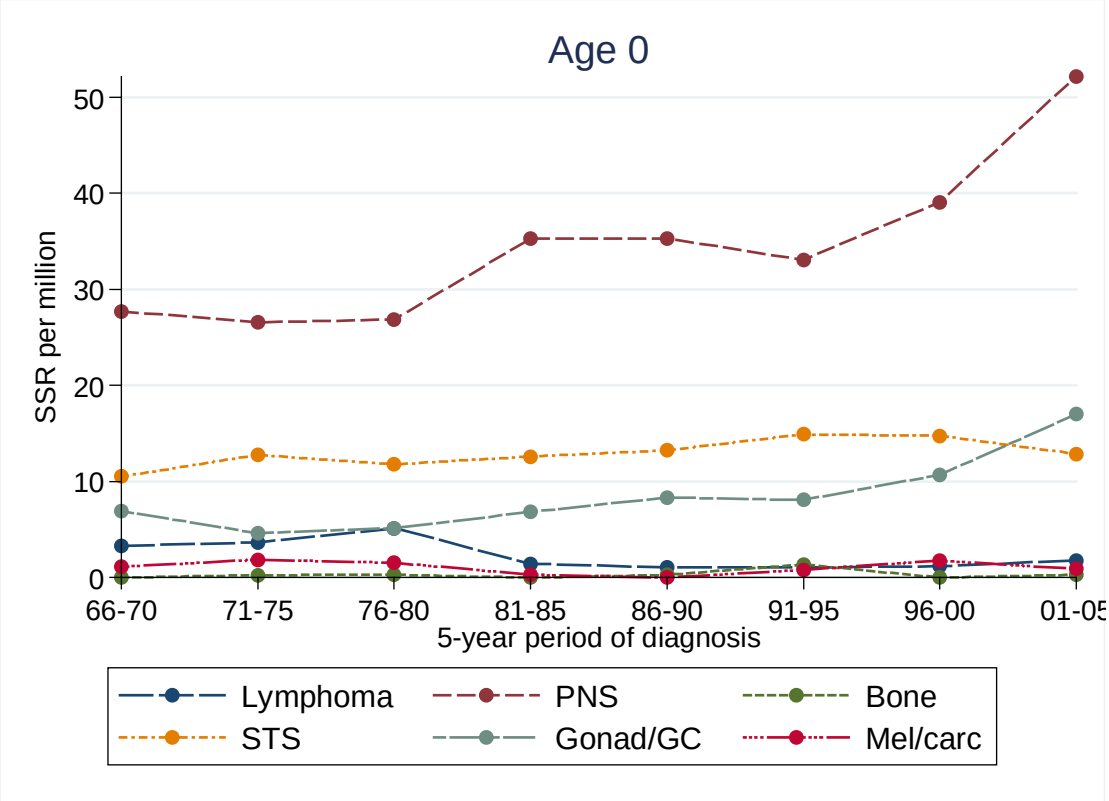


a) Standardised rate by single year of age at diagnosis, for successive diagnosis periods.

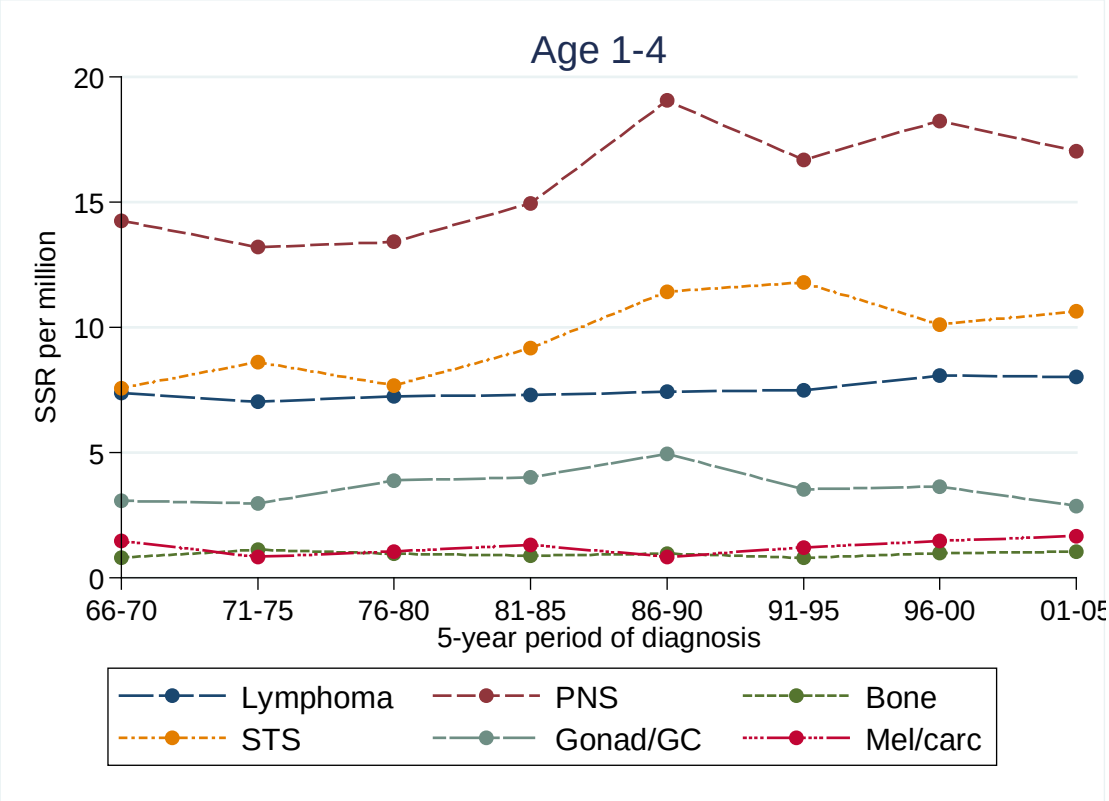


b) Standardised rate by year of diagnosis: actual (dotted), step model (solid) line.

Selected subtypes of non-CNS solid cancer: by year of diagnosis 1966-2005, Britain
Figures 5.3.13.2 (c) and (d).

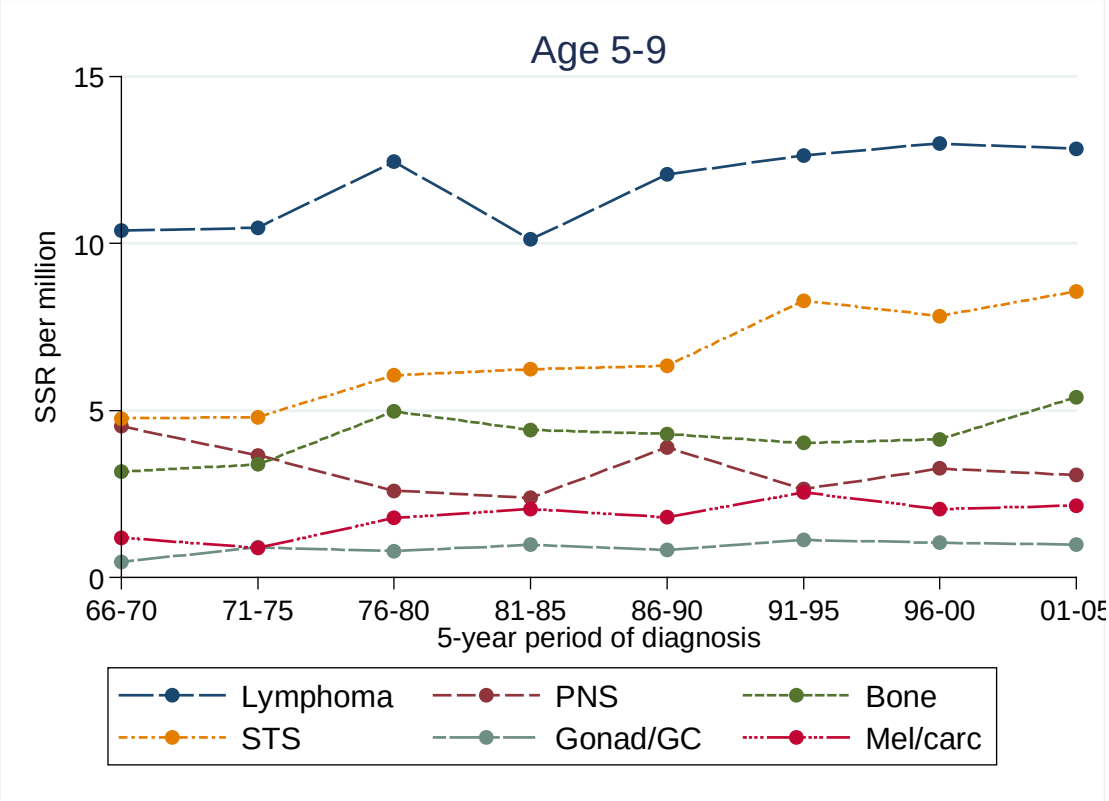


c) Standardised rate at age 0, by subtype and 5-year period of diagnosis.

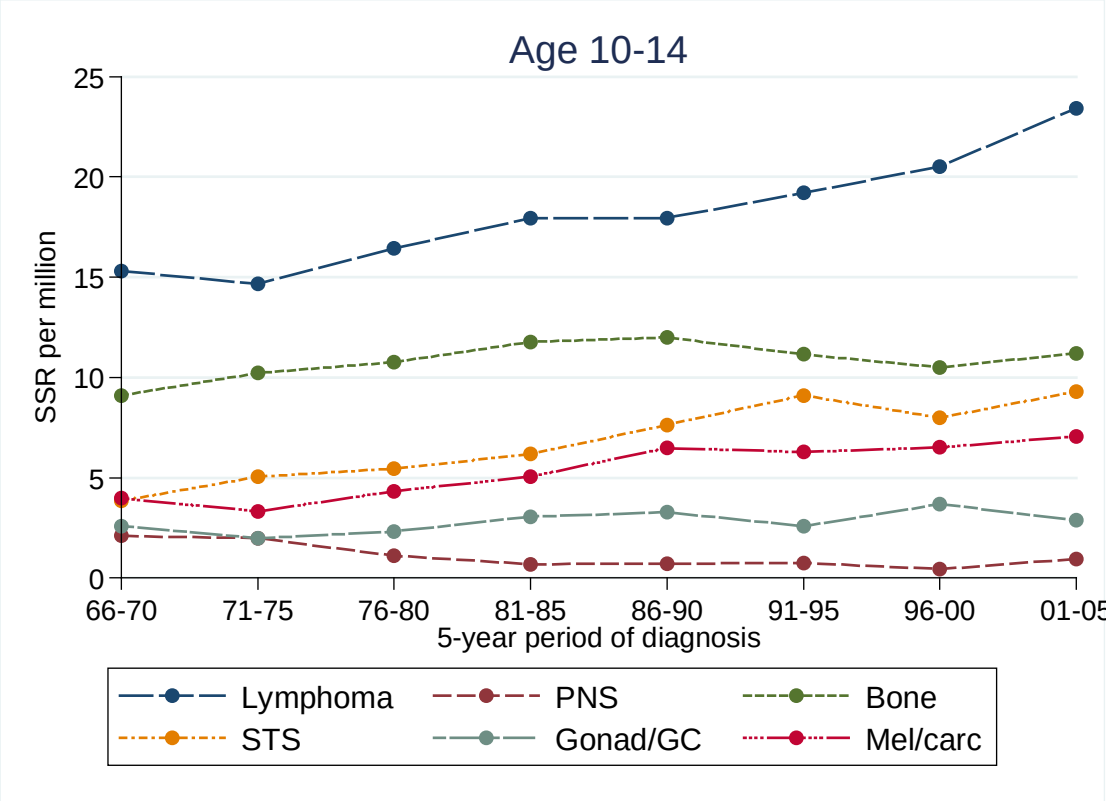


d) Standardised rate at age 1-4, by subtype and 5-year period of diagnosis.

Selected subtypes of non-CNS solid cancer: by year of diagnosis 1966-2005, Britain
Figures 5.3.13.2 (e) and (f).



e) Standardised rate at age 5-9, by subtype and 5-year period of diagnosis.



f) Standardised rate at age 10-14, by subtype and 5-year period of diagnosis.

Non-CNS solid cancer: by year of diagnosis 1976-2005, England and Wales.
Table 5.3.13.3.

Geographical analysis by decade of diagnosis.

Decade	1976-85		1986-95		1996-2005	
Estimates	IRR	95% CI	IRR	95% CI	IRR	95% CI
Region:						
North East	0.80	0.69 to 0.93	1.05	0.92 to 1.20	1.00	0.87 to 1.14
North West	0.80	0.72 to 0.89	0.93	0.84 to 1.03	0.92	0.84 to 1.02
York/Humber	0.88	0.79 to 0.99	1.01	0.90 to 1.13	0.99	0.89 to 1.11
E Midlands	0.86	0.76 to 0.97	0.98	0.87 to 1.10	0.88	0.78 to 0.99
W Midlands	0.82	0.73 to 0.93	1.02	0.92 to 1.14	0.91	0.82 to 1.01
Eastern	0.92	0.82 to 1.03	0.96	0.86 to 1.07	0.91	0.82 to 1.01
London	0.89	0.80 to 0.99	0.90	0.80 to 1.00	1.02	0.93 to 1.13
South East	1.00	n/a	1.00	n/a	1.00	n/a
South West	0.96	0.85 to 1.08	0.95	0.85 to 1.07	1.01	0.91 to 1.13
Wales	1.00	0.88 to 1.15	0.96	0.84 to 1.10	0.96	0.85 to 1.10
SES:						
1=affluent	1.00	n/a	1.00	n/a	1.00	n/a
2	1.03	0.94 to 1.12	1.04	0.96 to 1.14	0.96	0.88 to 1.04
3	1.04	0.95 to 1.14	1.00	0.92 to 1.09	1.01	0.93 to 1.10
4	0.98	0.89 to 1.07	1.00	0.92 to 1.09	1.06	0.97 to 1.15
5=deprived	1.02	0.93 to 1.13	0.97	0.89 to 1.06	1.01	0.93 to 1.11
SES trend:						
Estimates	1.00	0.98 to 1.02	0.99	0.97 to 1.01	1.01	0.99 to 1.03
Trend	-		-		-	
P (Region)	<0.001		0.290		0.091	
P (SES)	0.667		0.589		0.193	
Fit	-		-		*	

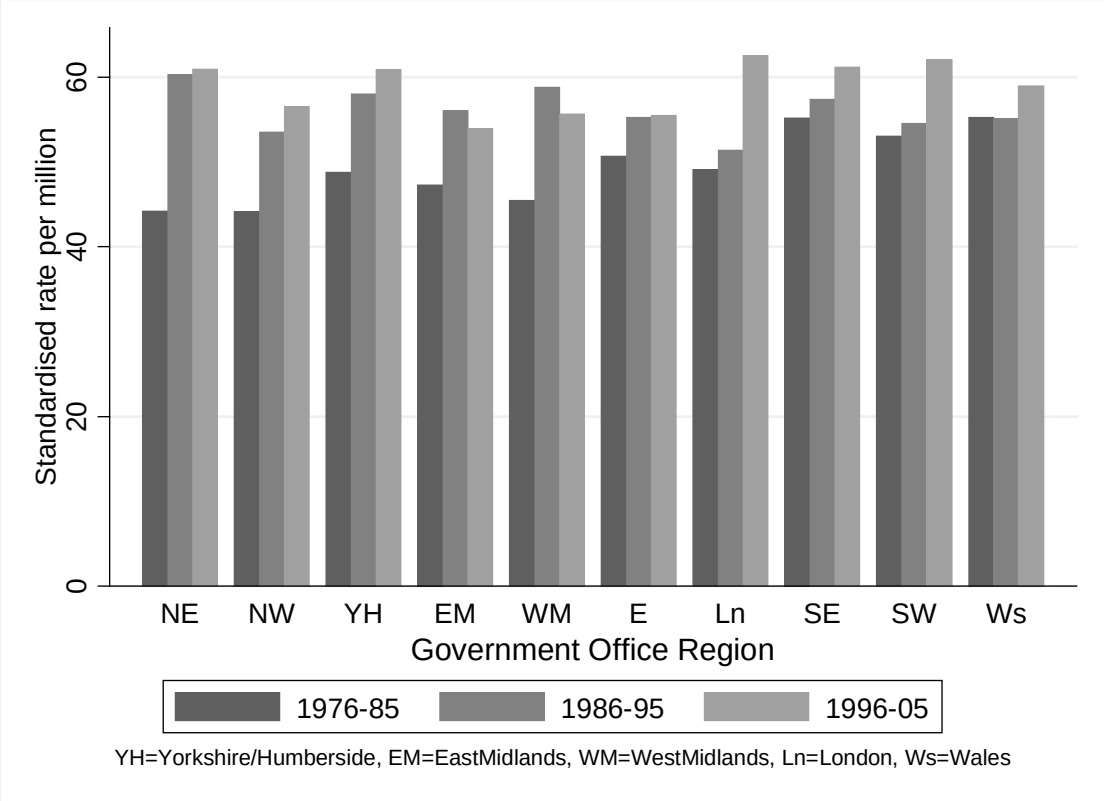
IRR: incidence rate ratio, standardised by age group and sex, for each Government Office Region and SES category (from a Poisson regression model that includes both region and SES as categorical factors), by decade of diagnosis, with estimated 95% confidence interval (CI). Reference categories: South East region; SES category 1 (most affluent).

P (Region): significance level of test for heterogeneity of IRRs between regions.
P (SES): significance level of test for heterogeneity of IRRs between SES categories.
Fit: significance level of deviance test for lack of fit to the categorical model.

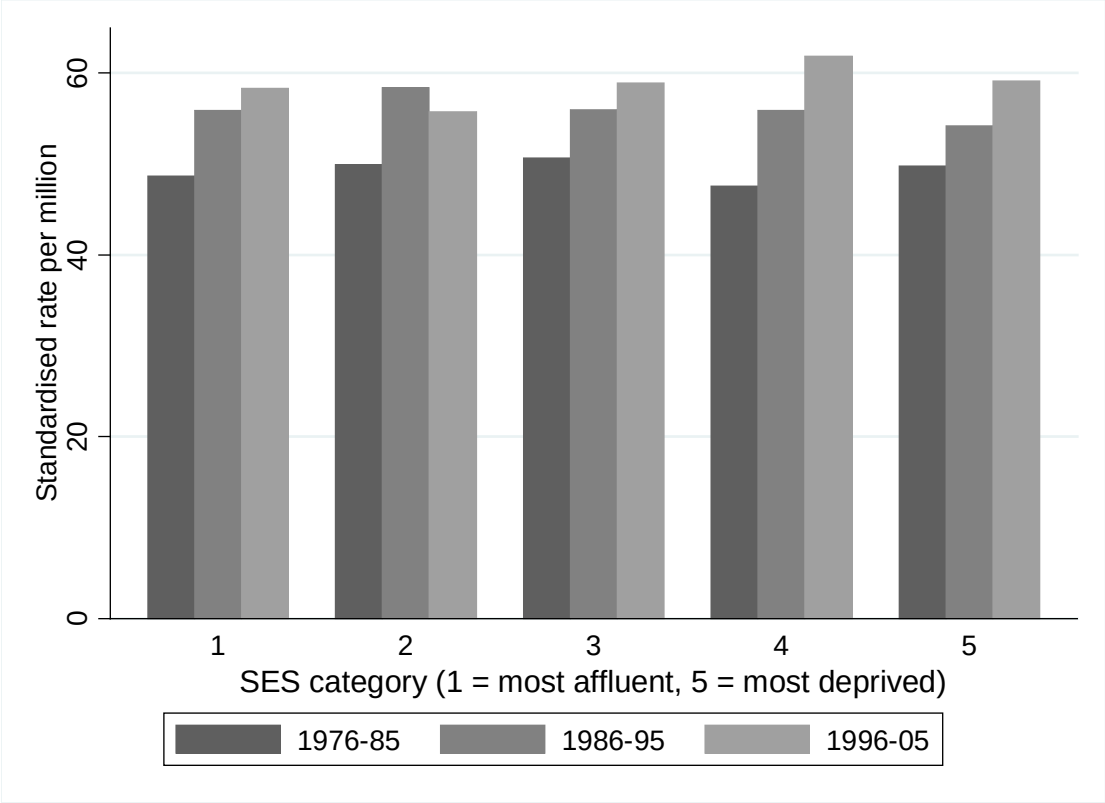
SES trend: IRR for an increase of one SES category, with estimated 95% CI (from a Poisson regression model that includes region as a categorical factor, and the SES category number as a continuous factor).

- = not significant; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Non-CNS solid cancer: by year of diagnosis 1976-2005, England and Wales.
Figures 5.3.13.3 (a) and (b).



a) SES-standardised ASSR by Government Office Region and decade of diagnosis.



b) Region-standardised ASSR by SES category and decade of diagnosis.

5.3.14 Total cases

This diagnostic group consists of all cases in the study. Its three subgroups are defined to be leukaemia, CNS tumours, and non-CNS solid cancer.

5.3.14.1 Year of birth

See Tables 5.3.14.1 (a) to (c), and Figures 5.3.14.1 (a) and (b).

By year of birth, there was an overall increase of 1.0% per year, and the Poisson model did not fit ($p<0.01$). In age groups 0 and 10-14 there were increasing time trends of 1.1% (0.5 to 1.6) and 1.3% (1.0 to 1.6) per year, respectively. In age groups 1-4 and 5-9 there were increases of 0.9% and 0.7% per year on average, but the Poisson model did not fit ($p<0.01$ and $p<0.05$ respectively) (Table 5.3.14.1(c)).

The step model indicates gradual change, with small increases at 1972-73, 1981-82 and 1985-86. (Figure 5.3.14.1(b)).

5.3.14.2 Year of diagnosis

See Tables 5.3.14.2 (a) to (c), and Figures 5.3.14.2 (a) to (f).

By year of diagnosis, there was an increasing time trend of 1.0% (0.9 to 1.1) per year. In age groups 0, 1-4, 5-9 and 10-14, there were increasing time trends of 1.4% (1.1 to 1.6), 0.9% (0.7 to 1.0), 0.9% (0.8 to 1.0) and 1.1% (1.0 to 1.2) per year, respectively. There were statistically significant differences between the time trends in the different age groups ($p<0.001$) (Table 5.3.14.2(c)).

The rates increased in all subgroups within all age groups (Figures 5.3.14.2 (c) to (f)).

The step model indicates increases at 1971, 1976, 1987 and 1993, and a temporary peak in 2002 (Figure 5.3.14.2(b)).

5.3.14.3 Discussion

The time trends by year of diagnosis are consistent with a general effect of diagnosis at an earlier stage of disease. Childhood cancer is generally more common in infancy and adolescence than in mid-childhood, and the largest increases were in age groups 0 and 10-14.

There is no sign of a plateau in the most recent years; in fact the rates for leukaemia and non-CNS cancer seem to have accelerated, mainly due to increases at age 0. The reasons are uncertain, but might include diagnosis at an earlier stage of disease, or more complete cancer registration due to a reduction in perinatal mortality, or both.

By year of diagnosis, the step model indicates increases in rate approximately coinciding with the revised scheme for cancer registration in 1971, the introduction of catecholamine testing for neuroblastoma in 1975, the introduction of US, CT and AFP/BHCG in 1986, the introduction of MRI, IHC for solid tumours and MIBG in 1992, mandatory cancer registration in 1993, and the action plan for cancer registration in 2001. All these associations seem reasonable. There is no indication of any effect of the change of responsibility for cancer registration from the region of diagnosis (or treatment) to the region of residence, or of the start of registration by the UKCCSG, on the overall rate.

Total cases: by 12-month birth cohort 1966-67 to 1989-90, Britain
Tables 5.3.14.1 (a) to (c).

Time trend analysis. 66-70 is the 48-month birth cohort from 1 July 1966 to 30 June 1970, etc.

Age	0		1-4		5-9		10-14		0-14	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	251	230	1231	946	950	685	870	650	3302	2511
70-74	231	198	1148	876	874	622	787	637	3040	2333
74-78	200	172	897	684	669	498	714	565	2480	1919
78-82	215	188	981	856	733	582	825	670	2754	2296
82-86	235	206	1053	857	851	613	832	697	2971	2373
86-90	247	245	1229	996	901	702	922	783	3299	2726
Total	1379	1239	6539	5215	4978	3702	4950	4002	17846	14158

a) Number of cases by age, sex and grouped birth cohort.

Age	0		1-4		5-9		10-14		ASR	
Sex	M	F	M	F	M	F	M	F	M	F
Born										
66-70	138.0	132.1	170.6	137.3	106.1	80.7	97.7	76.9	122.6	98.0
70-74	142.6	129.1	179.1	144.4	110.2	82.9	99.8	85.1	127.3	103.1
74-78	150.9	136.9	170.6	137.2	102.2	80.3	108.4	90.2	125.7	102.5
78-82	150.9	138.9	173.2	158.9	102.9	85.8	116.2	98.2	129.3	113.0
82-86	163.4	150.4	182.9	156.1	117.6	88.7	114.5	100.4	137.0	114.7
86-90	162.7	168.7	202.6	171.5	118.4	96.4	120.3	107.3	144.5	124.9

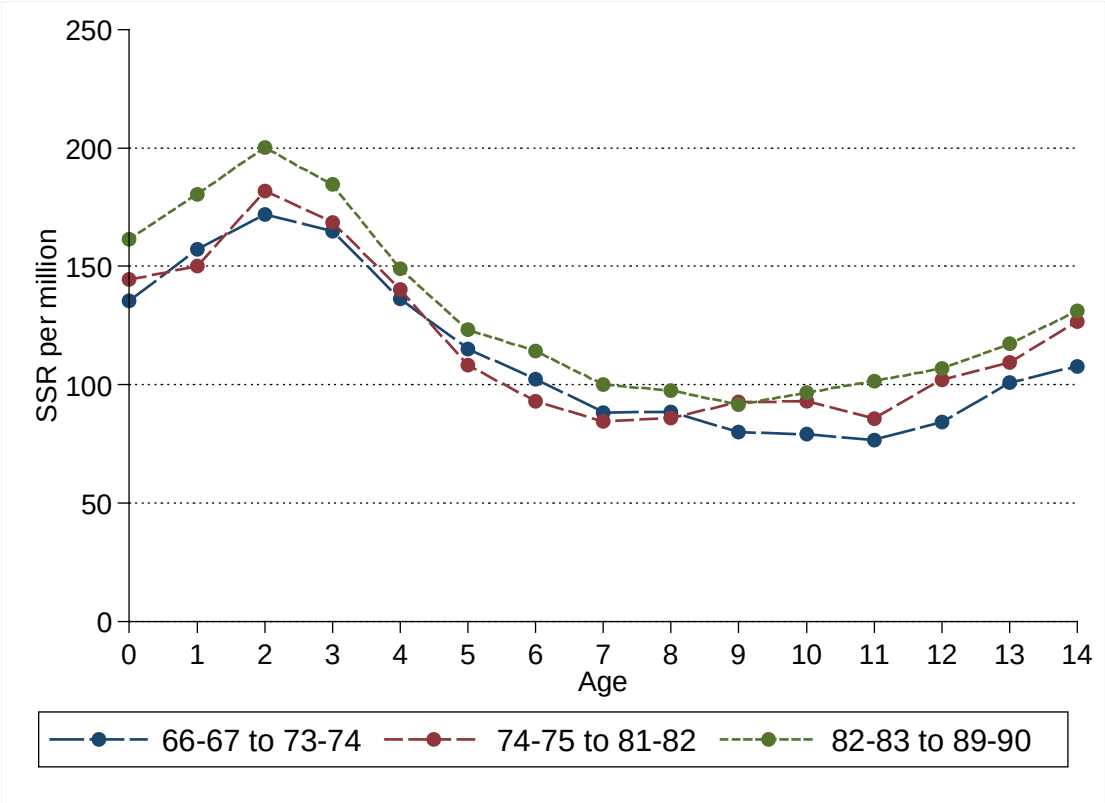
b) Incidence rate per million by age group, sex and grouped birth cohort.

Age	0	1-4	5-9	10-14	ASSR
Born					
66-70	135.1	153.9	93.4	87.3	110.3
70-74	135.8	161.7	96.6	92.4	115.2
74-78	143.9	153.9	91.2	99.3	114.1
78-82	144.9	166.0	94.3	107.2	121.1
82-86	156.9	169.5	103.1	107.5	125.8
86-90	165.7	187.1	107.4	113.8	134.7
Trend	***	***	***	***	***
AAPC	1.08	0.88	0.68	1.28	0.95
CI	0.54 to 1.62	*0.62 to 1.13*	*0.38 to 0.98*	0.99 to 1.58	*0.80 to 1.11*
Fit	-	**	*	-	**

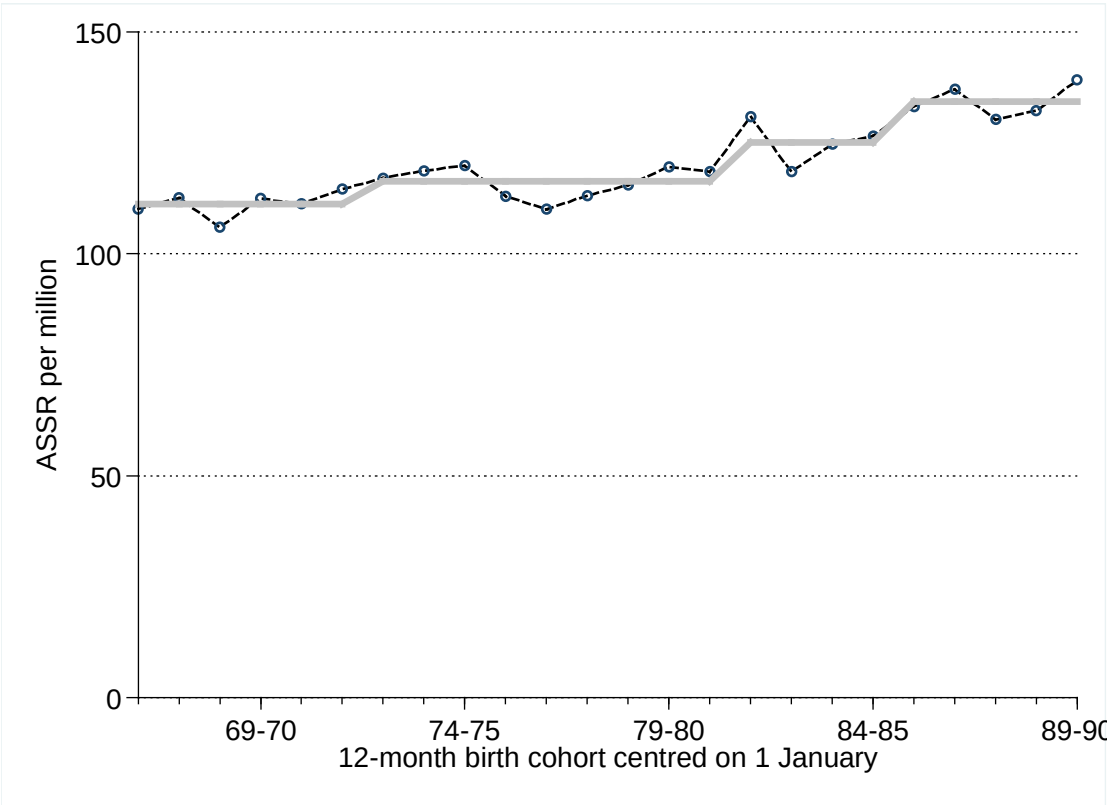
c) Sex-standardised incidence rate per million by age group and grouped birth cohort.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups = 0.033.

- = not significant; * p<0.05, ** p<0.01, *** p<0.001.

Total cases: by 12-month birth cohort 1966-67 to 1989-90, Britain
Figures 5.3.14.1 (a) and (b).



a) Standardised rate by single year of age at diagnosis, for successive birth periods.



b) Standardised rate by 12-month birth cohort: actual (dotted), step model (solid) line.

Total cases: by year of diagnosis 1966-2005, Britain
Tables 5.3.14.2 (a) to (c).

Time trend analysis.

Age/sex	0		1-4		5-9		10-14		0-14	
Diag.	M	F	M	F	M	F	M	F	M	F
66-70	316	303	1490	1192	991	770	869	711	3666	2976
71-75	278	234	1484	1112	1144	839	1025	752	3931	2937
76-80	249	224	1222	962	1133	787	1087	891	3691	2864
81-85	301	248	1188	1002	857	637	1034	817	3380	2704
86-90	303	305	1413	1130	933	760	914	740	3563	2935
91-95	362	296	1470	1226	1092	820	1037	838	3961	3180
96-00	355	306	1475	1197	1137	880	1051	861	4018	3244
01-05	380	358	1404	1220	1126	871	1235	1006	4145	3455
Total	2544	2274	11146	9041	8413	6364	8252	6616	30355	24295

a) Number of cases by age group, sex, and period of diagnosis.

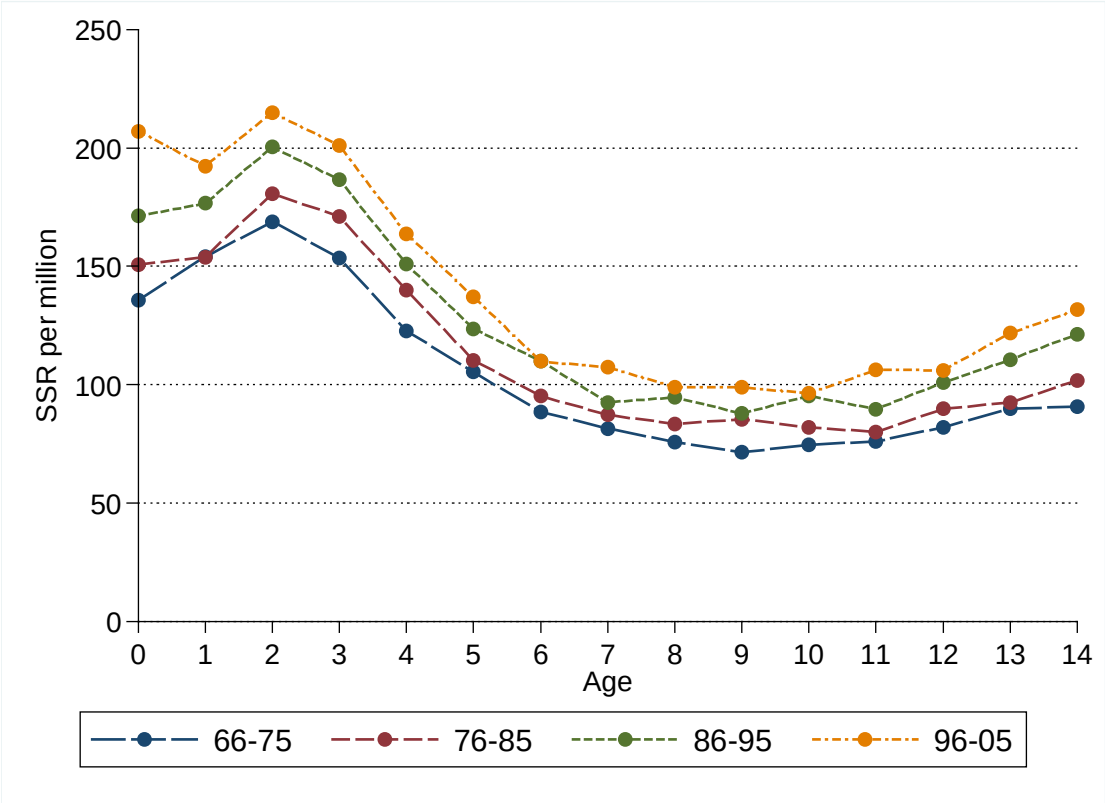
Age/s	0		1-4		5-9		10-14		ASR	
Diag.	M	F	M	F	M	F	M	F	M	F
66-70	137.8	138.1	158.6	132.1	89.6	73.1	88.4	77.1	110.8	94.5
71-75	141.1	125.5	172.4	136.3	99.2	76.6	92.8	71.8	119.4	94.2
76-80	147.4	139.9	176.8	146.9	108.5	79.6	94.2	81.5	124.5	102.2
81-85	169.1	146.2	170.4	151.1	100.4	78.7	99.6	82.9	123.4	103.9
86-90	160.5	169.1	193.1	161.8	105.9	90.6	106.4	90.7	133.0	114.8
91-95	191.3	164.1	192.3	167.6	118.1	92.7	117.9	99.3	142.7	119.6
96-00	201.7	182.8	202.7	173.0	119.0	96.5	113.2	97.1	144.9	122.8
01-05	223.8	221.4	207.4	189.0	124.7	101.3	128.5	110.3	154.6	135.7

b) Incidence rate per million by age group, sex and period of diagnosis.

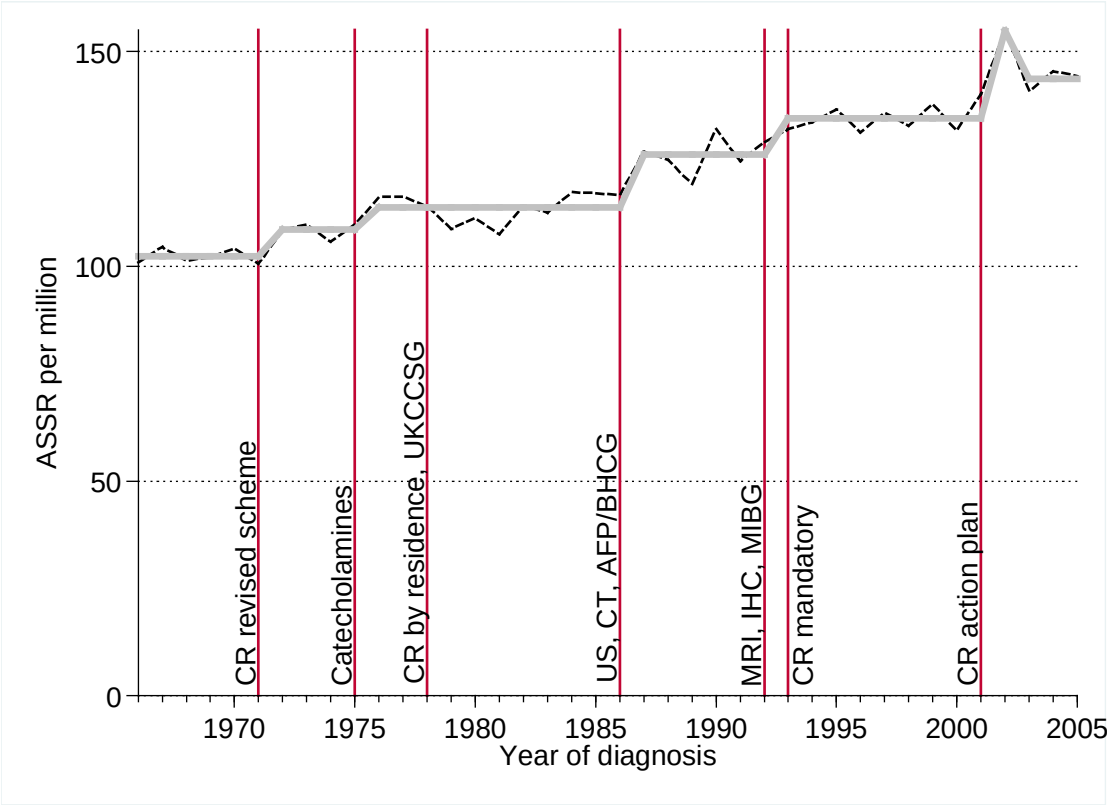
Age	0	1-4	5-9	10-14	ASSR
Diagnosed					
1966-70	137.9	145.3	81.3	82.8	102.6
1971-75	133.3	154.4	87.9	82.3	106.8
1976-80	143.6	161.8	94.0	87.8	113.3
1981-85	157.6	160.7	89.6	91.2	113.6
1986-90	164.8	177.4	98.2	98.6	123.9
1991-95	177.7	179.9	105.4	108.6	131.2
1996-00	192.3	187.9	107.8	105.1	133.9
2001-05	222.6	198.2	113.0	119.4	145.1
Trend	***	***	***	***	***
AAPC	1.38	0.85	0.90	1.09	0.97
CI	1.14 to 1.63	0.73 to 0.97	0.76 to 1.03	0.95 to 1.23	0.90 to 1.05
Fit	-	-	-	-	-

c) Sex-standardised incidence rate per million by age group and period of diagnosis.
Trend: significance level of log-linear time trend in annual rates.
AAPC, CI: annual average % change, with estimated 95% confidence interval.
Fit: significance level of deviance test for lack of fit to the time trend model.
P for heterogeneity of trend between age groups < 0.001.
- = not significant; * p<0.05, ** p<0.01, *** p<0.001.

Total cases: by year of diagnosis 1966-2005, Britain
Figures 5.3.14.2 (a) and (b).

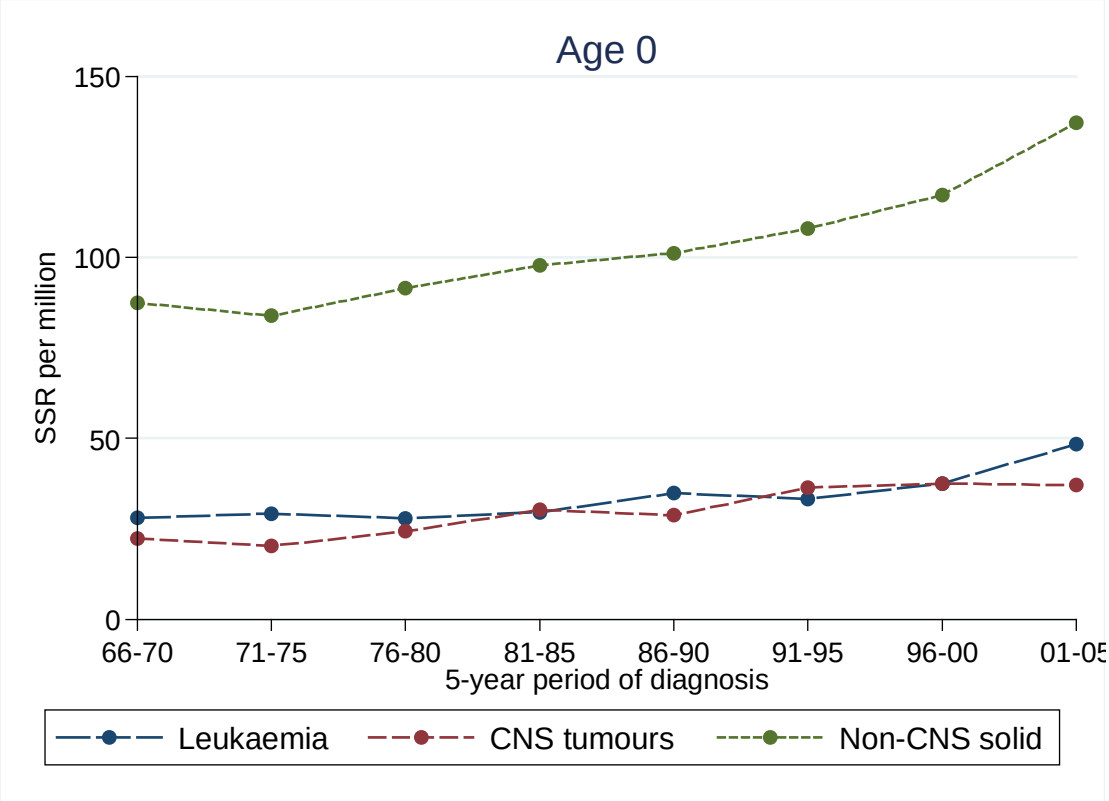


a) Standardised rate by single year of age at diagnosis, for successive diagnosis periods.

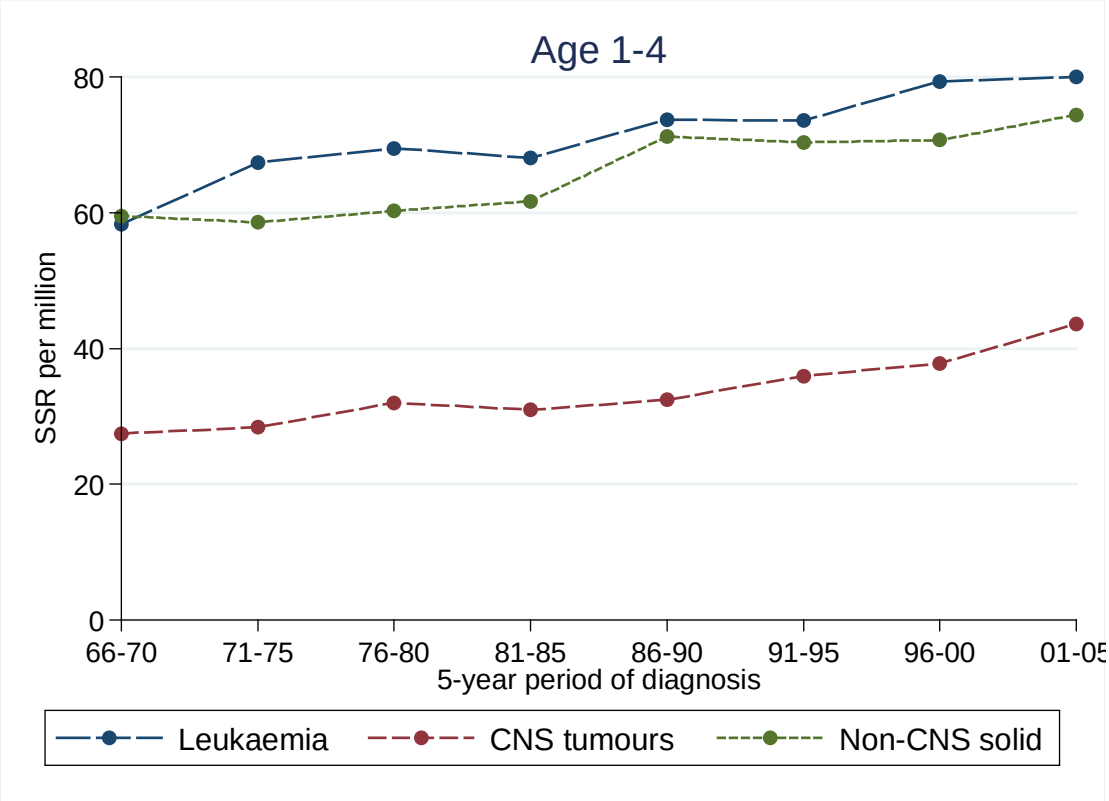


b) Standardised rate by year of diagnosis: actual (dotted), step model (solid) line.

Total cases: by year of diagnosis 1966-2005, Britain
Figures 5.3.14.2 (c) and (d).

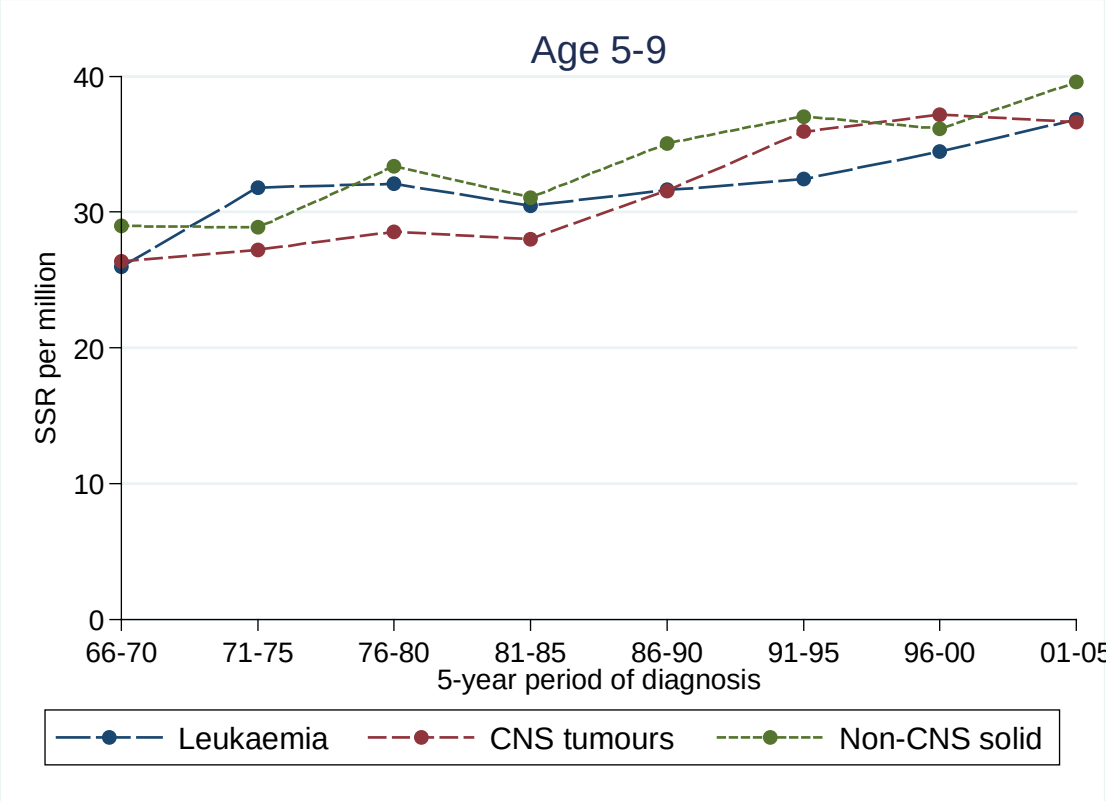


c) Standardised rate at age 0, by subtype and 5-year period of diagnosis.

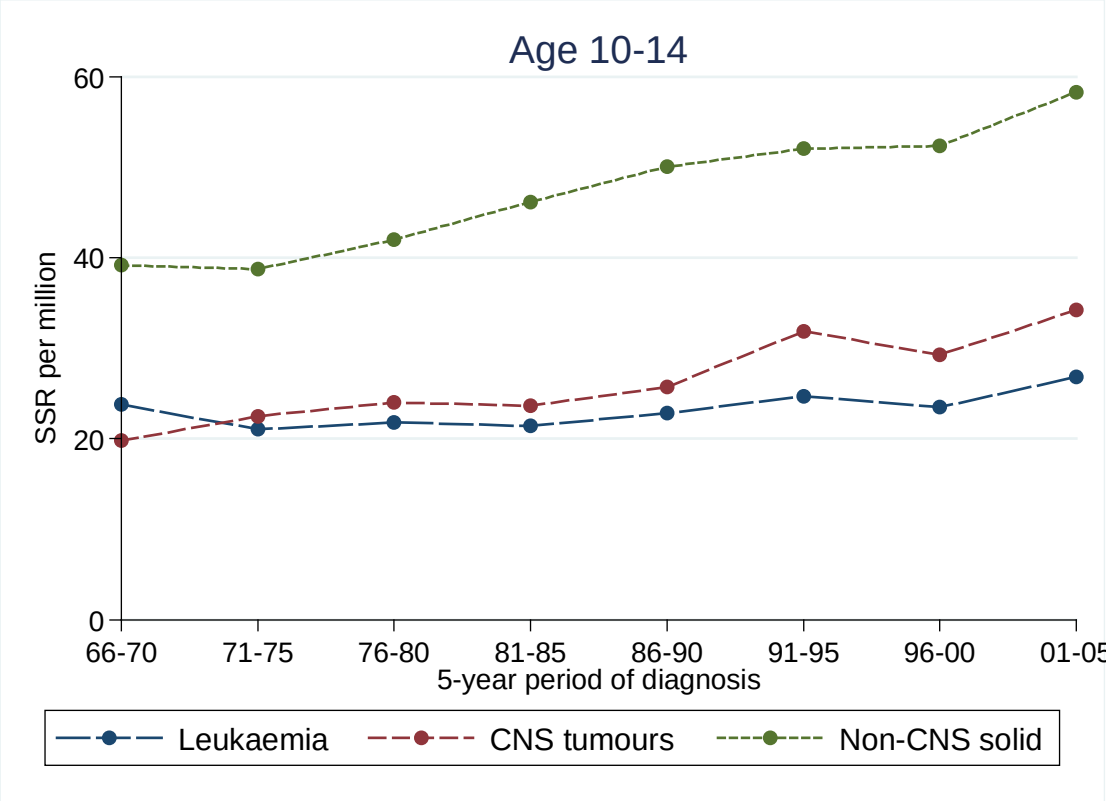


d) Standardised rate at age 1-4, by subtype and 5-year period of diagnosis.

Total cases: by year of diagnosis 1966-2005, Britain
Figures 5.3.14.2 (e) and (f).



e) Standardised rate at age 5-9, by subtype and 5-year period of diagnosis.



f) Standardised rate at age 10-14, by subtype and 5-year period of diagnosis.

5.4 National and international time trend comparisons

5.4.1 Introduction

Tables 5.4(a) and 5.4(b) summarize the time trend estimates reported in section 5.3, by year of birth and year of diagnosis respectively, and give trend estimates from some previous studies for comparison. For consistency with previous publications, these tables use ICCC3 nomenclature: the slight differences in the diagnostic grouping are listed in footnotes to the tables.

5.4.2 Time trends by year of birth

A previous analysis of NRCT time trends [24], published in 1994, included trend estimates in selected diagnostic groups for the 'cohort rate up to age 15' (a form of age-standardised rate by year of birth for ages 0-14), covering children born from 1953 to 1976 for leukaemia, and from 1962 to 1976 for other diagnostic groups. OSCC mortality data represented leukaemia incidence for the years before 1962 (see Chapter 3). Intracranial germ-cell cancer and intracranial neuroblastoma (a possibly spurious diagnosis – see Section 5.3.4.3) were included in the CNS tumour category. The resulting trend estimates are shown in Table 5.4(a), for comparison with equivalent estimates from the present study.

In the 1994 study, there were statistically significant increases of 0.7%, 1.1% and 2.1% per year in groups I (leukaemia), III (CNS neoplasms etc.) and IX (soft tissue sarcoma) respectively (Table 5.4(a)). There was a significant decrease (-2.3% per year) in group IV (neuroblastoma etc.), and a non-significant increase of 0.9% in group VI (renal tumours).

In both studies the recorded incidence of childhood leukaemia by year of birth increased by 0.7% per year on average: the close agreement seems remarkable, given the 40-year time span, the considerable difference between studies in the time periods covered, and the reliance of the 1994 study on mortality data. The trend estimates for CNS neoplasms and soft-tissue sarcoma differed very little between the two studies. The results for renal tumours were also consistent, since the estimate from the earlier study (0.9% per year) is well within the confidence interval from the present study (-0.1 to 1.2).

Only the results for 'neuroblastoma etc.' ('PNS cancer' in the present study) are contradictory: the annual average percent change in the 1994 study was -2.3% per year, which is completely outside the confidence interval for the PNS cancer trend in the present study (0.7 to 2.0). The explanation seems to be that, over the whole 30-year period, there was a decrease followed by an increase. The 1994 study found that the rates by birth cohort decreased during the 1960s but had levelled out by the mid-1970s; the present study did not include birth cohorts from the early 1960s, and found a rate increase in the birth cohorts of the 1980s (Tables 5.3.4.1 (a)-(c) and Figure 5.3.4.1(b)). The relatively high rates in the birth cohorts of the early 1960s may well have been due to over-diagnosis of neuroblastoma (see Section 2.5.2).

5.4.3 Time trends by year of diagnosis

As expected, the trend estimates from the present study by year of diagnosis 1966-2005 were similar to the corresponding estimates from a study [1 Chapter 4 (Kroll and Stiller)] of NRCT time trends during 1966-2000 that was published in 2007; see Table 5.4(b). For groups I (leukaemia), V (retinoblastoma) and VIII (malignant bone tumours), the trend estimates were essentially the same in the two studies. For all groups except X and XI, the trend estimate for 1966-2000 was within the 95% confidence interval for 1966-2005. The transfer of CNS germ-cell cancers to the CNS group in the present study may help to explain the lower trend estimate for group X (germ-cell/gonadal tumours etc.) in 1966-2005, and the slightly higher trend estimate for group III. The exclusion of skin carcinoma probably explains the lower trend estimate for group XI in 1966-2005.

In the 2007 publication, the NRCT trend estimates for 1966-2000 were shown to be generally consistent with previous estimates from the Manchester Children's Tumour Registry [13;14] (for North West England), the ACCIS group of registries in Europe [26] (including 30.5% cases from the British Isles), and the SEER group in the USA [124]. The trend estimates from the SEER and ACCIS groups of registries are reproduced in Table 5.4(b), with both sets of NRCT results. In all these registries or groups of registries, during various time periods between the mid-1960s and the mid-2000s, there was an

overall increasing time trend in childhood cancer of about 1% per year, and an increase in leukaemia of 0.6% or 0.7% per year.

In the NRCT, the overall trend estimate was 0.9% per year for 1966-2000 and 1.0% (95% confidence interval 0.9 to 1.1) for 1966-2005. This suggests that there was no reduction in the rate of increase during 2001-05, relative to the earlier period. Except perhaps for leukaemia, the very recent rate increases are likely to be due to changes in registration methods, since no important changes in diagnostic methods after the mid-1990s were identified in Chapter 2.

Table 5.4(a). Annual average percentage change in recorded incidence of childhood cancer at ages 0-14, by year of birth: results from this study (NRCT 1966-67 to 1989-90) and from a previous national study [24] (NRCT 1953/1962 to 1976).

Registry	NRCT [24]	NRCT
Setting	Britain	Britain
Centre date of 12-month birth cohorts	1 July	1 January
Period of birth	1953-76 for leukaemia 1962-76 otherwise	1966-67 to 1989-90
Diagnostic group (ICCC3)		
I Leukaemia etc.	**0.7**	**0.7** (0.4 to 1.0)
II Lymphoma etc.	–	**0.6** (0.2 to 1.1)
III CNS neoplasms etc.	† **1.1**	† **1.2** (0.8 to 1.5)
IV Neuroblastoma etc.	**-2.3**	**1.4** (0.7 to 2.0)
V Retinoblastoma	–	0.7 (-0.2 to 1.7)
VI Renal tumours	0.9	0.5 (-0.1 to 1.2)
VII Hepatic tumours	–	**1.8** (0.1 to 3.6)
VIII Malignant bone tumours	–	0.0 (-0.7 to 0.7)
IX Soft tissue sarcoma etc.	**2.1**	**2.2** (1.6 to 2.8)
X Germ-cell/gonadal tumours etc.	–	† **1.3** (0.3 to 2.4)
XI Other carcinoma and melanoma	–	**1.5** (0.5 to 2.5)
XII Other and unspecified cancer	–	**2.9** (0.6 to 5.2)
Total cancers	–	**1.0** (0.8 to 1.1)

Excludes skin carcinoma, and non-CNS disease formerly classified as non-malignant.
Estimated 95% confidence interval for trend shown in brackets.
Trends shown in bold are statistically significant at the 5% level.
† Intracranial germ-cell tumours transferred from X to III (see section 5.2.4)
– Statistic not reported in the original

Table 5.4.(b). Annual average percentage change in recorded incidence of childhood cancer at ages 0-14, by year of diagnosis: results from this study (NRCT 1966-2005) with international and national comparisons.

Registry or group of registries	SEER 124	ACCIS 26	NRCT 1	NRCT
Setting	USA	Europe	Britain	Britain
Period of diagnosis	1975-2003	1978-1997	1966-2000	1966-2005 (95% CI)
Diagnostic group (ICCC3)				
I Leukaemia etc.	**0.6**	**0.6**	**0.7**	**0.7** (0.6 to 0.9)
II Lymphoma etc.	-0.4	**0.9**	**0.7**	**0.8** (0.6 to 1.1)
III CNS neoplasms etc.	**1.2**	**1.7**	**1.2**	† **1.3** (1.2 to 1.5)
IV Neuroblastoma etc.	0.2	**1.7**	**0.5**	**0.6** (0.4 to 0.9)
V Retinoblastoma	0.6	0.5	**0.6**	**0.6** (0.2 to 1.1)
VI Renal tumours	0.3	**0.8**	**0.5**	**0.7** (0.4 to 1.0)
VII Hepatic tumours	–	0.8	**2.2**	**2.5** (1.7 to 3.3)
VIII Malignant bone tumours	-0.1	-0.3	**0.5**	**0.5** (0.2 to 0.9)
IX Soft tissue sarcoma etc.	0.6	**1.8**	**1.8**	**1.6** (1.3 to 1.9)
X Germ-cell/gonadal tumours etc.	1.0	**1.6**	**2.1**	† **1.1** (0.6 to 1.6)
XI Other carcinoma and melanoma	**0.8**	**1.3**	**2.5**	‡ **1.8** (1.3 to 2.3)
XII Other and unspecified cancer	–	1.1	**1.8**	**2.2** (1.2 to 3.2)
Total cancers	**0.6**	**1.1**	**0.9**	‡ **1.0** (0.9 to 1.1)
Approx. number of cases per year	<1000	3900	1400	1400

Estimated 95% confidence interval for trend shown in brackets.
Trends shown in bold are statistically significant at the 5% level.
† Intracranial germ-cell tumours transferred from X to III (see section 5.2.4)
‡ Excludes skin carcinoma, and non-CNS disease formerly classified as non-malignant.
– Statistic not reported in the original

5.5 Discussion

In almost all the main diagnostic groups, recorded incidence of childhood cancer in Britain has increased over time, both by birth cohort and by year of diagnosis. Similar trends are found in previous NRCT studies, and in studies from the Manchester Children's Tumour Registry, Europe and the USA. There is no indication that the overall rate of increase has become slower in the most recent time period.

Based on the timing indicated by 'step' models, there is ample evidence for coincidence of changes in rate with changes in methods for diagnosis and registration. A large increase in CNS tumours coincided with both the introduction of MRI and the start of mandatory cancer registration in Britain. A large increase in PNS cancer (mainly neuroblastoma) coincided with the widespread use of ultrasound scanning in paediatric oncology. Apparent exchange between various types of non-CNS solid tumour, and of subtypes of soft-tissue sarcoma and bone tumour, coincided with the introduction of urinary catecholamine testing for neuroblastoma, and of immunohistochemistry for diagnosis of solid cancer. Increases in rates of germ-cell and hepatic cancer coincided with the introduction of AFP and BHCG assays as biochemical markers of these diseases. There were signs of diagnosis at an earlier stage of disease in leukaemia, lymphoma, retinoblastoma, renal cancer, soft-tissue sarcoma and germ-cell cancer. There were strong regional differences in recorded incidence of non-CNS solid cancer in the decade around the 1981 census, but not in the two subsequent decades, consistent with the possibility that improvements in completeness reduced the differences between the regions. The smallest increasing trend was in bone cancer, the solid cancer group for which diagnostic methods have probably changed least, since the initial diagnosis is still usually made by conventional X-ray.

Noticeable rate increases in CNS tumours, retinoblastoma, and melanoma/carcinoma approximately coincided with the introduction of mandatory cancer registration in 1993. If even partly due to improvements in registration of diagnosed cases, these increases seem to contradict flow-method estimates suggesting that registration of diagnosed cases was almost 100% complete in 1991 (Chapter 4). However, it is possible that some patients with these types of cancer could have been missed by the CRs, because they

could have been successfully treated entirely by clinicians who were not cancer specialists; as discussed in Chapter 4, neither the flow method nor the capture-recapture method would be able to detect a deficit of this kind.

From the history of registration methods (Chapter 3), and various efforts to estimate completeness of registration (Chapter 4), it was tentatively suggested that in the past registration was more likely to have been incomplete among the youngest and the oldest children than in the other age groups. For CNS tumours and non-CNS solid cancers, and for total cases, the rate increases were indeed highest in the youngest (age 0) and oldest (age 10-14) children. For leukaemias, there was a large increase at age 0, but a relatively small increase at age 10-14; the latter might perhaps have been influenced by some transfer of T-precursor cases from 'leukaemia' to 'lymphoma', following improvements in diagnostic methods. Little evidence was found to support the prediction that registration might have been more incomplete in Wales and the constituents of the Thames Cancer Registry region (essentially the South East and London) than in other regions.

For leukaemia, unlike any of the other 11 main diagnostic groups, there was no indication of a change in recorded incidence coinciding with a change in diagnostic methods. The only relevant change was the introduction of immunohistochemistry, and this did not appear to affect either the proportions diagnosed as myeloid and lymphoid (except perhaps at age 0), or the overall rate. However, recorded incidence of leukaemia tended to be higher in more affluent geographical areas of England and Wales, even after adjusting for regional differences. Very similar results were found in three successive decades, each centred on a census year, and there was no sign of a weaker association in the most recent decade (1996-2005). There was little or no indication of a similar association for CNS tumours or non-CNS solid cancer.

There was a striking peak in total recorded incidence for cases diagnosed in the year 2002, reflecting spikes in several different diagnostic groups in 2002 (leukaemia, lymphoma, retinoblastoma, renal cancer and bone cancer). The only known relevant event in the history of methods for diagnosis and registration is the Action Plan for cancer registration in 2001, which provided the regional registries with additional funding

from central government for three years, with the aim of improving completeness of registration. It seems possible (if rather surprising) that this initiative could have had such apparently dramatic effects.

For leukaemia and CNS tumours (unlike non-CNS solid cancer) there were statistically significant SES-adjusted regional differences in the decade centred on the 2001 census, which might perhaps be due to different effects of the Action Plan in different regions.

As previously reported, there were small peaks in recorded incidence of leukaemia by year of diagnosis in 1976 and 1990, which were due to lymphoid leukaemia and coincided with influenza epidemics [32]. These peaks appeared, less clearly, as groups of small peaks in leukaemia incidence by year of birth. Otherwise, the birth cohort analysis for leukaemia did not reveal large peaks or troughs, and there was no apparent evidence for an effect of environmental factors acting during gestation in any particular years.

In the other main diagnostic groups, the annual rates were more variable, and it was difficult to see any patterns in the peaks and troughs, either by year of birth or by year of diagnosis.

5.6 Conclusions

Recorded incidence of childhood cancer in Britain, by year of diagnosis, increased by about 1% per year on average during the 40 years up to 2005. There were statistically significant increases in all the 12 main diagnostic groups, ranging from 0.5% per year for bone cancer to 2.5% for hepatic cancer. Similar time trends are reported in previous analyses from the NRCT, in other parts of Europe, and in the USA. There is no evidence that the increase has slowed down in recent years; the rate for total cases diagnosed in 2001-05 was 8% higher than the corresponding rate for 1996-2000.

By year of diagnosis, in almost every diagnostic group except leukaemia, the timing of the changes in rate indicated by a step model (on the assumption that the rates were constant during the intervening periods) coincides with important changes in methods for diagnosis or registration. Time trends by year of birth were similar to time trends by year of diagnosis, and step changes in rate by year of birth could generally be explained as the indirect effect of changes in rate by year of diagnosis.

For the first time, geographical patterns of recorded incidence in England and Wales have been compared between three successive decades of diagnosis, centred on the censuses of 1981, 1991, and 2001. There was a suggestion of heterogeneity between regions for non-CNS solid cancer in 1976-85, and for both leukaemia and CNS tumours in 1996-2005. In all three decades there was a similar tendency for the recorded incidence of childhood leukaemia to be higher in more affluent communities.

For every diagnostic group except leukaemia, increases in the reported incidence of childhood cancer in Britain approximately coincided with known changes in methods for diagnosis or registration. Coincidence is not proof of causation. Nevertheless, changes in recorded incidence cannot be assumed to represent real changes in rate without proof that changes in methods for diagnosis and registration were <u>not</u> involved.

There were no obvious patterns in the annual rates by birth cohort to suggest an effect of causal factors during gestation or around the time of birth, in any diagnostic group.

The changes in methods for diagnosis and registration identified in Chapters 2 and 3 are unlikely to account for the increase in reported incidence of childhood leukaemia in Britain during the study period. However, the consistent tendency for rates to be higher in more affluent areas suggests another possible explanation, which is investigated in Chapter 6.

Chapter 6
A potential source of diagnostic artefact in the recorded incidence of childhood leukaemia

6.1 Introduction

In Chapter 5 the recorded incidence of childhood leukaemia in Britain was shown to be higher in geographical areas of higher socio-economic status (SES) during each of the three most recent decades of the study period. This association could be important as a confounder of epidemiological studies of childhood leukaemia, since almost any factor of interest is likely to be associated with SES. In particular, an explanation for the SES association might also explain the increasing time trend, since living standards in Britain improved during the twentieth century. Previous studies suggest that both the time trend [32] and the association with SES [110] may be specific to B-precursor lymphoid leukaemia, the main component of the incidence peak at ages 2 and 3.

Ecological associations between affluence and the recorded incidence of childhood leukaemia are easy to illustrate. For example, a measure of national affluence, gross domestic product (GDP) per head, appears to be associated with the recorded incidence of childhood leukaemia in European countries around 1995 (Figure 6.1(a)). Variation in the standard of cancer registration is a possible explanation, although all these registries satisfied specified quality criteria as members of the ACCIS consortium. The gradient between European countries is analogous to the gradient in childhood leukaemia incidence between the North and South of England during 1969-93 (Figure 6.1(b)). The increase in childhood leukaemia in Britain since 1971-75 is dwarfed by the increase in real GDP over the same time (Figure 6.1(c)): only a weak association with affluence would be required to explain the leukaemia time trend.

Similar observations were made as long ago as 1955, in a pioneering paper by David Hewitt of the Social Medicine Unit in Oxford [125]. At that time, mortality was an accurate proxy for incidence of childhood leukaemia, because acute leukaemia was almost always

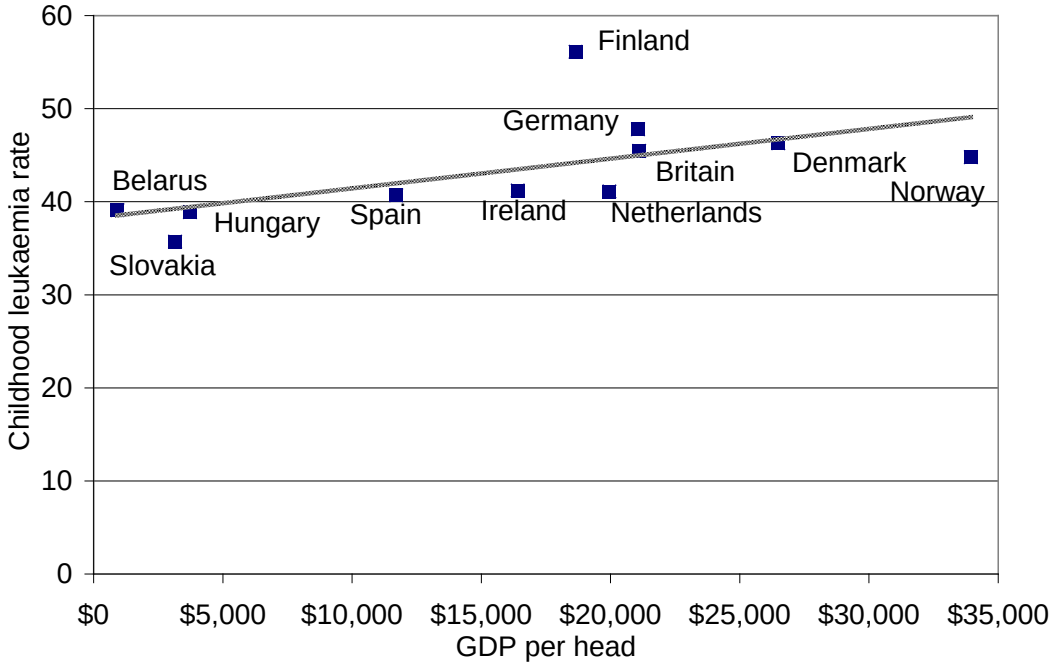
rapidly fatal. There was a marked peak in leukaemia mortality at ages 2 and 3, which was due to lymphoid ('lymphatic') leukaemia. Mortality from leukaemia in children under 5 years of age greatly increased between 1931 and 1953 in England and Wales, particularly at the peak ages. During periods within 1948-52, the ordering of relative age-sex-standardised leukaemia mortality rates under the age of 15[*] in the following communities was: USA non-white (62) < Germany (83) < Eire (84) < Northern Ireland (95) < England and Wales (100) < Denmark (104) < USA white (129); this appears to correspond to the order of living standards at that time.

The fact that these characteristics were originally observed in mortality data strongly suggests that they are not entirely due to registration artefact; and that, if artefact contributes to the variation in incidence, it probably does so mainly through diagnosis, not registration. This is consistent with the results of Chapter 4, which suggested that, at least in the most recent decade, the SES association with childhood leukaemia in the NRCT data is not likely to have been due to incomplete registration of diagnosed cases.

The interpretation (and even the existence) of the SES association is controversial. Section 2 of this chapter therefore discusses two successive systematic reviews of the evidence for this association. Section 3 investigates a possible mechanism for the association that might also help to explain the increasing time trend in childhood leukaemia in Britain.

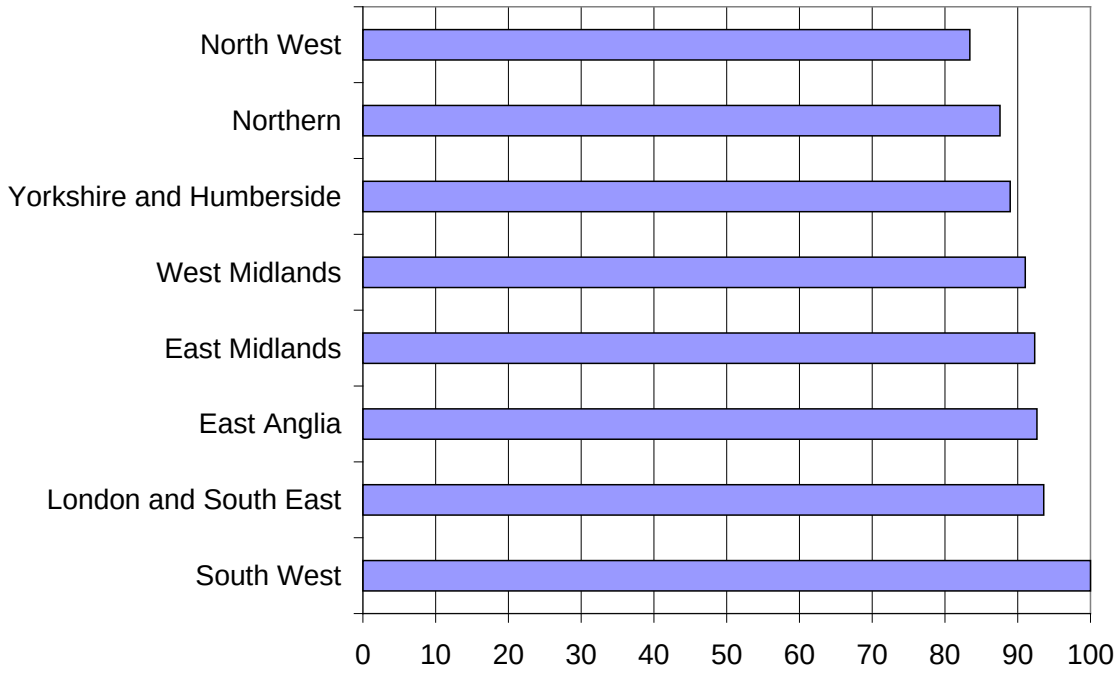
[*] Weighted average of reported mortality for age groups 0-4 and 5-14.

Figure 6.1(a). Affluence and childhood leukaemia in Europe around 1995.



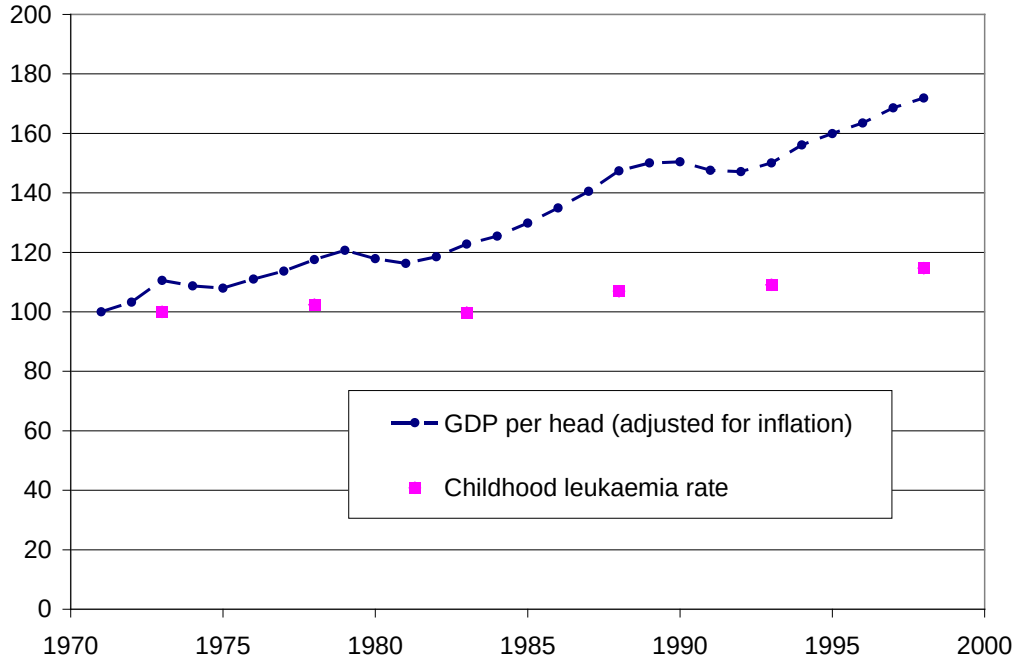
Age-standardised recorded incidence of childhood leukaemia.
Gross domestic product per head (GDP) in 1995 (US dollars 2000).
Leukaemia: [http://www-dep.iarc.fr/accis/data.htm] accessed 19-12-08.
European countries whose cancer registries included more than 100 cases aged 0-14 during available time period: i.e. 1993-97, except Ireland (1994-97), Spain and part of Netherlands (1993-95), and Britain (1991-2000). GDP: [http://www.ers.usda.gov/Data/Macroeconomics/#HistoricalMacroTables] accessed 19-12-08.

Figure 6.1(b). Affluence and childhood leukaemia in England, 1969-93.



Recorded incidence of childhood leukaemia (crude rate) in Standard Regions of England; South West region = 100. [109]

Figure 6.1(c). Affluence and childhood leukaemia in Britain 1971-2000.



Annual inflation-adjusted gross domestic product (GDP) per head (UK), 1971=100.
Quinquennial age-sex-standardised recorded incidence of childhood leukaemia (Britain), 1971-75 = 100.
Leukaemia: Quinquennial ASSRs from Table 5.3.1.2(c) in Chapter 5 of this thesis.
GDP:[http://www.statistics.gov.uk] accessed 24-12-08.

6.2 Evidence for an association with socio-economic status (SES)

6.2.1 Poole et al. 2006

A systematic review of the evidence concerning a possible association between socio-economic status (SES) and childhood leukaemia incidence was published in 2006 by Poole *et al.* [126].

The criteria for inclusion were: original research in English, published during 1945-2002, using (mainly) the keywords 'childhood', 'leukemia' and 'leukaemia', providing estimates of leukaemia incidence or mortality in children or young adults (ages 0-24), and containing sufficient information to allow an assessment of the direction and strength of association with some measure of SES (family income, parental education, paternal occupational class, paternal unemployment, or other household characteristics), at group or individual level. Several studies were restricted to lymphoid leukaemia (ALL), and a few to myeloid leukaemia (AML). The design of each study was classified as ecological, cohort or case-control; and the case-control studies as records-based or requiring individual participation (e.g. by interview or questionnaire). Settings varied widely, from North America and Europe to Australasia and China. A 'positive' association was defined as higher leukaemia rates in children with higher levels of SES. A 'negative' association was defined as lower leukaemia rates in children with higher levels of SES.

48 eligible studies were identified; the earliest was published in 1959. In general, records-based studies (i.e. ecological and cohort studies, and records-based case-control studies) tended to find positive associations, whereas case-control studies requiring participation tended to find negative associations. Unfortunately, study design and study period were confounded: in most of the records-based studies the study period started before 1980, whereas the case-control studies requiring participation tended to be more recent. Poole *et al.* suggested that new ecological analyses would be useful to disentangle these effects [*]. Nevertheless, they concluded that the negative associations found in case-control studies requiring participation might be due to participation bias. They did not suggest any explanation for the positive associations found in records-based studies.

[*] See Figure 6.1(a) in this thesis for an example of a positive ecological SES association in the mid-1990s.

6.2.2 Adam et al. 2008

6.2.2.1 Introduction

Adam *et al*. [127] extended the systematic review of Poole *et al*. by carrying out a search for original research in English, published during September 2002 - April 2008, assessing a possible association between SES and leukaemia incidence or mortality in children or adolescents (ages 0-20). Study designs and the results of subgroup analyses were recorded.

Adam *et al*. identified seven studies, but noted that two were difficult to compare with the others. These two studies do not contribute useful information for leukaemia diagnosed at ages 0-14, since one was very small and included adults (65 cases aged 0-35) [128], and the other was restricted to ages 13-24 [129]. The remaining five studies are listed in Table 6.2(a), in order of study start year.

Adam *et al*. concluded that the studies provided no clear evidence for a relation between SES and childhood leukaemia. They suggested that inconsistency between studies might be explained by selection bias. They seemed more inclined to believe that there was an association with SES at birth than with SES at diagnosis, and asserted that any associations were limited to the 10-20% extremes of the SES distribution. They concluded that SES was unlikely to be a strong confounder of epidemiological studies of risk factors for childhood leukaemia.

Since some of these conclusions do not appear to be justified by the evidence, the results given in the original papers are discussed below. A ‘positive’ association is defined as higher leukaemia rates in children with higher levels of SES.

6.2.2.2 Raaschou-Nielsen et al. 2004

Raaschou-Nielsen *et al*. [130] conducted a case-control study based on records from the national cancer and population registries of Denmark, with gross income data for each of the 275 municipalities in Denmark, and job titles from individual income tax records.

They used three measures of SES: average income of the municipality of residence at the time of birth, classified as the lowest 10% and the highest 10%, with the rest as the reference group; the same measure at time of diagnosis; and parental occupational class in five groups. There was no clear association with occupational class. For SES based on municipal income the results were disparate. Children aged 0-14 who were born in the poorest 10% of municipalities had a leukaemia risk of 2.44 (95% CI 1.35 to 4.38) relative to the central group (p=0.003); the corresponding relative risk for children born in the richest 10% was 0.80 (0.54 to 1.18). Children aged 0-14 who lived in the poorest 10% of municipalities at diagnosis had a leukaemia risk of 0.98 (0.54 to 1.78) relative to the central group; the corresponding relative risk in the richest 10% was 0.85 (0.57 to 1.29).

The results were interpreted as a negative association with SES of residence at birth, and no association with SES of residence at diagnosis, or with SES at the individual level. The evidence for these conclusions appears rather weak. The analyses using municipal-income estimates are based on relatively small numbers of subjects, because of the restriction of the comparison groups to the top and bottom 10% of the income distribution: the statistically significant result is based on only 27 cases and 33 controls in the 'exposed' category. The strong association with low SES based on residence at birth seems surprising, given the lack of association based on residence at diagnosis, and the results for the individual and the residence-based measures of SES are not internally consistent.

6.2.2.3 Borugian et al. 2005

Borugian *et al.* [131] calculated age-standardized incidence rates for leukaemia diagnosed at ages 0-19 from the national cancer registry records and population census data of Canada, for census areas containing approximately 400 persons, and compared these rates across neighbourhood-based quintile categories of income. They found a statistically significant positive trend in risk with increasing SES for total leukaemia (p=0.017) and for ALL (p=0.028).

6.2.2.4 Stiller et al. 2008

Stiller *et al*. [110] compared incidence rates of childhood ALL, stratified by age group, over neighbourhood-based quintile categories of deprivation, using national cancer registry (NRCT) records and population census data in England and Wales, for 9509 census wards containing approximately 5300 persons on average. For cases diagnosed at ages 1-4, there was a statistically significant positive trend in reported incidence of ALL with increasing SES (p=0.0014): the incidence rate ratios in quintile categories of SES, relative to the most affluent quintile, were 1.01, 0.99, 0.94 and 0.82 respectively. (Adam *et al*. quoted a different set of results, which had been adjusted for factors that were associated with SES). There was no association for cases diagnosed at ages 0 and 5-14.

6.2.2.5 Smith et al. 2006

Smith *et al*. [132] adapted a large interview-based case-control study set in Britain (the United Kingdom Childhood Cancer Study [104]; see Chapter 3) to include a records-based measure of SES (deprivation quintiles based on census areas containing about 360 persons) for residence at birth and residence at diagnosis. They presented several different sets of results, employing various different choices of cases and controls and using matched or unmatched analyses; the results for SES at birth and diagnosis were similar. They concluded that there is no real association between ALL and SES at birth or diagnosis, and commented that previous positive results might be artefactual.

Cases were ascertained mainly through specialist units in NHS hospitals, supported by cross-checks with the national cancer registration system. In England and Wales the accrual of cases ran from April or September 1992 to the end of 1994 for all childhood cancer diagnoses, to the end of 1995 for leukaemia and NHL, and the end of 1996 for leukaemia. In Scotland accrual ran from the beginning of 1991 to the end of 1994 for all diagnoses.

4433 cases were registered, and interviews with parents were requested. The parents of 3838 cases (87%) consented to be interviewed. Controls were selected for the interviewed cases only. They were matched to the cases by age, sex and district of residence (ie 98 ‘Family Health Service Authorities’ in England and Wales, and 15

'Health Boards' in Scotland (FHSA)). No consent by parents of controls was required at this stage, although consent by their GPs was required in some districts, mainly in Wales.

Smith *et al*. present two sets of results for ALL and SES at time of diagnosis (Table 6.2(b) below). The first compares all registered ALL cases (including 118 whose parents refused to be interviewed) with all controls (originally matched to cases of any type of childhood cancer) by unmatched logistic regression, adjusting for age, sex and 10 study regions. The second uses the conventional method of analysis for a matched case-control study, i.e. conditional logistic regression for the interviewed ALL cases and their individually matched controls. Both analyses include an odds ratio in a row labelled 'Mean deprivation score (SD)'. This is the odds ratio for an increase of one unit in the deprivation score, i.e. a test for trend with decreasing SES. "The risk estimates reported in the rows 'Mean deprivation score' refer to a one unit increase in deprivation score, that is the continuous deprivation score (-6.15 to +7.75) rather than the deprivation category (1 to 5)" (Alex Smith, personal communication 24-2-09). In Table 6.2(b), the corresponding row is labelled 'Trend with dep. score'.

In the unmatched analysis (Table 6.2(b)) no odds ratio is statistically significant, and it is not clear that adjusting for 10 study regions will compensate adequately for breaking the original matching on 113 districts within Britain. In the conventional matched analysis, on the other hand, the odds ratio in deprivation category 5 is 0.76 (95% confidence interval 0.61-0.95), and the trend with deprivation score is just significant at 0.96 (0.94-0.99). This suggests a positive association of ALL with SES at diagnosis, consistent with a previous matched analysis [133] of UKCCS data by Law *et al*., which found a 'significant' trend [*] in ALL incidence with septiles of SES (see Version (1) in Table 6.2(c)).

Since some details were not reported in the paper by Law *et al*. [133], Alex Smith kindly replicated their analysis on request (personal communication), and, as expected, found a statistically significant trend with SES (p=0.02) (Version (2) in Table 6.2(c)). In a further unmatched analysis that also included the 118 ALL cases whose parents refused to be interviewed (Version (3) in Table 6.2(c)), she found no significant trend. One possible explanation is as follows. Version (3) takes a matched case-control study of interviewed

[*] No further detail was given in the original.

ALL cases and puts in an extra 8% of non-interviewed cases, without changing the controls. Non-interviewed ALL cases are likely to be over-represented in the more deprived categories, due to participation bias. If this is so, the extra cases will appear to increase the risk in the more deprived categories, without affecting the risk in the more affluent categories, and hence the estimated risk in the more deprived categories (relative to the most affluent category) will be higher in Version (3) than in Version (2).

Smith *et al.* [132] suggested that the positive association previously found in record-based studies was caused by incomplete registration. They stated that their study was particularly well-designed for assessing associations between childhood leukaemia and SES, and that the reason that they found no association was that ascertainment of cases was unusually complete in their study. However, because of the matching on 113 FHSAs, the study was partially matched for SES, and therefore was not ideally designed to detect such an association. The study size was only moderate compared to that of Borugian *et al.* [131] or Stiller *et al.* [110] (see Table 6.2(a)). There is no evidence that the study included any cases that would have been missed by the national cancer registration system, and the sources of ascertainment were essentially the same as the sources of the NRCT (see Chapter 3).

I conclude that there is a positive association between childhood ALL and SES at diagnosis in the study by Smith *et al.*, and suggest that the reasons it does not appear very clearly in the published results are that the study was not well-designed to assess this question, and that some of the methods of analysis were inappropriate.

6.2.2.6 Adelman et al. 2007

Adelman *et al.* [134] calculated incidence rates of childhood ALL at ages 0-4 for 200 counties in the USA, using records from the Surveillance, Epidemiology and End Results (SEER) registry. Counties were categorized as 'higher-income' if the proportion of households with income above $5000 was greater than 99%. For both sexes combined, the risk of ALL was 1.6 (95% CI 1.3 to 2.0) in higher-income counties relative to lower-income counties ($p<0.01$), and there was a positive trend in risk over quartile categories of median household income ($p<0.01$). Adelman *et al.* commented 'In short, children in

higher-income counties had a higher incidence of childhood ALL than children in lower-income counties'.

6.2.2.7 Conclusions

All five relevant studies cited by Adam *et al.* [127] used records-based measures of SES. All except for the smallest study [130] found statistically significant positive associations between SES at diagnosis and childhood ALL, leukaemia, or both, based on study periods that began after 1980 [110;131;132;134]. This confirms the results of Poole *et al.* [126] (Section 6.2.1), and extends the time period covered by records-based studies of this association

Combining the results of Poole *et al*. with this re-interpretation of the results of Adam *et al*., I conclude that records-based studies consistently find a positive association between SES and recorded incidence of childhood leukaemia in many different settings, and that this association persists in relatively recent publications.

Table 6.2(a). Studies of childhood leukaemia and socio-economic status, published during 2002-08 and focused on young children (see Section 6.2.2.1) [127].

Publication	Country	Period	Age	Diagnosis	N
First author and date					
Raaschou-Nielsen 2004 [130]	Denmark	1976-1991	0-14	Leukaemia	377
Borugian 2005 [131]	Canada	1985-2001	0-19	Leukaemia	5240
Stiller 2008 [110]	England+Wales	1986-1995	0-14	ALL	3150
Smith 2006 [132]	Britain	1991-1996	0-14	Leukaemia	1910
Adelman 2007 [134]	USA (SEER)	1992-1998	0-4	ALL	836

Table 6.2(b). Odds ratio (OR) for childhood lymphoid leukaemia (ALL) by deprivation category at time of diagnosis, with 95% confidence interval (CI) (Smith *et al*. [132]).

OR (95% CI)	Unmatched	Matched
Number of ALL cases	1578	1460
Number of controls	7663	2919
Deprivation category		
1 Affluent	1	1
2	1.10 (0.93-1.30)	1.10 (0.90-1.34)
3	0.96 (0.81-1.14)	0.89 (0.73-1.09)
4	1.02 (0.86-1.22)	0.97 (0.79-1.19)
5 Deprived	0.90 (0.75-1.07)	0.76 (0.61-0.95)
Trend with dep. score *	0.99 (0.96-1.01)	0.96 (0.94-0.99)

* Odds ratio for a one unit increase in the continuous deprivation score (-6.15 to +7.75), not in the deprivation category (1 to 5).

Table 6.2(c). Odds ratio (OR) for childhood lymphoid leukaemia (ALL) by deprivation category at time of diagnosis, with 95% confidence interval (CI): (1) Law *et al*. 2003 [133], (2) and (3) Smith (personal communication) 2008.

	Published results	Further unpublished results	
Version	(1) Law *et al*. 2003	(2) Smith 2008	(3) Smith 2008
N cases	1460 approx. *	1460	1578
N controls	2920 approx. *	2919	2919
Case selection	Interviewed ALL cases	Interviewed ALL cases	Registered ALL cases
Control selection	Controls matched to interviewed ALL cases on age, sex and FHSA	Controls matched to interviewed ALL cases on age, sex and FHSA	Controls matched to interviewed ALL cases on age, sex and FHSA
Analysis	Conditional logistic regression	Conditional logistic regression	Unconditional logistic regression adjusting for age, sex and region
Significance level	"Significant" *	P=0.02 for trend	P=0.20 for trend
OR (95% CI)			
1 Affluent	1	1	1
2	1.11 (0.80-1.41)	1.14 (0.90-1.44)	1.12 (0.88-1.41)
3	1.13 (0.89 -1.43)	1.15 (0.91-1.46)	1.15 (0.91-1.45)
4	0.83 (0.66-1.06)	0.89 (0.70-1.13)	0.89 (0.71-1.13)
5	0.94 (0.74-1.21)	0.95 (0.74-1.21)	0.99 (0.78-1.26)
6	0.88 (0.69-1.14)	0.91 (0.71-1.75)	0.99 (0.79-1.26)
7 Deprived	0.83 (0.64-1.08)	0.85 (0.65-1.10)	0.99 (0.79-1.25)

* No further detail was given in the original.

6.3 The 'fatal infection' hypothesis: a potential explanation for both the SES association and the time trend in childhood leukaemia

6.3.1 Introduction

As suggested in Section 6.1, an explanation of the positive association between SES and childhood leukaemia might also explain the increasing time trend in childhood leukaemia. Current explanations for the SES association include (a) registration bias, and (b) the 'delayed infection' hypothesis. A third possibility, the 'fatal infection' hypothesis, has apparently received less attention. A formal test of this hypothesis is reported in Section 6.3.2.

6.3.1.1 Registration bias

Registration bias could explain the SES association if the registration of diagnosed cases were systematically less complete for patients of lower SES than for patients of higher SES. Cancer registration systems are unlikely to be perfect, and under-registration might be concentrated in relatively deprived social groups. Nevertheless, for two reasons, this is unlikely to be the whole explanation.

Firstly, death certification is much less likely to be incomplete than cancer registration, and a positive association between SES and childhood leukaemia mortality existed in the era before effective treatments existed, when acute leukaemia was almost invariably rapidly fatal [125] (Section 6.1).

Secondly, for England and Wales, the association was still present in NRCT data from the most recent decade of the study period (Table 5.3.1.3.). During this period almost all childhood leukaemia treatment in Britain was organised by a limited number of specialist centres, all of which were routine sources for the registration systems. This study has found no evidence of any association of sources of notification with SES, and the capture-recapture method suggests that NRCT leukaemia registration was nearly 100% complete for cases diagnosed during 2003-04 (Section 4.3). A cross-check with Hospital Episode Statistics for leukaemia patients born in 1998 and diagnosed before 2005

(including the peak age for B-precursor lymphoid leukaemia) found no convincing evidence that any eligible cases were missing from the NRCT (Section 4.4).

6.3.1.2 Delayed infection hypothesis

The 'delayed infection' hypothesis [10] (Greaves 1999) proposes that (a) exposure to common infectious agents, usually in early childhood, can trigger B-precursor lymphoid leukaemia in predisposed children, and (b) this predisposition is more likely to occur in children who were relatively sheltered from infection in infancy, through some failure of development of the immune system (Section 1.1). Unfortunately, exposure to unspecified (perhaps subclinical) infections in infancy is difficult to measure, and although many studies of the subject have been published [9], they have been rather inconclusive: see Gilham *et al.*[135] and Roman *et al.*[136], for example.

The delayed infection hypothesis can be related to the SES association on the assumption that a better standard of living entails less contact with infection in early life. A parallel has been drawn with type 1 diabetes, another childhood disease that is associated with affluence in European countries [137].

6.3.1.3 Fatal infection hypothesis

A simpler explanation of the SES association for childhood leukaemia could be as follows. By disrupting the immune system, leukaemia undoubtedly increases the risk of death from infection. Some leukaemic children may die of overwhelming infection without their leukaemia being diagnosed. Due to differences in exposure to infection and access to good medical care, this may happen more frequently in poorer communities than elsewhere. B-precursor lymphoid leukaemia may be more likely to be missed than other subtypes of leukaemia, since the clinical signs are less characteristic of leukaemia in this subtype than others.

This explanation is based on part of a 'working hypothesis' for causation of childhood cancer that was proposed in 1961 by Dr Alice Stewart [138]. Verbatim, the relevant section states:

> 'The recent increase in childhood leukaemia is a consequence of the falling death-rate for pneumonia and related diseases, and is due to prezygotic leukaemias'.

'Prezygotic' meant 'initiated before conception', becoming malignant 'at a later date if exposed to conditions of leucocyte stress, for example, bacterial infections'; this group included most childhood leukaemias, and was responsible for the early peak of leukaemia mortality. All these characteristics are now known or suspected to be typical of B-precursor lymphoid leukaemia (see Section 1.1). Stewart noted that cases of lymphatic (i.e. lymphoid) leukaemia in childhood and old age were:

> 'relatively common in populations which have experienced a continuous decrease in the pneumonia death rate since 1900 – for example Great Britain, Scandinavia and the white population of the USA – and rare in populations which maintained a high pneumonia death-rate until 1945, when penicillin first became available – for example, Ceylon, Japan, and the coloured populations of the USA'.

She observed that a proportional increase in childhood leukaemia mortality from 1943 to 1955 mirrored the proportional decrease in childhood mortality from pneumonia over the same period (Figure 6.3(a)). Since influenza predisposes to bacterial infections, the small peaks in incidence of ALL seen in the NRCT shortly after two influenza epidemics [32] are consistent with Stewart's suggestion that prezygotic leukaemia is promoted by 'leucocyte stress, for example, bacterial infections'; Stewart's explanation for the apparently contradictory effects of infection on leukaemia rates is that contact with infection promotes leukaemia through proliferative stress (analogous to part (a) of the delayed infection hypothesis - see section 6.3.1.2), whereas death from infection reduces the chance that the leukaemia will be diagnosed.

In 1989 Professor Richard Doll developed Stewart's explanation for the time trend into a mechanism for the SES association. In a review of the epidemiology of childhood leukaemia [139], Doll suggested that death from infection might account for 'the relatively low (leukaemia) mortality without any marked childhood peak in poor communities'. He also suggested that the apparent specificity of the SES association to B-precursor ('common ALL') rather than T-cell ('T ALL') lymphoid leukaemia might reflect differences in presentation between these subtypes:

> 'T ALL usually presents with a very high white cell count and an easily recognized enlargement of the lymph glands, while common ALL is easily overlooked because it tends to present with a severe defect of marrow function that makes the subjects particularly subject to serious infection. *If this is the case, we are left with the conclusion that the true incidence of childhood leukaemia may vary very little over time or between or within communities.*' [139] (my italics)

Oddly enough, this suggestion does not seem to have been very influential. Shah and Coleman [20] considered the idea, but rejected it on the grounds that, to explain the time trend, the incidence of leukaemia in children who died of infection would have to be much higher than the incidence of leukaemia in the rest of the population; since leukaemia undoubtedly predisposes to fatal infection, this does not seem conclusive [20]. A Science Citation Index search in November 2009 found 62 other journal articles referring to the paper by Doll [139]; according to their abstracts, none pursued the idea of competing deaths from infection, except for a discussion in a retrospective paper by Alice Stewart herself [140].

In the following section this 'fatal infection' hypothesis is developed and formally tested using clinical data.

6.3.2 Research question and hypothesis tests

Research question

Is the proportion of children suffering from B-precursor lymphoid leukaemia who die from infection, without leukaemia being diagnosed, higher in relatively deprived parts of Britain than in relatively affluent parts of Britain?

B-precursor leukaemia produces a wide range of blood abnormalities, and can disrupt the immune system without necessarily involving a grossly abnormal haemoglobin or platelet count. The signs that specifically suggest leukaemia (rather than infection in general) are pallor and bleeding/bruising, reflecting low levels of haemoglobin and platelets respectively. Children who died of infection caused by undiagnosed leukaemia might tend to lack these signs, and so might tend to have haemoglobin and platelet counts towards the higher end of the range of what is possible in acute leukaemia. So, among the children from relatively deprived areas who were actually diagnosed with B-precursor leukaemia, there might be a deficit of patients with high and intermediate haemoglobin and platelet counts, and hence an apparent excess with relatively low counts.

Conventional clinical criteria can be used to identify patients at high risk of sepsis and bleeding i.e. neutrophils below 0.5 $\times 10^9$/L [141] and platelets below 20 $\times 10^9$/L [142] respectively. High risk of abnormal pallor can be arbitrarily defined as haemoglobin below 5 g/dL, i.e. very severe anaemia. According to the hypothesis, the B-precursor leukaemic children most at risk of dying from infection without being diagnosed with leukaemia ('non-diagnosis') would be those at high risk of sepsis and low risk of pallor and bleeding. So there might be a deficit of these cases among the clinical trial patients from relatively deprived areas.

Hypothesis Test (1)

Among children who were diagnosed with B-precursor leukaemia and recruited to a clinical trial, those who lived in more deprived areas will have a different distribution of haemoglobin and platelet counts at diagnosis from those who lived in more affluent areas, with a higher proportion of relatively low counts.

This test was defined before any blood count data had been obtained. The neutrophil count was not included in the test because it was not expected to be available.

Hypothesis Test (2)

Among children who were diagnosed with B-precursor leukaemia and recruited to a clinical trial, the proportions at high risk of sepsis and at low risk of pallor and bleeding, and hence at high risk of non-diagnosis (i.e. high risk of sepsis combined with low risk of pallor and bleeding), will tend to be lower among those who lived in more deprived areas than among those who lived in more affluent areas.

This test was defined *a priori*, but after Test (1) had been carried out.

6.3.3 Materials and methods

The Clinical Trials Service Unit in Oxford (CTSU) holds initial blood counts for several thousand children who were registered on Medical Research Council (MRC) clinical

trials of leukaemia treatment in the UK during three decades. By linkage with the NRCT, trial patients can be allocated to deprivation categories based on address at diagnosis. Hence the distributions of blood counts, and the risk of non-diagnosis, can be compared between deprivation categories.

Four successive MRC trials recruited childhood lymphoid leukaemia patients in the UK during 1980-2002: UKALL VIII, UKALL X, UKALL XI and ALL 97/99 (Table 6.3(a)). Patients with mature B-cell disease were excluded from all these trials except UKALL VIII. Patients aged less than one year old at diagnosis were excluded from UKALL XI and ALL 97/99. Upper age limits varied between trials, but none was below the 15th birthday.

For this investigation, the CTSU provided lists of trial serial numbers, with an initial blood count for each patient (usually the last measurement taken before the start of treatment). Haemoglobin and platelet counts were supplied for all four trials; neutrophil counts were provided for UKALL VIII and X only. These data were linked to the NRCT through the serial numbers (Table 6.3(b)). Trial patients with serial numbers not found in the NRCT, or found but known to be over age 14 or not resident in England, Wales or Scotland at diagnosis, were excluded. Patients aged 0 or 14 at diagnosis were excluded because they were not evenly distributed over the trials: the linkage identified only one NRCT patient aged 14 in UKALL VIII. Patients who were known to have mature B-cell disease were also excluded. The remaining patients were classified as having acute lymphoid leukaemia of B-precursor, T-cell or unknown immunophenotype. Most of the unknowns would have been of the B-precursor type, because this is the most frequent subtype in the population.

For all the trials except UKALL VIII, the blood count data had been computerised and checked by the CTSU, and could be assumed to represent the information on the trial forms accurately; this was verified by comparing a small sample of extreme values against the original forms. For UKALL VIII only, the blood count data had been supplied to the CTSU in electronic format and had not been previously checked (or used) by the CTSU. As there was some risk of confusion between zero and ‘missing value’ for neutrophils, the electronic records for all UKALL VIII cases with zero or missing

neutrophil counts (101 of 703) were checked against the original forms; cases with neutrophil, haemoglobin or platelet count in the top or (for haemoglobin and platelets) bottom centile were also checked. 14 records were amended.

Patients were classified by the 1981 Carstairs deprivation index for the census ward of their address at diagnosis. Those above the median value for this index among the four trials (0.04032) were categorized as having low SES ('poorer'), and the remainder as high SES ('richer'). As in Chapter 5, patients were also grouped by national child-population-weighted quintile categories of the 1981 Carstairs index for the census ward of their address at diagnosis, within England, Wales and Scotland. One patient was excluded from these analyses because the address at diagnosis was in a ward that recorded no children at the 1981 census.

For Test (1), each type of blood count was categorized by tertiles of its distribution as 'Low', 'Medium' and 'High'. The numbers of patients differed between groups because there were many ties. Standard chi-squared tests were used to test for associations between these categories and the median categories of SES defined above.

For Test (2), conventional clinical criteria were used to identify patients at high risk of sepsis and bleeding. These were: neutrophils below 0.5×10^9/L [141], and platelets below 20×10^9/L [142], respectively. High risk of abnormal pallor was arbitrarily defined as haemoglobin below 5 g/dL, i.e. very severe anaemia. High risk of non-diagnosis was defined as high risk of sepsis combined with low risk of pallor and bleeding. Logistic regression was used to compare between SES categories the odds of a diagnosed patient having been at high risk of pallor, sepsis, bleeding, or non-diagnosis.

Analyses involving neutrophils, sepsis and non-diagnosis were restricted to patients from trials UKALL VIII and UKALL X, because neutrophil counts were not available for the later trials. All other analyses included patients from all four trials.

6.3.4 Results

6.3.4.1 Descriptive statistics

Table 6.3(c) shows the numbers of patients from each trial included in this study, classified by immunophenotype and by median SES category (richer / poorer). There was a strong association between trial and immunophenotype ($p<0.001$), which was mainly due to higher proportions of unknowns in UKALL VIII and UKALL XI than in the other trials. This is probably explained by technical advances over time, combined with the fact that immunophenotyping was done locally for the early trials, whereas central validation was introduced for UKALL XI (Sue Richards, personal communication). Among patients with known immunophenotype, there was no significant association between trial and cell type ($p=0.077$), or between trial and the two median-based SES categories (richer / poorer) ($p=0.370$).

Neutrophil, haemoglobin and platelet counts were positively correlated ($p<0.001$, Table 6.3(d)). The proportions of missing values were small: 3% (71/2098) for neutrophils (UKALL VIII and X only), and 1% (65/5595 and 60/5595) for haemoglobin and platelets respectively.

The tertile categories for each type of blood count are defined in Table 6.3(e). There was a statistically significant association between the two SES categories (richer / poorer) and the three categories of neutrophils (low / medium / high) ($p=0.046$ for B-precursor cases, and $p=0.029$ for all cases, Table 6.3(f)). The proportions of cases with 'low' neutrophil counts were higher in the richer group than the poorer group.

6.3.4.2 Results of Test (1)

For B-precursor leukaemia, there was a statistically significant association between the two SES categories (richer / poorer) and the three tertile categories of haemoglobin (low / medium / high) ($p=0.024$), but not between SES and the three categories of platelets ($p=0.114$) (Table 6.3(f)). As predicted by the hypothesis, the proportions of patients with low values were slightly larger in the poorer category than the richer category: 38%

compared with 34% for haemoglobin, and 38% compared with 35% for platelets. For all cases combined, there was a statistically significant association of SES category with platelet category (p=0.033), and some suggestion of an association with haemoglobin (p=0.065).

6.3.4.3 Results of Test (2)

For B-precursor leukaemia, the odds of being in the groups pre-defined as at high risk of sepsis, pallor, bleeding and non-diagnosis differed significantly between the two SES categories (Table 6.3(g)). The odds ratios for the poorer category relative to the richer category were 0.80 (95% confidence interval 0.66 to 0.97; p=0.021) for sepsis, 1.22 (1.07 to 1.40; p=0.004) for pallor, 1.24 (1.08 to 1.41; p=0.002) for bleeding, and 0.69 (0.55 to 0.85; p<0.001) for non-diagnosis. As predicted, the odds of being in the high-risk groups for pallor and bleeding were higher in the poorer than the richer category, and the odds of being in the high risk groups for sepsis and non-diagnosis were lower in the poorer than the richer category. Fitting odds ratio trends to population-weighted quintile categories of SES produced consistent results (Table 6.3(h)): with increasing deprivation there was a decreasing trend in the odds of being in the group at high risk of non-diagnosis (p=0.011). The results were similar (but perhaps slightly less strong) for all cases combined.

6.3.5 Discussion

These results are consistent with the hypothesis that diagnostic artefact contributes to the positive association between SES and reported childhood leukaemia incidence. Children suffering from B-precursor lymphoid leukaemia may be more likely to die of infection, without leukaemia being diagnosed, if they live in relatively deprived communities than if they live in relatively affluent communities.

Comparing B-precursor patients from census wards with SES above and below the median, the odds of having a very low haemoglobin or platelet count were greater in patients from poorer areas (p<0.005), and the odds of severe neutropenia were lower in the patients from poorer areas (p<0.05). As predicted by the hypothesis, these

associations were in opposite directions, in spite of the positive correlations between neutrophil, platelet and haemoglobin counts. The children at high risk of non-diagnosis were predicted to be those who were simultaneously at high risk of sepsis (with low neutrophils) and low risk of pallor and bleeding (with relatively high haemoglobin and platelet counts). The odds of being in this group were lower for patients from poorer areas ($p<0.005$). The associations were essentially the same, although less statistically significant, if expressed as a trend on five population-based quintile categories of SES, as in Chapter 5.

The results for all cases combined were similar to the results for known B-precursor patients, and the significance levels were similar. There was an insufficient number of non-B-precursor cases to assess whether the effect was specific to this type of leukaemia.

The blood count data derived from paper forms that might not always have been filled in correctly, and a few values seemed rather implausible (e.g. haemoglobin 0.6, see Table 6.3(e)). Nevertheless, the results seem unlikely to be entirely due to blood count errors: the data were collected routinely at the treatment centres, and the sample size is large.

The most likely sources of bias would be non-random entry of patients to the four MRC trials, or non-random failure of linkage to the NRCT. The proportion of lymphoid leukaemia patients aged 0-14 who entered these trials was only 50-60% in the early 1980s, increasing to 80-90% in the late 1990s. About 5% (328/6469) of cases were not linked to the NRCT, and it was impossible to check that these patients were (as expected) ineligible for the NRCT due to age or residence at diagnosis. However, these possibilities do not seem to account for the results of the study. There was no time trend in the proportion of poorer children (odds ratio 1.00 per year; $p=0.692$), and including year of diagnosis in the main logistic regression models made almost no difference to the associations with SES. Restricting the analyses for pallor and bleeding to the earlier trials, UKALL VIII and UKALL X, reduced the significance of the results but did not change the directions of the associations.

Measures of SES were based on the 1981 Carstairs deprivation index for the census ward of the patient's residence at diagnosis, within England, Wales and Scotland (see Chapter

5). For Test (1), and the other analyses that extend to 2002, the index derived from the 1991 census would have been more appropriate. However, the available 1991 Carstairs index excludes Scotland, and restricting the study to England and Wales would have reduced the sample size by about 10%. The 1981 index is appropriate for Test (2), because this test requires neutrophil counts, and is therefore restricted to1980-90, the period covered by UKALL VIII and X.

If there really is a deficit of childhood leukaemia diagnoses in poorer areas, a compensating surplus of infection deaths in poorer areas might be expected. In fact the age-standardised infection death rate in England during 2001-05 was about twice as high in the 20% of children living the poorest Local Authority districts as in the 20% living in the richest Local Authority districts (Figure 6.3(b), calculated from cause-specific death count data supplied by ONS). To account for the leukaemia-SES association in England and Wales during 1996-2005, only about 5-10% of childhood infection deaths would have to be caused by undiagnosed leukaemia, i.e. about 25 deaths per year. The proportion could have been much smaller in earlier years, because childhood infection mortality rates were much higher (Figure 6.3(c)). The very large decrease in infection mortality over time suggests that fatal infections could easily explain the increasing time trend in recorded incidence of childhood leukaemia.

Neutropenia predisposes to bacterial and fungal infections, which cause death mainly through pneumonia, septicaemia or meningitis. If there is an overall deficit of childhood leukaemia diagnoses in any particular time period, there might be a compensating surplus of these types of infection death during the same period, and vice versa. In fact, annual reported leukaemia incidence mirrored infection mortality during 2001-05, and some of the fluctuation does indeed appear to be related to deaths from pneumonia, septicaemia and meningitis (Figure 6.3(d)).

A conjugate vaccine for the serogroup C meningococcus was introduced into the routine UK infant immunisation schedule in November 1999, with a catch-up campaign for children and adolescents during the following year. There had been no previous immunisation against meningococcal infection, and the C serogroup had been an important cause of death from septicaemia and meningitis in children [143]. During the next

few years there was a large reduction in recorded cases of serogroup C disease in children and adolescents in England [144;145], which probably contributed to the reduction in mortality shown in Figure 6.3(c). Hence it seems possible that part of the increase between 2001 and 2002 in recorded incidence of childhood leukaemia in Britain (see Chapter 5) might be related to the introduction of this vaccine.

Table 6.3(a). MRC clinical trials for childhood lymphoid leukaemia 1980-2002. Eligibility criteria and numbers of patients recruited.

Trial	Period	Age at diagnosis	Excluded diagnostic groups	Reported number of trial patients
UKALL VIII [146]	1980-84	0-14	None	829
UKALL X [147]	1985-90	0-15	Mature B-cell	1614
UKALL XI [148]	1990–97	1-18	Mature B-cell	2090
ALL 97/99 [149]	1997-02	1-18	Mature B-cell	1948

Table 6.3(b). Construction of data set for this study: MRC clinical trial patients successfully linked to NRCT registrations and diagnosed with lymphoid leukaemia (excluding mature-B-cell disease) at ages 1-13 while resident in England, Wales and Scotland.

Number of cases	Clinical trial				Total
	UKALL VIII	UKALL X	UKALL XI	ALL 97/99	
Supplied by CTSU	832	1612	2090	1935	6469
Linked to NRCT	773	1546	2007	1815	6141
GB residents aged 0-14	727	1464	1901	1717	5809
GB residents aged 1-13	707	1396	1850	1650	5603
Mature B-cell excluded	703	1395	1848	1649	5595

Table 6.3(c). Distribution of cases from each clinical trial by immunophenotype and socio-economic status (SES).

Trial	Immunophenotype			SES		Total
	B-precursor	T-cell	Unknown	Richer	Poorer	
UKALL VIII	560	61	82	364	339	703
UKALL X	1228	116	51	671	724	1395
UKALL XI	1485	193	170	932	916	1848
ALL 97/99	1454	167	28	831	818	1649
Total	4727	537	331	2798	2797	5595

Patient's SES category derived from Carstairs deprivation index of census ward of address at diagnosis ('richer' or 'poorer').

Table 6.3(d). Spearman rank coefficients of correlation between initial blood counts. All cases, missing values excluded.

Blood count	Neutrophils	Haemoglobin	Platelets
Neutrophils	1.00 (N=2027)		
Haemoglobin	0.38 (N=2014, P<0.001)	1.00 (N=5530)	
Platelets	0.26 (N=2021, P<0.001)	0.38 (N=5518, P<0.001)	1.00 (N=5535)

N = Number of observations.
P = Significance level of test for correlation between different types of blood count.

Table 6.3(e). Definition of tertile categories (low, medium and high) for each type of initial blood count, excluding unknown values; group sizes differ because there are many ties. All cases, missing values excluded.

Blood count	Low		Medium		High		Total
	Range	N	Range	N	Range	N	
Neutrophils $\times 10^9$/L	0.0 to 0.3	798	0.4 to 1.0	580	1.1 to 46.9	649	2027
Haemoglobin g/dL	0.6 to 5.6	1860	5.7 to 7.9	1831	8.0 to 18.9	1839	5530
Platelets $\times 10^9$/L	0 to 26	1881	27 to 72	1833	73 to 899	1821	5535

Table 6.3(f). Distributions of initial blood counts by patient's SES category derived from address at diagnosis ('richer' or 'poorer'). Known B-precursor cases, and all cases. Missing values excluded.

	Known B-precursor cases					All cases				
Initial blood count	Low	Medium	High			Low	Medium	High		
	%	%	%	N	P	%	%	%	N	P
Neutrophils										
Richer	44.1	29.4	26.5	875	0.046	42.0	28.4	29.7	1015	0.029
Poorer	38.3	32.3	29.5	865		36.8	28.9	34.4	1012	
Haemoglobin										
Richer	33.9	35.1	31.0	2350	0.024	32.2	33.9	34.0	2771	0.065
Poorer	37.8	33.1	29.2	2342		35.1	32.4	32.5	2759	
Platelets										
Richer	34.6	33.5	31.8	2350	0.114	32.4	34.2	33.4	2772	0.033
Poorer	37.5	31.5	31.0	2346		35.6	32.0	32.4	2763	

N = Number of observations.
P = Significance level of chi-squared test for differences in blood count distribution between SES categories.

Table 6.3(g). Odds of being in a group at high risk of sepsis, pallor, bleeding or non-diagnosis, for diagnosed patients in 'poorer' SES category, compared with diagnosed patients in 'richer' SES category. Known B-precursor cases, and all cases. Missing values excluded.

	Known B-precursor cases			All cases		
Group at high risk of:	OR poorer:richer (95% conf. int.)	N	P	OR poorer:richer (95% conf. int.)	N	P
Sepsis	0.80 (0.66 to 0.97)	1740	0.021	0.80 (0.67 to 0.95)	2027	0.013
Pallor	1.22 (1.07 to 1.40)	4692	0.004	1.18 (1.04 to 1.34)	5530	0.011
Bleeding	1.24 (1.08 to 1.41)	4696	0.002	1.22 (1.08 to 1.38)	5535	0.002
Non-diagnosis	0.69 (0.55 to 0.85)	1728	<0.001	0.70 (0.57 to 0.86)	2009	<0.001

OR = Odds ratio (with estimated 95% confidence interval) for poorer relative to richer.
N = Number of observations.
P = Significance level of test for heterogeneity of odds between SES categories.

Table 6.3(h). Odds of being in a group at high risk of pallor, sepsis, bleeding or non-diagnosis, by quintile category of SES (1 = richest, 5 = poorest), relative to category 1. Known B-precursor cases, and all cases. Missing values excluded.

	OR by SES category					Trend per category	N	P	
	1	2	3	4	5	(95% conf. int.)		Het.	Trend
Known B-precursor									
Sepsis	1.00	1.04	1.13	0.91	0.80	0.95 (0.89 to 1.01)	1739	0.228	0.105
Pallor	1.00	0.88	0.92	1.01	1.29	1.07 (1.02 to 1.12)	4691	0.006	0.009
Bleeding	1.00	1.06	1.12	1.17	1.24	1.05 (1.01 to 1.11)	4695	0.305	0.028
Non-diagnosis	1.00	0.92	1.19	0.83	0.60	0.90 (0.84 to 0.98)	1727	0.005	0.011
All cases									
Sepsis	1.00	1.06	1.03	0.92	0.83	0.95 (0.89 to 1.01)	2026	0.428	0.104
Pallor	1.00	0.84	0.89	0.97	1.17	1.05 (1.00 to 1.10)	5529	0.014	0.048
Bleeding	1.00	1.05	1.14	1.17	1.24	1.05 (1.01 to 1.10)	5534	0.237	0.020
Non-diagnosis	1.00	0.99	1.11	0.84	0.67	0.91 (0.85 to 0.98)	2008	0.036	0.016

Trend = Estimated odds ratio (with 95% confidence interval) for a change in SES of one quintile category.
N = Number of observations.
P = Significance levels of tests for heterogeneity and trend in odds ratio over SES categories.

Figure 6.3(a). Proportional mortality rates at ages 0-10 years: pneumonia and leukaemia.

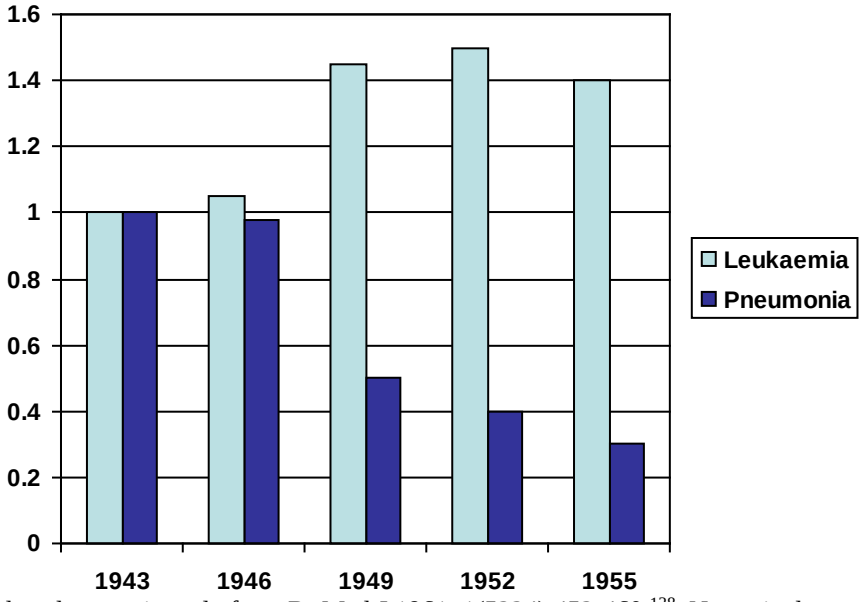
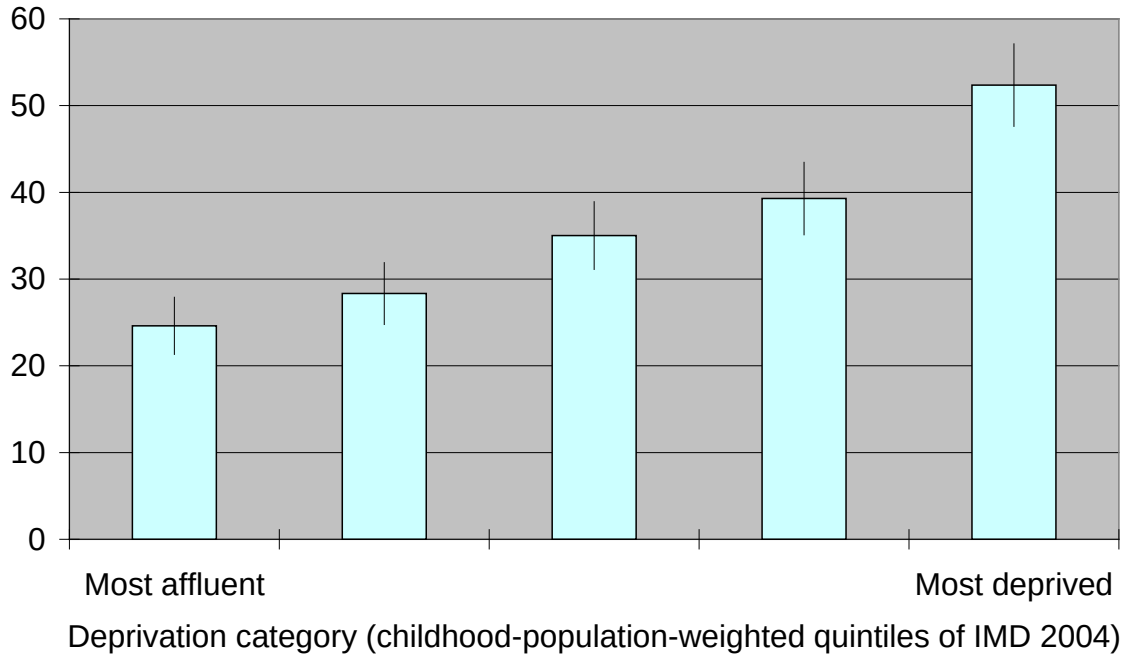


Chart reproduced approximately from Br Med J 1961; 1(5224):452-460 [138]. Numeric data not given in the original. Setting: probably England and Wales, but not clear in the original.

Figure 6.3(b). Childhood (age 0-14) infection mortality in England 2001-05.
Local Authority districts categorized by childhood-population-weighted quintiles of the Index of Multiple Deprivation (IMD), 2004.
Age-standardised rate per million with estimated 95% confidence interval.



Calculated from annual counts of deaths in Local Authority Districts available on request from ONS.

Figure 6.3(c). Childhood (age 0-14) infection mortality (ONS) and reported leukaemia incidence. Age-standardised rate per million. England and Wales 1966-2000/2005.

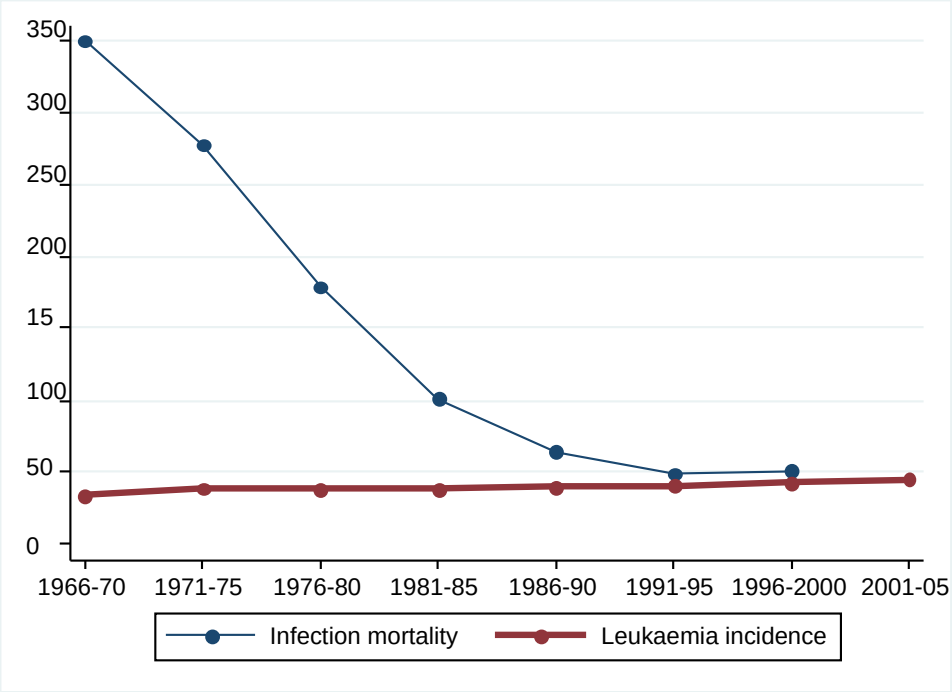
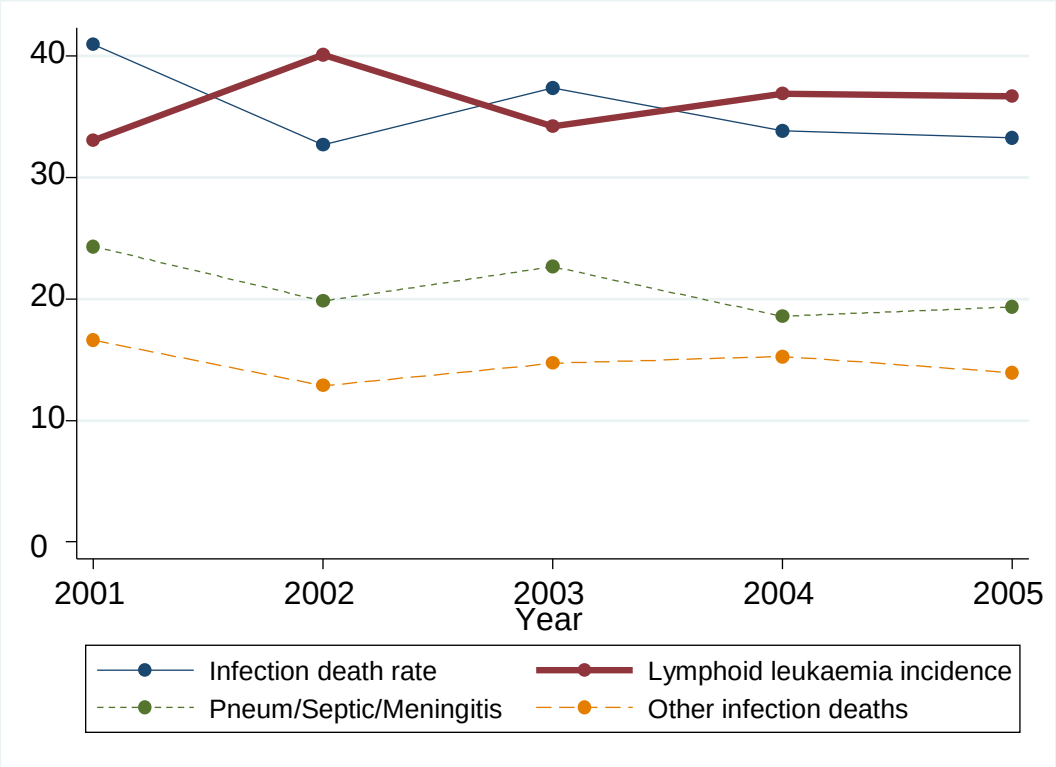


Figure 6.3(d). Childhood (age 0-14) infection mortality (pneumonia/septicaemia/meningitis, other infection, total; source: ONS) and reported lymphoid leukaemia incidence (NRCT).
Age-standardised rate per million. England and Wales 2001-05.



6.4 Conclusions

A positive association between childhood leukaemia and SES is consistently found in records-based and ecological studies in many different settings. It seems to be specific to lymphoid leukaemia (ALL).

This association is unlikely to be entirely due to biased registration of diagnosed cases, because it was originally observed in cancer mortality data. Moreover, in the NRCT, the association extends to the most recent decade of the study period, when childhood leukaemia registration in Britain appears to have been essentially complete.

The 'fatal infection' explanation for the SES association suggests that, particularly in the B-precursor lymphoid subtype, leukaemic children are more likely to die from overwhelming infection, without leukaemia being diagnosed, if they live in poorer communities. This hypothesis was developed by Professor Richard Doll in 1989 from the ideas of Dr Alice Stewart. Surprisingly, it does not appear to have received much attention. It is tested here in a clinical data set.

Initial blood counts were obtained for 1788 children who had been diagnosed with B-precursor lymphoid leukaemia in Britain during 1980-90 and registered on a MRC clinical trial. Children at high risk of sepsis and low risk of pallor and bleeding, according to the initial blood count, were defined to be at high risk of non-diagnosis, i.e. at high risk of sudden death from infection, without the typical signs of leukaemia. As predicted, there was a deficit of children from poorer communities at high risk of non-diagnosis. For pallor and bleeding, but not sepsis, it was possible to extend the study to a more recent time period (1980-2002), with consistent results.

These findings suggest that incomplete diagnosis of leukaemia due to fatal infections might explain both the SES association and the increasing time trend in reported childhood leukaemia incidence in Britain. This factor might be an important source of bias in epidemiological studies of childhood leukaemia. Moreover, if the explanation is correct, and if the missing cases had been correctly diagnosed and treated, some deaths might have been prevented: the five-year survival rate for diagnosed and treated

childhood lymphoid leukaemia patients in Britain during 1991-2000 was 82% [1].

Chapter 7
Summary and conclusions

In this thesis I describe changes in the recorded incidence of cancer diagnosed under the age of 15 in residents of Britain during 1966-2005, and investigate in detail the possibility of artefact as an explanation for these changes, using data from the National Registry of Childhood Tumours (NRCT).

Chapter 1 is a brief introduction to some aspects of the epidemiology of childhood cancer, and to previous work related to time trends in Britain and elsewhere. Increasing time trends in many types of childhood cancer have been reported in registration data from many different countries, including Britain. The extent to which these trends reflect real changes in incidence is both important and controversial, because of the potential effects of registration bias in epidemiological studies, and the implication that some children with cancer may not have been correctly diagnosed. No previous publication using NRCT data has presented rates by individual year of birth or year of diagnosis (except for leukaemia), or considered potential artefacts in detail.

Chapters 2 and 3 review the history of methods for diagnosis and registration of childhood cancers in Britain. There were revolutionary changes during the study period, which might have led to increases in recorded incidence. Patients would have been diagnosed at an earlier stage of disease: for some, this would reduce the age at diagnosis from above to below the 15th birthday, the age limit for registration by the NRCT. Children who died from complications of cancer would have been more likely to have been diagnosed with cancer, and hence more likely to be registered through death certificate notification. Children suffering from neuroblastoma (which occasionally remits spontaneously without treatment) would have been more likely to be diagnosed before going into remission. Mandatory cancer registration from 1993, and other initiatives, may have reduced the chance of regional general cancer registries missing successfully-treated patients not seen in specialist cancer treatment centres.

Chapter 4 describes some attempts to estimate the recent completeness of the NRCT, and to assess changes in completeness over time. Conventional methods suggest that the overall level in the NRCT was at least 93% for cases diagnosed in 1981, and close to 100% for cases diagnosed in 2003-04. It has to be acknowledged that these estimates may be too high, because they rely on assumptions about registration that may not be entirely valid for the NRCT; moreover, they refer only to registration of diagnosed cases, and provide no information about completeness of diagnosis.

Chapter 5 presents a detailed analysis of changes in recorded incidence over time, and relates these changes to the changes in methods for diagnosis and registration outlined in Chapters 2 and 3. Recorded incidence of childhood cancer in Britain, by year of diagnosis, increased by about 1% per year on average during the 40 years up to 2005. There was no evidence that the rate of increase slowed in recent years. There were statistically significant increases in all the 12 main diagnostic groups, ranging from 0.5% per year for bone cancer to 2.5% for hepatic cancer, with 0.7% for leukaemia. In almost every diagnostic group except leukaemia, changes in the recorded incidence rate by year of diagnosis appeared to coincide with important changes in methods for diagnosis and/or registration. While association is not proof of causation, the changes in rate cannot be assumed to represent real changes in incidence without proof that these changes in methods for diagnosis and/or registration were not involved. There is also some evidence of diagnostic inaccuracy at the level of the 12 main diagnostic groups, particularly in the first decade of the study period. In general, time trends by year of birth were similar to time trends by year of diagnosis, and changes in rate by year of birth could be explained as the indirect effect of changes in rate by year of diagnosis. There was no clear evidence for any effect on annual rates of real causal factors acting during gestation or around the time of birth. For leukaemia, there were no known relevant changes in diagnostic methods during the study period. There were no apparent patterns in the variation in annual rates by year of diagnosis that could be related to potential causal factors acting shortly before diagnosis, other than the previously-reported small peaks in lymphoid leukaemia in 1976 and 1990 (shortly after influenza epidemics), and a further small peak in 2002.

Chapter 6 investigates the possibility of a special type of diagnostic artefact in childhood leukaemia. The 'fatal infection' hypothesis is a potential explanation for both the increasing time trend and the positive association with affluence that is found in childhood leukaemia records in many different contexts; the evidence for this association is reviewed here. It is suggested that, particularly in the B-precursor lymphoid subtype, leukaemic children are more likely to die from overwhelming infection, without leukaemia being diagnosed, if they live in poorer communities. As predicted, among children treated for B-precursor lymphoid leukaemia in MRC clinical trials in Britain during 1980-90, there was a deficit of children from poorer communities with initial blood counts suggesting a high risk of dying suddenly from infection without the typical signs of leukaemia; a less specific test covering a more recent time period (1980-2002) gave similar results. There was much greater childhood mortality attributed to infection in deprived areas of England than in affluent areas, even in very recent years. Moreover, during the study period there was a strong increasing time trend in national wealth (measured by GDP per head) and a strong decreasing time trend in childhood infection death rates; during 2001-05 fluctuations in annual reported childhood leukaemia incidence mirrored childhood infection mortality in England and Wales. Hence, the 'fatal infection' hypothesis seems a plausible explanation for the increasing time trend in recorded childhood leukaemia incidence in Britain.

I conclude that the recorded incidence of childhood cancer in Britain increased during the 40-year period 1966-2005 in almost every diagnostic group, and that these increases are probably a result of improvements in methods for diagnosis and registration. Childhood cancer may have been considerably under-recorded in the past: the overall rates for 1966-75, 1976-85 and 1986-95 were respectively 75%, 81% and 91% of the rate for 1996-2005. There may be a deficit of cases even in the most recent records, since the rates were still increasing during 2001-05. Possible implications for epidemiological studies should be considered.

Childhood leukaemia may still be under-diagnosed in Britain, particularly in relatively deprived communities. Clinicians should perhaps be more ready to investigate the possibility of leukaemia in cases of severe infection in childhood.

Appendix 1. International Classification of Childhood Cancer, third edition [111]

First and second levels of classification; third level ('Division') not shown.

Site Group	ICDO-3 Histology (Type)	ICDO-2/3 Site
I Leukemias, myeloproliferative diseases, and myelodysplastic diseases		
(a) Lymphoid leukemias	9820, 9823, 9826, 9827, 9831-9837, 9940, 9948	C000-C809
(b) Acute myeloid leukemias	9840, 9861, 9866, 9867, 9870-9874, 9891, 9895-9897, 9910, 9920, 9931	C000-C809
(c) Chronic myeloproliferative diseases	9863, 9875, 9876, 9950, 9960-9964	C000-C809
(d) Myelodysplastic syndrome and other myeloproliferative diseases	9945, 9946, 9975, 9980, 9982-9987, 9989	C000-C809
(e) Unspecified and other specified leukemias	9800, 9801, 9805, 9860, 9930	C000-C809
II Lymphomas and reticuloendothelial neoplasms		
(a) Hodgkin lymphomas	9650-9655, 9659, 9661-9665, 9667	C000-C809
(b) Non-Hodgkin lymphomas (except Burkitt lymphoma)	9591, 9670, 9671, 9673, 9675, 9678-9680, 9684, 9689-9691, 9695, 9698-9702, 9705, 9708, 9709, 9714, 9716-9719, 9727-9729, 9731-9734, 9760-9762, 9764-9769, 9970	C000-C809
(c) Burkitt lymphoma	9687	C000-C809
(d) Miscellaneous lymphoreticular neoplasms	9740-9742, 9750, 9754-9758	C000-C809
(e) Unspecified lymphomas	9590, 9596	C000-C809
III CNS and miscellaneous intracranial and intraspinal neoplasms		
(a) Ependymomas and choroid plexus tumor	9383, 9390-9394	C000-C809
(b) Astrocytomas	9380	C723
	9384, 9400-9411, 9420, 9421-9424, 9440-9442	C000-C809
(c) Intracranial and intraspinal embryonal tumors	9470-9474, 9480, 9508	C000-C809
	9501-9504	C700-C729
(d) Other gliomas	9380	C700-C722, C724-C729, C751, C753

	9381, 9382, 9430, 9444, 9450, 9451, 9460	C000-C809
(e) Other specified intracranial and intraspinal neoplasms	8270-8281, 8300, 9350-9352, 9360-9362, 9412, 9413, 9492, 9493, 9505-9507, 9530-9539, 9582	C000-C809
(f) Unspecified intracranial and intraspinal neoplasms	8000-8005	C700-C729, C751-C753
IV Neuroblastoma and other peripheral nervous cell tumors		
(a) Neuroblastoma and ganglioneuroblastoma	9490, 9500	C000-C809
(b) Other peripheral nervous cell tumors	8680-8683, 8690-8693, 8700, 9520-9523	C000-C809
	9501-9504	C000-C699, C739-C768, C809
V Retinoblastoma	9510-9514	C000-C809
VI Renal tumors		
(a) Nephroblastoma and other nonepithelial renal tumors	8959, 8960, 8964-8967	C000-C809
	8963, 9364	C649
(b) Renal carcinomas	8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8143, 8155, 8190-8201, 8210, 8211, 8221-8231, 8240, 8241, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8401, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8576	C649
	8311, 8312, 8316-8319, 8361	C000-C809
(c) Unspecified malignant renal tumors	8000-8005	C649
VII Hepatic tumors		
(a) Hepatoblastoma	8970	C000-C809
(b) Hepatic carcinomas	8010-8041, 8050-8075, 8082, 8120-8122, 8140, 8141, 8143, 8155, 8190-8201, 8210, 8211, 8230, 8231, 8240, 8241, 8244-8246, 8260-8264, 8310, 8320, 8323, 8401, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8576	C220, C221
	8160-8180	C000-C809
(c) Unspecified malignant hepatic tumors	8000-8005	C220, C221
VIII Malignant bone tumors		
(a) Osteosarcomas	9180-9187, 9191-9195, 9200	C400-C419, C760-C768, C809

(b) Chondrosarcomas	9210, 9220, 9240	C400-C419, C760-C768, C809
	9221, 9230, 9241-9243	C000-C809
(c) Ewing tumor and related sarcomas of bone	9260	C400-C419, C760-C768, C809
	9363-9365	C400-C419
(d) Other specified malignant bone tumors	8810, 8811, 8823, 8830	C400-C419
	8812, 9250, 9261, 9262, 9270-9275, 9280-9282, 9290, 9300-9302, 9310-9312, 9320-9322, 9330, 9340-9342, 9370-9372	C000-C809
(e) Unspecified malignant bone tumors	8000-8005, 8800, 8801, 8803-8805	C400-C419
IX Soft tissue and other extraosseous sarcomas		
(a)Rhabdomyosarcomas	8900-8905, 8910, 8912, 8920, 8991	C000-C809
(b) Fibrosarcomas, peripheral nerve sheath tumors, and other fibrous neoplasms	8810, 8811, 8813-8815, 8821, 8823, 8834-8835	C000-C399, C440-C768, C809
	8820, 8822, 8824-8827, 9150, 9160, 9491, 9540-9571, 9580	C000-C809
(c) Kaposi sarcoma	9140	C000-C809
(d) Other specified soft tissue sarcomas	8587, 8710-8713, 8806, 8831-8833, 8836, 8840-8842, 8850-8858, 8860-8862, 8870, 8880, 8881, 8890-8898, 8921, 8982, 8990, 9040-9044, 9120-9125, 9130-9133, 9135, 9136, 9141, 9142, 9161, 9170-9175, 9231, 9251, 9252, 9373, 9581	C000-C809
	8830	C000-C399, C440-C768, C809
	8963	C000-C639, C659-C699, C739-C768, C809
	9180, 9210, 9220, 9240	C490-C499
	9260	C000-C399, C470-C759
	9364	C000-C399, C470-C639, C659-C699, C739-C768, C809
	9365	C000-C399, C470-C639, C659-C768, C809
(e) Unspecified soft tissue	8800-8805	C000-C399, C440-

sarcomas		C768, C809
X Germ cell tumors, trophoblastic tumors, and neoplasms of gonads		
(a) Intracranial and intraspinal germ cell tumors	9060-9065, 9070-9072, 9080-9085, 9100, 9101	C700-C729, C751-C753
(b) Malignant extracranial and extragonadal germ cell tumors	9060-9065, 9070-9072, 9080-9085, 9100-9105	C000-C559, C570-C619, C630-C699, C739-C750, C754-C768, C809
(c) Malignant gonadal germ cell tumors	9060-9065, 9070-9073, 9080-9085, 9090, 9091, 9100, 9101	C569, C620-C629
(d) Gonadal carcinomas	8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8143, 8190-8201, 8210, 8211, 8221-8241, 8244-8246, 8260-8263, 8290, 8310, 8313, 8320, 8323, 8380-8384, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8573, 9000, 9014, 9015	C569, C620-C629
	8441-8444, 8450, 8451, 8460-8473	C000-C809
(e) Other and unspecified malignant gonadal tumors	8590-8671	C000-C809
	8000-8005	C569, C620-C629
XI Other malignant epithelial neoplasms and malignant melanomas		
(a) Adrenocortical carcinomas	8370-8375	C000-C809
(b) Thyroid carcinomas	8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8190, 8200, 8201, 8211, 8230, 8231, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8510, 8560-8573	C739
	8330-8337, 8340-8347, 8350	C000-C809
(c) Nasopharyngeal carcinomas	8010-8041, 8050-8075, 8082, 8083, 8120-8122, 8130-8141, 8190, 8200, 8201, 8211, 8230, 8231, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8500-8576	C110-C119
(d) Malignant melanomas	8720-8780, 8790	C000-C809
(e) Skin carcinomas	8010-8041, 8050-8075, 8078, 8082, 8090-8110, 8140, 8143, 8147, 8190, 8200, 8240, 8246, 8247, 8260, 8310, 8320, 8323, 8390-8420, 8430, 8480, 8542, 8560, 8570-8573, 8940, 8941	C440-C449
(f) Other and unspecified	8010-8084, 8120-8157, 8190-8264,	C000-C109, C129-

carcinomas	8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030	C218, C239-C399, C480-C488, C500-C559, C570-C619, C630-C639, C659-C729, C750-C768, C809
XII Other and unspecified malignant neoplasms		
(a) Other specified malignant tumors	8930-8936, 8950, 8951, 8971-8981, 9050-9055, 9110	C000-C809
	9363	C000-C399, C470-C759
(b) Other unspecified malignant tumors	8000-8005	C000-C218, C239-C399, C420-C559, C570-C619, C630-C639, C659-C699, C739-C750, C754-C809

Appendix 2. Recent procedures of two regional general cancer registries.

In April 2007 I contacted staff at the Trent Cancer Registry and the Oxford Cancer Intelligence Unit to ask how they were currently processing registrations (for patients of all ages, not only children). The following description confirms and updates the information about cancer registration that was obtained from written sources (see Chapter 3). Abbreviations are included in the list given at the start of the thesis.

Trent Cancer Registry received most of its data electronically and automatically. The system had been place for 10-15 years. Death certificates mentioning cancer arrived from ONS in weekly batches, for deaths occurring 2-3 weeks previously. Computerised hospital episode information (PAS) and pathology data arrived from hospitals in monthly batches. Cancer cases were selected automatically via SNOMED coding, which was done by the coding department of the hospital. A death certificate was the first notification for about 40% of cases. These cases were flagged as 'death-certificate-only' (DCO). Routine PAS or pathology data was expected to arrive spontaneously (within 6 weeks of the death certificate) for some of them. In that case, the DCO flag was removed. After 6 weeks all remaining DCO cases were 'traced back' for information confirming the diagnosis, from the coding department of the hospital if they died in hospital, or from the GP if they died at home. If 'trace-back' was successful the DCO flag was removed. At the time of the interview, about 3% of all cases were not traced.

Oxford Cancer Intelligence Unit had been largely electronic since 1993. It received death certificates from ONS within a month of death, and monthly or quarterly batches of PAS, pathology and treatment data from the hospitals. These did not go on the database immediately, but in quarterly updates. A cancer was not formally registered until after the time that data from hospital sources would have arrived and been put on the system, if available, taking the date of the pathology report as the date of diagnosis. At this point, any cases notified only from the death certificate were permanently flagged as 'death-certificate-initiated' (DCI), and medical notes are requested from the GP. If the trace-back was successful the extra information was added to the record. If the trace-back was unsuccessful the case was flagged as DCO as well as DCI.

Presumably the date of death was used to represent the date of diagnosis for DCO cases in both regions. The Trent system was more automated than the Oxford Cancer Intelligence Unit system, and the Oxford system may have been more typical of cancer registries in general. Both systems appeared to date from approximately 1993, the year of change to mandatory registration.

Appendix 3. Stata commands for analysis reported in Chapter 5.

Time trend analysis for each diagnostic group, by year of birth and by year of diagnosis

Within each age group.

```
Model 1:  poisson ncases i.sex year, exp(pop)
Model 2:  poisson ncases i.sex i.sex*year, exp(pop)
```

Over all age groups.

```
Model 3:  poisson ncases i.age*i.sex year, exp(pop)
Model 4:  poisson ncases i.age*i.sex i.sex*year, exp(pop)
Model 5:  poisson ncases i.age*i.sex i.age*year, exp(pop)
```

Categorical factors: age (age group), sex (male or female)
Continuous factor: year (year of birth or year of diagnosis)
Dependent variable: ncases (number of cases)
Exposure variable: pop (person-years)

Geographical analysis for each of three broad diagnostic groups, over all age groups

Within each census decade (i.e.10-year period of diagnosis, centred on a census year).

```
Model 1:  poisson ncases i.age*i.sex i.reg*i.soc, exp(pop)
Model 2:  poisson ncases i.age*i.sex i.reg i.soc, exp(pop)
Model 3:  poisson ncases i.age*i.sex i.soc, exp(pop)
Model 4:  poisson ncases i.age*i.sex i.reg, exp(pop)
Model 5:  poisson ncases i.age*i.sex i.reg soc, exp(pop)
```

Categorical factors: age (age group), sex (male or female), reg (region), soc (SES)
Continuous factor: soc (SES category number treated as a continuous variable)
Dependent variable: ncases (number of cases)
Exposure variable: pop (person-years)

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