A Study of the Aetiology and Epidemiology of Cancers in Teenagers And Young Adults

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Contents

1. Abstract

A Study of the Aetiology and Epidemiology of Cancers in Teenagers And Young Adults

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Introduction

Little is known about the aetiology of cancer in teenagers and young adults (TYA) aged 15-24 years, although in England, cancer is the most common cause of disease-related mortality in this age group. The most common cancers at this age are lymphomas, central nervous system (CNS) tumours and germ cell tumours (GCT). The commonest carcinomas seen at older ages including lung, breast, large bowel and prostate account for only 3-4% of TYA cancers. In this thesis I describe the incidence patterns of selected cancers in TYA and the variation seen with geography, time and in population subgroups. The focus is on CNS tumours, GCT and bone tumours as they either peak in incidence in TYA and/or contribute disproportionately to cancer-related mortality in TYA. This will allow formulation of hypotheses regarding aetiology of cancer in this age group which can then be tested by further research.

Methods

For the majority of the analysis, anonymised national cancer registration data from England on individual patients of all ages with newly diagnosed cancer between 1979 and 2003 were used. To contrast the incidence patterns in England with that of India, data from five Indian urban population based cancer registries were used for part of the analysis. Age, sex, site and histology specific incidence rates were calculated and expressed per million person years. All rates, where appropriate, were adjusted to the world standard population using direct methods.

To explore the link of growth with development of osteosarcoma and Ewing sarcoma, a random-effects meta-analysis was undertaken on studies which investigated an association of these tumours with height at diagnosis.

Results

The incidence of cancer in TYA overall in England exceeded that of India. This was also true for most individual sites including epithelial cancers of lung, colon/rectum, breast, ovary and cervix, and non-epithelial cancers including melanoma, Hodgkin lymphoma and testicular cancer. Notable exceptions to this pattern were cancers of the mouth, gall bladder and stomach (females only) where incidence was higher in India.

In England, CNS tumours in TYA were a composite of pilocytic astrocytomas and embryonal tumours (representing tail end of childhood CNS tumours), pituitary tumours, nerve sheath tumours, high grade astrocytomas and meningiomas (representing early-onset of CNS tumours that peak in incidence in the 6^{th} and 7^{th} decade of life), and of CNS GCTs, pleomorphic xanthoastrocytomas and neurocytomas which show a peak incidence in TYA.

Irrespective of site or histology, GCT in England showed a peak in incidence between ages of 10 to 39 years which was more marked in males. This however varied by site and the peak incidence was seen at 10 to 14 years in the CNS, 15 to 19 years in ovary, 25 to 29 in mediastinum & thorax and abdomen & pelvis, and 30 to 34 years in testicular tumours.

Osteosarcoma and Ewing sarcoma were the predominant bone tumours in TYA in England and showed a distinct peak of incidence at 10 to 14 years age in females and a larger peak at 15 to 19 years age in males. The peak incidence of osteosarcoma of long bones of the lower limb was six times more than that at any other site while the peak incidence of Ewing sarcomas located in the bones of the central axis exceeded those in long bones of the lower limb. The average height of patients with osteosarcoma at diagnosis was found to be significantly above the average height of the reference population, at the 95% level. The association of greater height at diagnosis with Ewing sarcoma was also significant at the 95% level but much weaker.

Conclusion

In this thesis I have explored the epidemiology of cancer in TYA using some of the established methodologies which have previously been used in advancing our knowledge of childhood and older adult cancers. These studies provide some clues to aetiology. Variation in environmental exposures and lifestyle factors between England and India can explain the majority of the differences in incidence patterns observed. Genetic predisposition to cancer along with carcinogen exposure could lead to early onset of some cancers generally seen in older adults. Regardless of site, the similarity in age-incidence patterns of GCT, suggests a common initiation of these tumours in embryonic/foetal life with variable rates of tumour progression as a result of local factors or events during postnatal and pubertal period. The incidence patterns of osteosarcoma along with the strong and consistent association with a greater height at diagnosis indicate that bone growth is important in the development of this tumour while different biological pathways which may be unrelated to growth could also be relevant for Ewing sarcoma.

2. Declaration

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5. Introduction

5.1 Background

Cancer is one of the leading causes of death worldwide and in 2004 accounted for 7.4 million deaths (around 13% of all deaths) [1]. In England, each year nearly 250,000 people are newly diagnosed with cancer and 65% of these are in people aged 65 years and over [2]. Cancer in teenagers and young adults (TYA) aged 15 to 24 years constitutes a small fraction (<1%) of this overall cancer burden [3]. But, it is a major cause of mortality and morbidity in TYA. In England, cancer is the most common cause of disease-related death in TYA and second only to accidents as the overall cause of death [4]. The impact of late effects of treatment in this age group can be considerable, including loss of fertility, secondary malignancies and organ failure. In addition, at this critical period of life, disruption of educational, vocational and professional training can potentially have profound and long lasting effects on the future quality of life of patients [5].

What are Teenage and Young Adult (TYA) Cancers?

Biologically, adolescence begins with onset of puberty, at about 10 years in girls and 12 years in boys [6]. Adolescence ends and early adulthood begins with attainment of adult height and full reproductive maturity. However if physiological and psychobehavioural attributes are taken into account, attainment of early adulthood equates to about age 19 years in women and 21-25 years in men [7]. In practice, adolescence is a flexible concept that encompasses most young people. For the specific purpose of this report, TYA refers to individuals aged 15 to 24 years. However, where appropriate for specific tumours, variations to this definition will be used and clearly specified.

In 2002 Birch et al proposed a cancer classification scheme [8] which is largely morphology-based and has now become the accepted vehicle for cancer incidence studies in TYA [9]. The main groups of cancer types in TYA (Table I) are lymphomas, carcinomas, central nervous system (CNS) tumours, germ cell tumours (GCT), leukaemias, melanomas, bone tumours and soft tissue sarcomas [10]. In contrast to older age groups, carcinomas in TYA arise mainly in the thyroid and female genitourinary tract. Carcinomas of lung, breast, large bowel and prostate, which represent half of all cancers overall, account for only 3-4% of TYA cancers.

Table I - Incidence of cancers (rate per million person years at risk) in those aged 13 to 24 years in England, 1979–2001, by cancer group and sex from Alston et al 2007 [10]

	Male		**Female**		**All**	
	N	**Rate**	***N***	**Rate**	***N***	**Rate**
Leukaemia	2375	25.2	1560	17.1	3935	21.2
Lymphoma	4794	50.5	3704	40.0	8498	45.3
CNS tumours	2671	28.2	2373	25.9	5044	27.1
Bone tumours	1308	13.9	884	9.8	2192	11.9
Soft tissue sarcoma	930	9.8	774	8.4	1704	9.1
Germ cell tumour	4152	43.3	544	6.0	4696	24.8
Melanoma	967	10.1	1813	19.4	2780	14.7
Carcinoma	1658	17.4	4126	44.0	5784	30.6
Other Specified	200	2.1	235	2.6	435	2.3
Unspecified	95	1.0	128	1.4	223	1.2
Total	19150	201.5	16141	174.5	35291	188

Cancers in TYA with the highest mortality differ from those with the highest incidence. CNS tumours, lymphoid leukaemias and bone tumours are TYA cancers with the highest mortality rates. [4]. In England, the 5-year overall survival of cancers in TYA for the period 1996 to 2001 was 77% [11]. However the relative overrepresentation in TYA of cancers with higher survival (Hodgkin lymphoma, testicular GCT, melanoma and thyroid carcinoma) obscures a more grim reality. Detailed analysis reveals that current survival of leukaemias, CNS tumours, and bone and soft tissue sarcomas in TYA is worse than that of children with these groups of diseases [11,12] and worryingly there have been no sustained improvements in survival over time among TYA with high-grade brain tumours and bone and soft tissue sarcomas [11].

Aetiology of Cancers in TYAs

Much of our understanding of cancer causation has come from epidemiological approaches describing the patterns of cancer in human populations and identifying risk factors through case-control and cohort studies. Using these approaches, we now know much more about the exogenous and endogenous factors associated with causation of common cancers in adults [13,14]. 20% of cancers are associated with chronic infections (e.g. chronic hepatitis viruses, human papilloma viruses, human immunodeficiency virus and helicobacter pylori). Lung carcinoma is strongly associated with tobacco smoke. Breast carcinoma is linked to hormonal and reproductive factors but is also influenced by diet and lifestyle. Colorectal carcinoma is associated with a diet rich in fat, refined carbohydrates and animal protein and a lifestyle involving low physical activity. For most of these cancers, clinical onset follows a prolonged period of exposure.

As TYA with these cancers will not have had the same duration of diet and lifestyle-related exposures, other factors including genetic susceptibility may play a greater role in this age range than in older people [5]. There is some evidence that there may be a relatively greater proportion of high-penetrance mutations in some cases of early-onset carcinomas, although few systematic studies have addressed this issue [15,16]. Nevertheless, we know that the contribution of high-penetrance mutations in the causation of childhood cancer is 5-10% [17] and it is unlikely that their role would be greater in the causation of cancer in TYA. Low-penetrance cancer susceptibility cancer genes could also be relevant and this needs to be explored in the future. Polymorphisms in drug metabolism pathways like that involving the cytochrome p450 system have an established role in the causation of several adult-onset cancers [18].

An association of birth weight and childhood growth has been reported with several adult-onset cancers like breast [19,20] and prostate [21] as well as with childhood cancers [22-25]. The possible explanation for these associations are that growth is a biomarker for biological mediators of risk (like cellularity or growth promoting hormones) or alternatively is a biomarker for other exposures that influence cancer risk (like foetal nutrition, chronic infection, calorie intake or exposure to high levels of sex hormones) [26]. Growth spurt linked to puberty is a key physiological event in adolescence and this makes it a candidate for further investigation in the evolution of cancers in TYA, particularly those which peak in incidence in this age group like bone tumours and GCT.

5.2 Rationale and format of this thesis

There is clearly a need for better understanding of the occurrence and causation of tumours in TYA. This can be achieved in a variety of ways. In this thesis I explore the descriptive epidemiology and what that may imply for aetiology of cancer in TYA applying some of the established methodologies which have previously been used in advancing our knowledge of childhood and older adult cancers. My work focuses on selected cancers and uses data obtained from a variety of sources. The common theme running through the research is the relevance of these cancers in TYA. Because of this, my thesis lends well to being presented in the alternative format where the results are presented as a collection of papers. Each of these papers is of a journal manuscript length and is suitable for submission for publication.

My first paper looks at the variation in the incidence of cancer at all sites in those aged 15 to 29 years in England and contrasts this with the incidence patterns in India. Data for this study were obtained from five urban population-based cancer registries (PBCR) of India and from the eight regional PBCR in England. Geographic and ethnic variations in the incidence of adult cancer have enhanced our understanding of their causation [13,27]. For example, elucidation of the high incidence of liver cancer in Africa and Asia secondary to food contamination by aflatoxins, of bladder cancer in Egypt as a result of chronic cystitis from Schistosoma haematobium, and of oral cancer in South Asia from highly prevalent use of oral tobacco all stem from epidemiological observations. Similar examination of geographical variation in cancer incidence in TYA may provide important aetiological clues and stimulate further investigations. Such studies can give an indication of the extent to which environmental factors are implicated in the causation of each cancer type although part of the international difference in cancer risks may be genetic rather than environmental.

The next four papers in this thesis deal with detailed age-incidence patterns and longitudinal trends with a focus on three individual cancer groups: CNS tumours, GCT and bone tumours. These cancers have been selected based on their distinct incidence patterns and/or disproportionate contribution to cancer-related mortality in TYA. The variation of incidence patterns over time and in population subgroups will allow formulation of hypotheses that might explain the observed differences and which can then be tested by further research

The final paper in this thesis is a meta-analysis of the possible link of osteosarcoma and Ewing sarcoma risk with height at diagnosis. Some evidence exists that patients with osteosarcoma and Ewing sarcoma are taller than the general population [28-31]. However, these studies are under-powered and/or lack comprehensive data and there are inconsistencies. Meta-analysis is a commonly used statistical tool where the results from two or more separate studies are combined. This increases the chance of detecting a real effect as being statistically significant if it exists, as well as improving the estimation of an intervention effect. My objective was to do a comprehensive literature search to identify relevant studies in order to meta-analyse the strength of association between height at diagnosis and risk of developing the above tumours. This can then assist with developing areas for future research.

In addition to the work done above, I have also been actively involved in developing the protocol and associated study materials for a grant-funded project on bone tumours in children and young people. Prof Jillian Birch successfully secured funding to conduct a pilot study of osteosarcoma and Ewing sarcoma as the forerunner of a multi-centre international case-control study. The main objectives of the pilot study are to ascertain and recruit a population-based sample of patients diagnosed up to 24 years of age with osteosarcoma and Ewing sarcoma; interview families, collect DNA samples and abstract relevant medical records. The results of

the pilot will enable us to determine the feasibility of setting up the full international study of bone tumour aetiology. Cases of histologically confirmed osteosarcoma and Ewing sarcoma in persons aged 0-24 years diagnosed during a 2 year period, July 2009 to June 2011, resident in the North West and Yorkshire and the Humber Strategic Health Authority areas are currently being recruited. By the end of 2010, 12 patients had been recruited and another six have been approached.

My contribution to this has been in writing the initial draft of the ethics application using the online Integrated Research Application System (IRAS) forms. As part of this application, I was also involved in designing the protocol and drafting the patient and parent interview proformas, age-appropriate information leaflets and consent forms (see appendix) for use in this pilot interview-based study. In order to investigate the association between growth from birth to adulthood and development of these tumours, specific questions with regards to physical growth in childhood and adolescence, onset of puberty, and related sports and exercise activities were added to the proforma. I sought the advice of experts in paediatric and adolescent endocrinology to aid the construction of the proforma in addition to searching the literature. The questionnaires and other study materials will be evaluated when data collection is complete and I hope to contribute to data analysis, interpretation and development of the protocol for the future full study.

5.3. Cancer registration and population estimates

The core of the work carried out for this thesis is based on cancer registration data for England and India. In this section, I will describe the cancer registration systems in England and India. Calculation of incidence rates needs population denominators and I will also discuss how these are derived for each of the countries. Specific details about coding and classification of cancer, and statistical analysis are given in the methods sections of the individual papers.

Cancer Registration in England

The beginning of cancer registration in several parts of UK was in the 1920s with the main purpose of finding the outcome of patients treated with radium at that time. Gradually the objectives became broader, the coverage expanded and by 1962 there was complete geographic national coverage via a series of regional population-based cancer registries [32,33]. The coding and classification of individual cancer cases has followed international standards: International Classification of Diseases [34,35] and International Classification of Diseases for Oncology [36-38]. At the present time, there are 11 cancer registries in the UK. Cancer registration in England is conducted by eight regional registries (Figure 1), which submit a standard dataset of information to the Office for National Statistics (ONS), for the collation of national cancer incidence data. Northern Ireland, Scotland and Wales have national cancer registries.

Figure 1 Areas covered by the regional cancer registries, England 2007

The information for cancer registration is acquired from a variety of sources including hospitals, cancer centres, treatment centres, hospices, private hospitals, cancer screening programmes, other cancer registers, general practices, nursing homes, death certificates and Hospital Episode Statistics. There is a high degree of case ascertainment, and registry records are largely complete, accurate, and reliable with less than 0.1% of serious errors detected on regular completeness and validity checks [32]. The quality of registration is reflected by the high

percentages of histological verification of cancers (84.9% in England for the year 2009) and low proportion of registrations by death certificate alone (2.8% in England for the year 2009) [39].

A particular aspect of importance of cancer registration is the link with the National Health Service Central Register (NHSCR). Since 1971, as far as possible all registrations in England and Wales have been recorded ('flagged') on the NHSCR, a register of almost all of the population of England and Wales. This allows completeness of registration and eliminates duplication. The proportion of cancer registrations received by ONS that were successfully linked to an NHSCR record was on average about 96 per cent from 1971 up to 1989 and has been over 99 per cent for data for 1993 and subsequent years [40].

Population Estimates for England

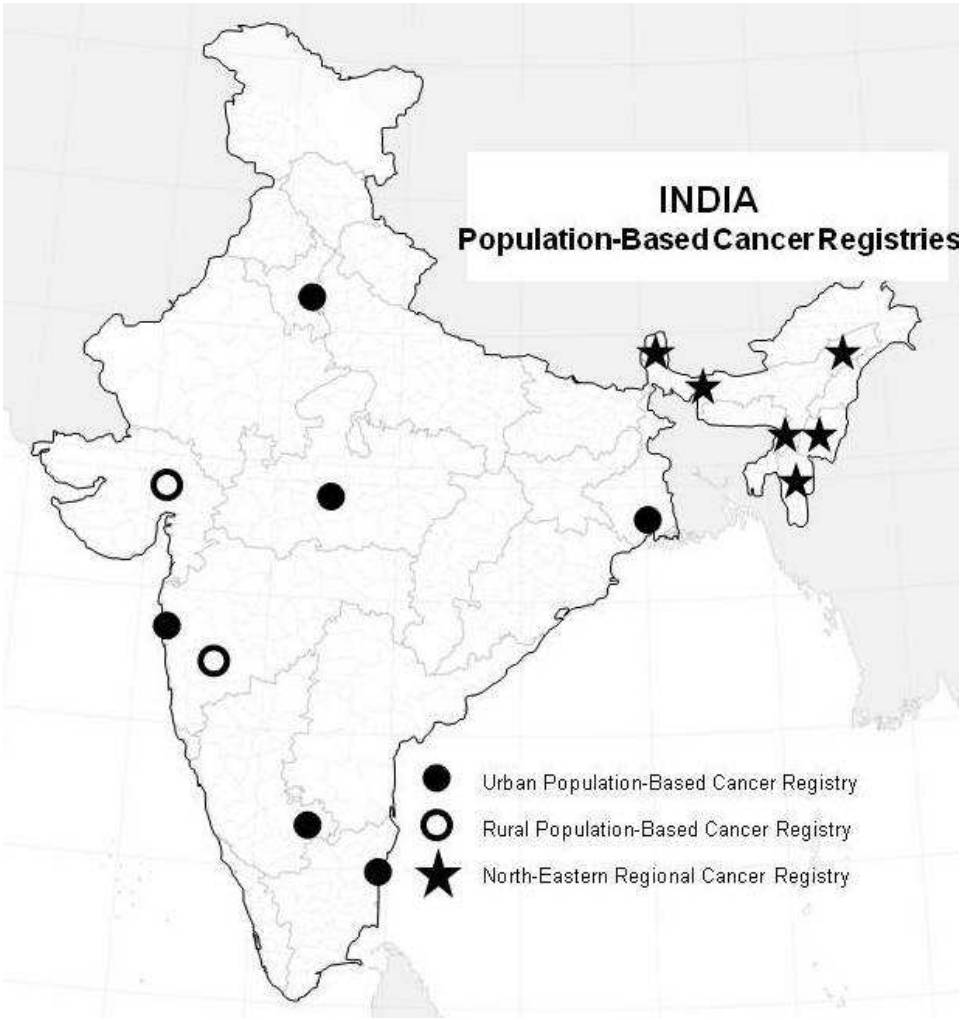
National population estimates by single year of age, sex and calendar year are supplied by the Population Estimates Unit, ONS. They are produced based on decennial census (conducted in England and Wales every ten years) data together with information on births, deaths and migration using a well established demographic approach called the cohort component method [41]. The compulsory registration of births and deaths with the General Register Office ensures that administrative records for these life events are accurate. International migration is estimated using survey data and internal migration is estimated using changes in administrative data as a proxy measure of movements of individuals between areas within the UK. Adjustments are made for changes to special population subgroups, including prisoners, school boarders, and the armed forces and their dependents. Extensive analysis is carried out to validate and quality assure the data and estimates at every stage of the process.

Cancer Registration in India

Information on cancer occurrence in India was available only from cross-sectional surveys until 1964, when the first PBCR was set up in Bombay (now Mumbai) [42]. The next major milestone was the initiation of the National Cancer Registry Programme by Indian Council of Medical Research in 1982 which included the existing Bombay PBCR and establishment of two new PBCR at Bangalore and Madras (now Chennai). Over the years several other urban PBCR (Bhopal & Delhi in 1987, and Kolkata in 2005) and two rural PBCR (Barshi in 1987 and Ahmedabad district in 2003) have been set up [43]. Additionally, a North Eastern Regional Cancer Registry has been initiated from 1 January 2003 in six areas at Guwahati, Dibrugarh and Silchar in Assam, Aizawl in Mizoram, Imphal in Manipur and Gangtok in Sikkim with a Monitoring Unit at Regional Medical Research Centre, Dibrugarh [44]. Together all these urban, rural and regional registries cover around 5% of the Indian population (with a predominantly urban skew) and less than 1% of the total geographical area [43,44]. A map of India depicting the locations of the various cancer registries in the National Cancer Registry Programme is shown in figure 2.

Cancer is not a notifiable disease in India and registration is active but voluntary. Staff of registries visit hospitals on a routine basis and scrutinise the records in various departments that include pathology, radiology, radiotherapy, in-patient wards and out-patient clinics to elicit the desired information on reported cancer cases using a common core proforma that has been standardised for all cancer registries in India [42,43]. Death certificates are also scrutinised from the municipal corporation units. Every attempt is made by registries to register all cancer patients in the registration area who are resident (at least for one year) in the area in all hospitals and copy all death certificates in which cancer is mentioned.

Figure 2 Location of Cancer registries in India which are part of the National Cancer Registry Programme



Coding of the disease is done according to International Classification of Diseases [34,35] and according to International Classification of Disease for Oncology [36-38]. Certain basic checks of data, especially those related to duplicate registrations verification and matching with mortality records, are carried out by the individual registries. After this, the data are sent to the Coordinating Unit in Bangalore for checks on variable specific value ranges, consistency and unlikely combinations together with a further round of possible duplicates. The Coordinating Unit collates the data and performs tabulations to prepare the consolidated report for that year.

The completeness and quality of registration is variable. Several of the above mentioned registries have been listed in the Cancer Incidence in Five Continents published by the International Agency for Research in Cancer [45]. An earlier survey had estimated completeness of population coverage previously to be 72% in Bangalore, 100% in Chennai and 78% in Mumbai [46]. In the Mumbai PBCR there has been progressive increase in percentages of histological verification for cancers, decrease in the proportion of registrations by death certificate alone as well as the proportion of cases registered to other and unspecified sites [47]. Similar data for other PBCR in India at present are not available.

Population Denominators in India

In India, population figures are based on census conducted every 10 years starting from the year 1951. The latest Census was conducted in the year 2001. The exponential growth rate method is in use to estimate the total population for the given year. The total population denominators for calculating the incidence rates are calculated in this way. The same method is used to estimate population by five-year age groups according to sex. Recently, this approach has been shown to suffer from bias and often corrections become necessary in five yearly age group populations [48].

5.4. Summary of studies included in this thesis

A summary of the individual studies which form part of this thesis is displayed in Table II. In all these studies I have been the lead investigator with support from various colleagues. My role and their contributions are detailed in Table III.

Table II – Summary of individual studies presented in this thesis

Title of Paper	Type of Study	Cancer	Source of Data	Time Period
Cancer at ages 15–29 years: The contrasting incidence in India and England	Geographical comparison of incidence patterns	All Cancers	Cancer registration data from England and India	2001 to 2003
Age-incidence patterns of primary CNS tumours in children, adolescents, and adults in England	Analyses of incidence by age groups 0-14, 15-24 & 25-84 years	CNS Tumours	Individual patient level cancer registration data from England	1995 to 2003
Are reported increases in incidence of primary CNS tumours real? An analysis of longitudinal trends in England, 1979-2003	Longitudinal trends by age groups 0-14, 15-24, 25-64 & 65-84 years	CNS Tumours	Individual patient level cancer registration data from England	1979 to 2003
Comparative incidence patterns and trends of gonadal and extragonadal germ cell tumours in England, 1979 to 2003	Analysis of incidence and longitudinal trends by age groups 0-9, 10-49 & 50-84 years	Germ Cell Tumours	Individual patient level cancer registration data from England	1979 to 2003
The contrasting age-incidence patterns of bone tumours in teenagers and young adults: Implications for aetiology	Age-specific incidence patterns and longitudinal trends	Osteosarcoma, Ewing sarcoma, Chondrosarcoma	Individual patient level cancer registration data from England	1979 to 2003
Relationship between height at diagnosis and bone tumours in young people: A meta-analysis	Meta-analysis of results from previously published reports	Osteosarcoma, Ewing sarcoma	Pubmed	1950 to 2010

Table III – Details of my contribution and that of my co-authors in the individual studies presented in this thesis

Title of Paper	My Role	Assistance of Others
Cancer at ages 15–29 years: The contrasting incidence in India and England	Conceived and designed the study Data analysis Data interpretation & writing of manuscript	Advice on data analysis – JMB, RDA Comments on draft of manuscript – JMB, MG, RDA, TOE
Age-incidence patterns of primary CNS tumours in children, adolescents, and adults in England	Conceived and designed the study Data analysis Data interpretation & writing of manuscript	Advice on data analysis – JMB, RDA Comments on draft of manuscript – AM, EJE, JMB, MG, RDA, TOE
Are reported increases in incidence of primary CNS tumours real? An analysis of longitudinal trends in England, 1979-2003	Conceived and designed the study Data analysis Data interpretation & writing of manuscript	Advice on data analysis – JMB, RDA Comments on draft of manuscript – AM, EJE, JMB, MG, RDA, TOE
Comparative incidence patterns and trends of gonadal and extragonadal germ cell tumours in England, 1979 to 2003	Conceived and designed the study Data analysis Data interpretation & writing of manuscript	Advice on data analysis – JMB, RDA Comments on draft of manuscript – JMB, MG, RDA, TOE
The contrasting age-incidence patterns of bone tumours in teenagers and young adults: Implications for aetiology	Conceived and designed the study Data analysis Data interpretation & writing of manuscript	Advice on data analysis – JMB, RDA Comments on draft of manuscript – JMB, RDA, TOE
Relationship between height at diagnosis and bone tumours in young people: A meta-analysis	Conceived and designed the study Data analysis Data interpretation & writing of manuscript	Data Analysis – EK Advice on data analysis – JMB, MG, RDA Comments on draft of manuscript – EK, JMB, MG, RDA

AM – Anthony Moran, EJE – Edward J Estlin, EK – Evangelos Kontopantelis, JMB – Jillian M Birch, MG – Marco Geraci, RDA – Robert D Alston, TOE – Tim O Eden

6. Results

6.1 Cancer at ages 15 to 29 years: The contrasting incidence in India and England

Arora RS, Alston RD, Eden TO, Moran A, Geraci M, O'Hara C, Birch JM

Pediatric Blood Cancer (in press)

Cancer at Ages 15–29 Years: The Contrasting Incidence in India and England

Ramandeep S. Arora, MRCPCH,[1]* Robert D. Alston, PhD,[1] Tim O.B. Eden, FRCP,[2] Anthony Moran, FFPH,[3] Marco Geraci, PhD,[1] Catherine O'Hara, PhD,[3] and Jillian M. Birch, PhD[1]

Background. There has been a steady increase in published research from Europe and North America on the epidemiology of cancers in young people. There are limited data from the developing world. We contrast the incidence of cancer at ages 15–29 years in India and England. ***Procedure.*** Malignant neoplasms in those aged 15–29 years registered during 2001–2003 in five urban population-based cancer registries (PBCRs) of India and in eight PBCRs in England were included. Site-based classification was used. Age-standardized incidence rates were expressed per 100,000 person years. ***Results.*** In India, 4,864 (5.8%) of 84,450 cases and in England, 8,137 (1.2%) of 65,6752 cancer cases occurred in those aged 15–29 years. For this age group, the incidence rate for males and females in India were 12.91 and 14.19, and in England were 27.75 and 28.88, respectively. In males aged 15–29 years, the three most common cancers in India were leukemia, lymphoma, and central nervous system tumors and in England were cancers of male genital organs, lymphoma, and leukemia. Cancers of female genital organs, breast, and leukemia were most common in females in India and cancers of female genital organs, lymphoma, and melanoma in England. For cancers of mouth, stomach, and gall bladder, the incidence was higher in India. ***Conclusion.*** Incidence of cancer at ages 15–29 years in England is higher at most sites than in India. Variation in environmental exposures between the two countries might be an explanation. Under-ascertainment of cases and gender bias in seeking healthcare may also influence reported incidence rates in India. Pediatr Blood Cancer. © 2010 Wiley-Liss, Inc.

Key words: adolescents; cancer incidence; developing world; England; young Adults; India

INTRODUCTION

In 2002, Birch et al. [1], defined the incidence of cancers in people 15–24 years of age in England using a morphology-based classification scheme. Subsequently, other countries in Europe have done similar analyses for their local populations using the same classification scheme [2,3]. Incidence data in this age group have also been published from USA although a site-based classification was used [4]. As a result of these studies from Europe and North America, our understanding of the cancers which occur in teenagers and young adults (TYA) has improved. However, there are little or no data on cancers in this age group from the developing world. Based on a single recent review with a more limited age range, the incidence of cancer in adolescents aged 15–19 years was reported to range from 9.5 to 25.5 per 100,000 person years across the world [5]. The highest incidence rates were reported from Australia and among Jews in Israel with the lowest in India and Japan.

We present here incidence rates of cancer among males and females aged 15–29 years (henceforth, referred as TYA) in India and contrast this with the rates for the same age range in England. Studying variations in cancer incidence in these age groups in different populations and geographical areas is likely to be informative as the relative exposures to potential environmental risk factors will be different.

METHODS

Data were obtained for the period 2001 to 2003 in the five urban population-based cancer registries (PBCR) of India (Bangalore, Bhopal, Chennai, Delhi, and Mumbai, shown in Figure 1, which cover 3.7% of the population of India and equate to 36 million person years) and eight regional registries in England (which cover the entire population and equate to 28 million person years) [6,7]. All primary neoplasms of malignant behavior, except non-melanoma skin cancer, registered for individuals 15–29 years of age were included. Cancer registration in India is active and data are collected from relevant hospital departments, pathology laboratories, and death certificates from the municipal corporation units. Reliability of data and quality of registration are constantly monitored by re-abstraction and coding on a random sample of cases. Checks related to duplicate verification and matching with mortality records are also carried out by the individual registries. After this, data are sent to the Coordinating Unit at Bangalore where various range, consistency, and unlikely combination checks are carried out [6]. Completeness of population coverage by the registries does vary and has been estimated to be 72% in Bangalore, 100% in Chennai, and 78% in Mumbai [8].

Cancer registration in England is carried out by a network of eight population-based regional registries. Registration is coordinated by the Office for National Statistics in London, which maintains the national cancer registry covering all age groups. There is a high degree of case ascertainment and reviews have shown that registry records are largely complete, accurate, and reliable [9]. National population estimates by single year of age, gender, and calendar year are supplied by the Population Estimates Unit, Office for National Statistics. Annual mid-year estimates of population in England, based on census data together with information on births, deaths, and migration are very accurate on a national basis [9].

As available data in India were coded by site and not morphology, tumors in both countries were categorized based on International Classification of Diseases site codes [7]. Incidence rates were expressed per 100,000 person years and where appropriate, rates

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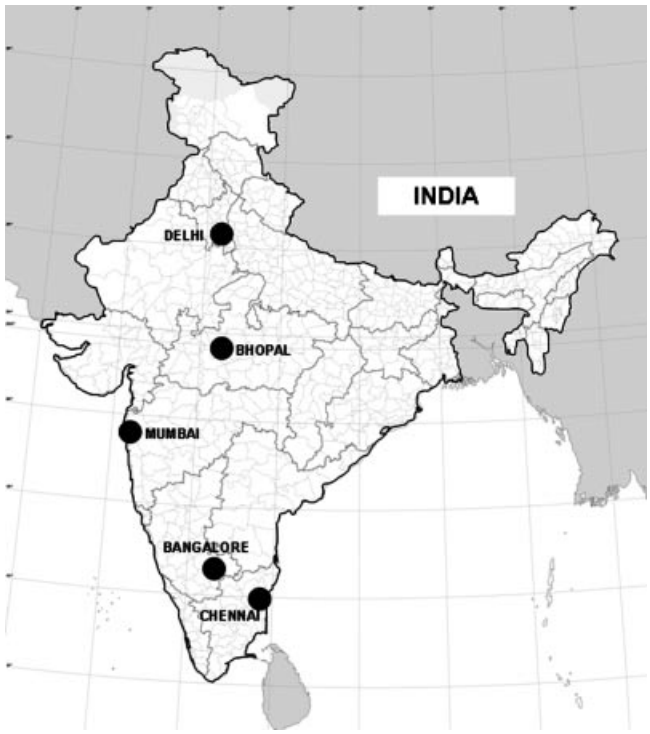

Fig. 1. Location of urban population-based cancer registries in India.

were adjusted to the world standard population using direct methods. *P*-values for variability in cancer-specific incidence rates by country for both males and females were calculated. R and Microsoft Excel were used for analyzing the data and producing tables and graphs.

RESULTS

During the period 2001–2003, 4,864 of the 84,450 overall cancer cases (5.8%) registered in the five urban cancer registries in India occurred in those aged 15–29 years (TYA). Two thousand five hundred fifty-nine were male (52.6%) and 2305 were female and the overall age-standardized incidence rates were 12.91 and 14.19 per 100,000 person years, respectively. Correspondingly, 8,137 of the 656,752 cases (1.2%) registered in England occurred in TYA. There were 3,992 males (49.1%) and 4,145 females and the overall age-standardized incidence rates were 27.75 and 28.88 per 100,000 person years, respectively. Further analysis by 5-year age groups showed that incidence rates in both sexes in both countries increased with age with the incline of slope steeper in females (Fig. 2). The result was that while for ages 15–19 years the incidence was higher in males, this pattern reversed and the incidence for those aged 25–29 years was higher in females.

Age-adjusted cancer incidence rates for all major sites and selected sub-sites are shown in Tables I and II. The three most common cancers in India in TYA males were leukemia, lymphoma, and central nervous system (CNS) tumors and in females cancers of the female genital organs, breast, and leukemia. In contrast, the three most common cancers in England in TYA males were those of the male genital organs, lymphoma, and leukemia and in females were cancers of the female genital organs, lymphoma, and melanoma. The incidence of melanoma in males in England was 61 times higher than the incidence in India and in females was 188 times higher. Similarly, the incidence of testicular cancer was 14 times higher and of cancer of the cervix uteri 6 times higher in England. Cancer at all sites generally, had a significantly higher incidence in England. Notable exceptions to this pattern were cancer of the mouth (in males), stomach (in females), gall bladder (in males and females) and bone (in males) which had higher rates in India.

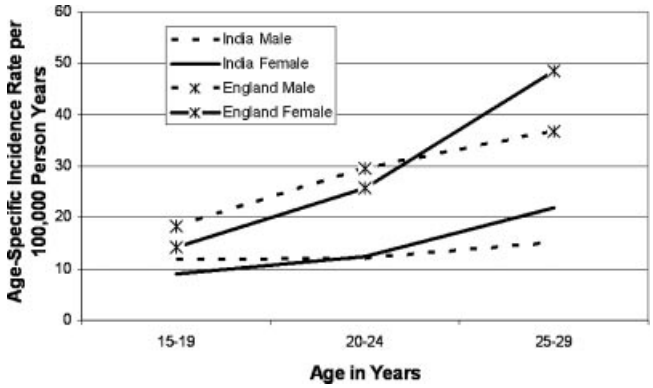

Fig. 2. Age- and sex-specific cancer incidence rates in those aged 15–29 years in England and India, 2001–2003.

DISCUSSION

In this paper, we have contrasted the incidence of cancers in India and England in TYA. Our analysis shows that the incidence of cancer at these ages in England is around double that in India and the gap between the reported incidence rates in the two countries appears to increase with age. Similar patterns are observed when we contrast the incidence rates from India to published data from USA and other European countries [2–4]. The observed difference in incidence may be real but when interpreting these observations, one needs to consider a number of factors including under ascertainment of cases and gender bias in seeking health care which may influence reported incidence rates in India [8,10]. In addition, while data from England are national with high levels of ascertainment and completeness [9], the data from the Indian registries cover only 3.7% of the total Indian population. However, these registries are distributed across India and cover 42 million persons, 12.5% of the urban population. In this latter respect the population covered is more comparable to the English population since England is a densely populated industrialized nation. In terms of ethnic and religious sub-groups the populations covered can be considered as representative of India as a whole [6]. It is noteworthy that cancer in TYA as a proportion of cancer at all ages is five times higher in India than England despite the actual incidence being lower in India. This possibly reflects the higher percentage of young people in the population pyramid (31% of the population in India are TYA compared to only 19% in England).

Certain epithelial cancers which typically occur in older adults (lung, colorectal, breast, and ovarian cancer) have a higher incidence in the developed world which is well-recognized. This is explained by the prevalence of tobacco smoking and other western lifestyle-related exposures (high-caloric diet, low physical activity), together with differences in reproductive history (early menarche, late or no pregnancy) [11,12]. Our analysis shows that the incidence of lung, breast, colorectal, and ovarian cancer in TYA is higher in England than in India. TYA with these cancers will not have had the decades

TABLE I. Site-Specific Cancer Incidence Rates (Expressed Per 100,000 Person Years) and Male to Female Incidence Ratio in Those Aged 15–29 Years in England and India, 2001–2003

	India			England		
	Number	Incidence	Male:female	Number	Incidence	Male:female
All sites	4,864	13.51	0.9	8,137	28.33	1.0
Lip, oral cavity, pharynx	309	0.85	1.7	146	0.51	1.0
Tongue	51	0.14	2.0	37	0.13	1.1
Mouth	74	0.20	1.9	23	0.08	0.7
Salivary gland	71	0.20	1.1	41	0.14	0.8
Nasopharynx	58	0.17	2.6	38	0.14	1.7
Other	55	0.15	1.5	7	0.02	1.3
Digestive organs	490	1.33	1.0	352	1.22	1.0
Stomach	78	0.21	0.9	36	0.12	1.4
Colorectum	225	0.61	1.0	224	0.78	1.0
Liver	54	0.15	1.8	44	0.16	0.9
Gall bladder	44	0.12	0.7	6	0.02	3.0
Other	89	0.24	0.8	42	0.16	0.9
Respiratory and intrathoracic Organs	107	0.29	1.7	117	0.41	1.3
Lung	51	0.14	2.0	70	0.24	0.8
Other	56	0.15	1.5	47	0.16	2.3
Bone and articular cartilage	382	1.10	1.7	245	0.89	1.5
Melanoma	11	0.03	2.0	1003	3.44	0.5
Mesothelial and soft tissue	225	0.63	1.3	229	0.81	1.2
Mesothelioma	2	0.01		2	0.01	
Kaposi's sarcoma	0	0.00		21	0.07	1.3
Connective and soft tissue	223	0.62	1.3	206	0.73	1.1
Breast	347	0.02	0.0	398	1.34	0.0
Female genital organs	422	2.59		991	6.81	0.0
Cervix uteri	108	0.64	0.0	604	4.09	0.0
Ovary	257	1.60	0.0	328	2.32	0.0
Other	57	0.34	0.0	59	0.40	0.0
Male genital organs	142	0.70		1271	8.74	
Testis	126	0.63		1262	8.67	
Other	16	0.08		9	0.07	
Urinary tract	76	0.21	1.0	93	0.32	1.3
Eye	15	0.04	3.0	28	0.10	1.4
Central nervous system	491	1.53	1.3	562	1.98	1.3
Thyroid and other endocrine	292	0.80	0.2	403	1.39	0.3
Thyroid	279	0.76	0.2	391	1.35	0.3
Other	13	0.04	0.8	12	0.04	0.3
Lymphoma	633	1.77	1.8	1562	5.52	1.3
Hodgkin's lymphoma	255	0.72	1.7	982	3.48	1.2
Non-Hodgkin's Lymphoma	378	1.05	1.9	580	2.03	1.6
Leukemia	777	2.19	1.6	585	2.09	1.4
Lymphoid leukemia	250	0.72	1.7	232	0.85	1.7
Myeloid leukemia	421	1.18	1.3	338	1.19	1.2
Other	106	0.29	2.7	15	0.05	2.7
Other and unspecified	145	0.41	1.0	152	0.53	1.7

of tobacco, diet, reproductive, and other lifestyle exposures experienced by older adults. Genetic susceptibility may play a greater role in this age range [13]. In Britain, a relatively high proportion of predisposing mutations in BRCA1, BRCA2, and TP53 have been found in a series of breast cancer patients diagnosed at age 30 years or under [14], and of mismatch repair genes MSH2 and MLH1 in colorectal cancer patients aged less than 30 years [15]. The relative frequency of these high-penetrance mutations reported in Indian patients with these cancers is similar [16,17].

Although variation in low-penetrance cancer susceptibility genes could also play a role and needs to be explored in future studies, our observations imply that the differences seen in the incidence of these cancers in TYA in India and England are more likely to be the result of differences in lifestyle-related factors. This is supported by studies of cancer incidence among populations of South Asian extract in England. Less than 4% of the UK population is of Asian extraction (1.8% Indian, 1.3% Pakistani, 0.5% Bangladeshi, and 0.4% other Asian). Analyses of cancer incidence among South Asians resident in England have shown that whereas overall rates for all cancers among all ages combined were lower in South Asians than non-South Asians these rates were higher than in the Indian sub-continents [18]. Furthermore, English South Asian rates for 0- to 29-year olds were similar or higher than non-South Asian rates [19]. A more recent study analyzed cancer incidence trends in the

TABLE II. Site- and Sex-Specific Cancer Incidence Rates (Expressed Per 100,000 Person Years) in Those Aged 15–29 Years in England and India, 2001–2003

	Male			Female		
	India	England	*P*-value	India	England	*P*-value
All sites	12.91	27.75	<0.0001	14.19	28.88	<0.0001
Lip, oral cavity, pharynx	1.04	0.52	<0.0001	0.62	0.50	0.15
Tongue	0.18	0.13	0.22	0.09	0.12	0.28
Mouth	0.26	0.06	<0.0001	0.14	0.09	0.27
Salivary gland	0.20	0.12	0.1	0.19	0.16	0.54
Nasopharynx	0.23	0.17	0.28	0.09	0.10	0.73
Other	0.18	0.03	<0.0001	0.12	0.02	0.0002
Digestive organs	1.31	1.22	0.45	1.34	1.22	0.25
Stomach	0.20	0.14	0.19	0.22	0.10	0.01
Colorectum	0.61	0.77	0.07	0.61	0.79	0.07
Liver	0.18	0.15	0.44	0.10	0.16	0.22
Gall bladder	0.10	0.03	0.005	0.14	0.01	<0.0001
Other	0.21	0.16	0.07	0.28	0.17	0.06
Respiratory and intrathoracic organs	0.36	0.46	0.25	0.21	0.36	0.02
Lung	0.18	0.21	0.45	0.09	0.27	0.0001
Other	0.18	0.25	0.21	0.12	0.11	0.31
Bone and articular cartilage	1.35	1.07	0.02	0.78	0.70	0.44
Melanoma	0.04	2.22	<0.0001	0.02	4.67	<0.0001
Mesothelial and soft tissue	0.71	0.87	0.09	0.53	0.75	0.02
Mesothelioma	0.01	0.01	0.75	0.00	0.00	—
Kaposi's sarcoma	0.00	0.08	<0.0001	0.00	0.06	0.0002
Connective and soft tissue	0.70	0.77	0.43	0.53	0.69	0.09
Breast	0.03	0.02	0.62	2.04	2.66	0.0003
Female genital organs				2.59	6.81	<0.0001
Cervix uteri				0.64	4.09	<0.0001
Ovary				1.60	2.32	<0.0001
Other				0.34	0.40	0.37
Male genital organs	0.70	8.74	<0.0001			
Testis	0.63	8.67	<0.0001			
Other	0.08	0.07	0.54			
Urinary tract	0.20	0.35	0.01	0.21	0.28	0.21
Eye	0.06	0.11	0.07	0.02	0.08	0.02
Central nervous system	1.53	2.25	<0.0001	1.17	1.71	<0.0001
Thyroid and other endocrine	0.33	0.63	<0.0001	1.38	2.17	<0.0001
Thyroid	0.29	0.61	<0.0001	1.34	2.11	<0.0001
Other	0.03	0.02	0.72	0.04	0.06	0.45
Lymphoma	2.22	6.21	<0.0001	1.21	4.81	<0.0001
Hodgkin's lymphoma	0.89	3.72	<0.0001	0.51	3.23	<0.0001
Non-Hodgkin's lymphoma	1.33	2.49	<0.0001	0.69	1.58	<0.0001
Leukemia	2.62	2.42	0.22	1.65	1.76	0.44
Lymphoid leukemia	0.88	1.06	0.12	0.52	0.62	0.19
Myeloid leukemia	1.33	1.28	0.72	0.99	1.11	0.29
Other	0.41	0.08	<0.0001	0.15	0.03	0.0002
Other and unspecified	0.40	0.66	0.001	0.41	0.40	0.93

city of Leicester, in the East Midlands region of England, where 22% of residents are of South Asian extract [20]. Overall cancer rates were lower in South Asians than in non-South Asians but younger South Asians were at somewhat increased risk compared with non-South Asians. Furthermore, across all ages incidence increased over time in South Asians but decreased in non-South Asians. This was accounted for by increases in lung and prostate cancer in men and colorectal and breast cancer in women. The pattern of cancers in South Asians was therefore becoming more like that in non-South Asians. These changes are consistent with the adoption of Western life-style among the South Asian community in England.

Differences in lifestyle can also explain the variation seen in the incidence of oral cancer in TYA in India and England. Chewing tobacco is a major causative factor responsible for Indians having among the highest rates of oral cancer in the world [11]. Tobacco consumption (predominantly in the oral form) begins in childhood in India and is more prevalent in males [21]. It is mistakenly believed to be good for the teeth and indeed to have medicinal properties [21]. Despite legislation prohibiting the use of tobacco as an ingredient in dental products, the practice continues [22].

In contrast to the above cancers, where the incidence is either higher in both younger and older adults in England (colorectal,

lung, breast, and ovarian cancer) or in younger and older adults in India (oral cancer), the incidence of cervical cancer is higher in TYA females in England (Table I), while it is much higher in older females in India [11]. This paradox probably reflects differences in sexual behavior and screening practices in the two countries. Since the introduction of national cervical screening programme in England the overall incidence of cervical cancer has halved [23]. The incidence is much higher in developing countries like India where no national screening programmes exist. As cervical screening in England starts at 25 years of age, there may be an artefactual higher incidence of cervical cancers in those aged 25–29 years of age compared with India, where cancers are only diagnosed when symptomatic. Although cervical cancer screening in India is not national policy and no organized screening programmes exist, trials of simple, and inexpensive screening methodologies have been conducted to assess their suitability and effectiveness in a low-resource setting. Two such trials were carried out in Kerala, in Southern India, and Osmanabad in Central India, respectively [24,25]. These trial areas do not overlap with those covered by the five urban cancer registries and will therefore have had no impact on cervical cancer incidence rates presented here. A third trial was conducted in Mumbai but included only women aged 35–64 years [26]. The interim results of these trials are promising and it is to be hoped that future introduction of more widespread screening programmes will have an impact on incidence and mortality.

The other cancers with significantly higher incidence in TYA in India are stomach cancer (females only) and gall bladder cancer. The higher incidence of stomach cancer in TYA females in India is unexpected. Despite a high prevalence of helicobacter pylori infection, reported stomach cancer rates in India are among the lowest in the world [27]. Within India, the overall incidence of gastric cancer is reported to be four times higher in Southern India compared with Northern India [28]. In our analysis, stomach cancer incidence in TYA in Bangalore (0.36 per 100,000 person years) and Chennai (0.32 per 100,000 person years) is twice that of other parts of India (Bhopal 0.15, Delhi 0.18, and Mumbai 0.13 per 100,000 person years). Higher intake of spicy food in Southern India is hypothesized to be associated [29,30], although there have been no epidemiological studies to verify this. Gall bladder cancer rates in North and Central India are among the highest in the world and long-standing cholelithiasis is a reported major risk factor [31]. Compared to England, gall stone disease in India starts at a younger age, has a higher prevalence and patients have a much longer median duration of symptoms at presentation [31].

Several non-epithelial cancers (melanoma, Hodgkin lymphoma, and CNS tumors) have higher incidence in England in TYA, and while in some cases a biological/behavioral explanation exists or is plausible, for others there is no clear explanation at present. The incidence of melanoma worldwide is related to sun exposure, although this association is complex. Chronic, continuous sun exposure seen in tropical countries like India is inversely associated with risk of melanoma [32] and increased melanin in dark-skinned individuals acts as a natural sun-protection factor [33]. On the other hand, intermittent sun exposure, which is seen at higher latitudes like England, and where frequency of fair-skinned people is greater, is positively associated with the risk of melanoma. In addition, sharp increases in the incidence of melanoma have been seen in TYA in England [34] which may be attributed to changing behaviors (increased travel and sunbathing, and use of sunbeds) which are more prevalent in young people [35–37].

Hodgkin lymphoma has a classical bimodal age distribution in developed countries [38]. The first incidence peak of Hodgkin lymphoma (mainly nodular sclerosis type) is seen in TYA and then again in the 8th decade of life. In contrast, in the developing world the first peak of Hodgkin lymphoma, mainly mixed cellularity type associated with Epstein–Barr virus, is more common in childhood. Delayed exposure to childhood infections and maturation of cell immunity as a result of less overcrowding in the developed world are the proposed explanations behind these observations [39].

An increase in the incidence of CNS tumors seen mainly in young people and the elderly has been observed all over the Western world in the 1970s–1990s. Much of the increase in incidence in the USA has been attributed to advances in neuroimaging, neurosurgery, and neuropathology, and to changes in registration practice [40–42]. Availability and use of similar resources are likely to be less widespread in India due to the cost and expertise needed and this may account for lower CNS cancer incidence rates. Additional evidence comes from the observation that the incidence of CNS tumors in England among children, TYA and older adults of South Asian and non-South Asian origin is not significantly different [18,19].

In conclusion, the incidence of cancer in TYA in England is generally higher at most sites compared with India. Notable exceptions to this pattern are cancer of the mouth, stomach, and gall bladder. Variation in environmental exposures between the two countries might explain the majority of the observations. Under ascertainment of cases and gender bias in seeking health care might also influence reported incidence rates in India. These patterns help us to identify cancers with a known etiology which are potentially avoidable. Societal initiatives including education and legislation leading to modification of behavior at the individual level should be able to help reduce the incidence of cancers of the oral cavity in India and cervical carcinoma and melanoma in England in TYA.

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6.2 Age-incidence patterns of primary CNS tumours in children, adolescents, and adults in England

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Age–incidence patterns of primary CNS tumors in children, adolescents, and adults in England

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Around 25% of all tumors in those 0–14 years of age and 9% in those 15–24 years of age involve the CNS. They are the most common cause of cancer-related deaths in both age groups. In adults 25–84 years of age, the proportion of CNS tumors is 2%; 5-year overall survival is 10%–15%; and survivors have considerable morbidity. Comprehensive up-to-date population-based incidence data on these tumors are lacking. We present incidence rates for primary CNS tumors based on data derived from the high-quality national cancer registration system in England. A total of 54,336 CNS tumors of malignant, benign, and uncertain behavior were registered across the whole of England from 1995 through 2003. The age-standardized rates for all ages (0–84 years) was 9.21 per 100,000 person-years. This is higher than previously reported for England because it includes nonmalignant CNS tumors and hence gives a more accurate picture of burden of disease. The age-standardized rates for those 0–14 years of age, 15–24 years of age, and 25–84 years of age were 3.56, 3.26, and 14.57 per 100,000 person-years, respectively. In this article, we describe the changing patterns in the epidemiology of primary CNS tumors in these three age groups with respect to sex, tumor behavior, and histology using the current WHO classification. This information will provide a reference for future studies nationally and internationally and make comparisons relevant and meaningful. *Neuro-Oncology 11, 403–413, 2009 (Posted to Neuro-Oncology [serial online], Doc. D08-00192, November 24, 2008. URL http://neuro-oncology.dukejournals.org; DOI: 10.1215/15228517-2008-097)*

Keywords: cancer registry, central nervous system, England, epidemiology, tumor incidence

Previous data from regional registries show that, overall, 1.5%–1.9% of all cancers registered in England are tumors of the CNS, including brain and spinal cord tumors.[1] Although CNS tumors are predominantly a disease of old age, the proportion of CNS tumors among all cancers falls significantly with increasing age. CNS tumors represent 24.5% of all tumors in those 0–14 years of age[2] and 8.9% in those 15–24 years of age.[3] Their importance as a health problem in young people is further highlighted by the fact that CNS tumors are the most common cause of cancer-related deaths in both the 0- to 14-year age group[2] and the 15- to 24-year age group.[4] Even histologically benign tumors can be life-threatening because of their space-occupying effects within the cranium, local infiltration, and for some, a tendency to undergo malignant transformation over time.[5] There is also significant morbidity both from the disease and from the treatment required, with varying degrees of physical, cognitive, neurological, endocrino-

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logical, and other deficits in survivors resulting in significant handicap and diminished quality of life.[6]

Establishing accurate incidence rates for these tumors is a challenge not only because they are a very heterogeneous group with more than 100 distinct pathological entities, but also because of variations in registration practice, changes in classification, and improvements in neurodiagnostic techniques over time. Previously, in Britain, studies by morphological type have been based on regional registry data only or cases ascertained from hospitals.[7] There have been no national studies describing the epidemiology of CNS tumors in detail in adolescents and adults. Studies from Norway[8] and Japan[9] analyzed national data sets across all ages, but the diagnostic classifications used were historical and differed (1979 and 1993 WHO CNS tumor classification[10,11] in the study from Norway and the 1945 International Union against Cancer classification[12] in the study from Japan), which does not permit easy comparison. Similarly, the Automated Childhood Cancer Information System (ACCIS) has reported Europe-wide CNS tumor incidence data in children and has used the International Classification of Childhood Cancer (ICCC),[13] which is morphology based but is not suited to older ages. The Central Brain Tumor Registry of the United States (CBTRUS) has published incidence rates from 1998–2002[14] based on the 2000 WHO CNS tumor classification,[15] but these are from 18 state cancer registries and cover only 32% of the U.S. population. There is also huge variability in the reporting of tumors among U.S. states, with the percentage of nonmalignant tumors varying from 27% to 60% of overall CNS tumors. Also, because data are collected from each registry without a unique identifier, there is the possibility of duplicate registration.

Cancer registration is conducted by eight regional cancer registries in England, and the essential features of the system of registration have remained unchanged for more than 30 years.[16] England has a high degree of case ascertainment, and reviews have shown that registry records are largely complete, accurate, and reliable.[16] Notification of cancer registrations to the National Health Service Information Centre allows completeness of registration and eliminates duplication. Data on CNS tumors obtained from these registries have been grouped using the current WHO[15] classification. We present here incidence rates of CNS tumors for ages 0–14 years, 15–24 years, and 25–84 years for the whole of England during the period 1995–2003. We describe the differences in the site and pathology distributions of CNS tumors in these age ranges. This will allow us to better understand the changes with age in this large, heterogeneous collection of tumors. Use of the current WHO classification will make comparisons across geographical areas as well as over time more meaningful in the future.

Materials and Methods

Source of Data

Cancer registration in England is carried out by a network of eight population-based regional registries. Registration is coordinated by the Office for National Statistics in London, which maintains the national cancer registry covering all age groups. Anonymized individual-level national cancer registration data were obtained from the Office for National Statistics for all CNS tumors (tumor at any of the following sites: brain, meninges, spinal cord, cranial nerves, other parts of the CNS, pituitary, and pineal glands) of malignant, benign, and uncertain behavior newly diagnosed between 1995 and 2003. Information was available on the year of diagnosis, age at diagnosis, sex of patient, primary site code, morphology code, and behavior code. Individual-level data on ethnicity was not available. National population estimates by single year of age, gender, and calendar year were supplied by the Population Estimates Unit, Office for National Statistics.

Classification

The data obtained were classified into diagnostic groups to match the WHO 2000 classification on the basis of International Classification of Diseases for Oncology (ICD-O) M and T codes.[15] Modifications had to be made to make the classification more comprehensive by including pituitary tumors, not otherwise specified (NOS), and unspecified CNS tumors. This is consistent with the modified version of the new WHO 2000 classification used by CBTRUS.[14] We excluded metastatic tumors and tumors that were of uncertain primary/metastatic status. Also excluded were CNS lymphomas, hemopoietic neoplasms, mesenchymal nonmeningothelial tumors, and olfactory tumors. The final version of our classification is given in appendix A, where any departure from the current WHO classification are in bold and italicized.

Statistical Methods

Age- and sex-specific incidence rates were calculated and expressed per 100,000 person-years. Histology and site-specific incidence rates were also calculated for three different age groups: 0–14 years, 15–24 years, and 25–84 years. Those older than 85 years of age were excluded because of possible underascertainment and lower specificity in diagnosis. All rates were adjusted to the world standard population[1] using direct methods, except where specifically stated. SPSS version 15.0 (SPSS Science, Inc., Chicago, IL, USA) and Excel version 2003 (Microsoft Corp., Redmond, WA, USA) were used to analyze the data and produce tables and graphs.

Results

Overall Incidence

During the period 1995–2003, 54,336 primary CNS tumors of malignant, benign, and uncertain behavior located in the brain, meninges, spinal cord, cranial nerves, other parts of the CNS, and pituitary and pineal glands were registered in England in persons 0–84 years of age, which gives an annual average of just more than 6,000 new cases. The population covered was all individuals between 0 and 84 years of age in England from 1995 through 2003, which equates to 432 million person-years. There were 28,069 male cases (51.7%) and 26,267 female. The overall incidence rate was 9.21 per 100,000 person-years, and the male and female incidence rates were 9.96 and 8.52 per 100,000 person-years, respectively, giving a male-to-female ratio of 1.17:1.

Age-Specific Incidence

The age-specific incidence rates for primary CNS tumors are shown in Fig. 1. Peak incidence was seen in the 75- to 79-year age group for males and females. The number of 0- to 14-year-olds with primary CNS tumors was 2,959, with an annual average of approximately 330 new cases and an incidence rate of 3.56 per 100,000 person-years. The male and female incidence rates for the 0- to 14-year age group were 3.72 and 3.39 per 100,000 person-years, respectively. There were 1,764 cases among persons 15–24 years of age, with an annual average just below 200 new cases and an incidence rate of 3.26 per 100,000 person-years. The male and female incidence rates for the 15- to 24-year age group were 3.47 and 3.04 per 100,000 person-years, respectively. There were 49,612 cases, with an annual average of about 5,500 new cases, in the 25- to 84-year age group; the incidence rate was 14.57 per 100,000 person-years, and the male and female incidence rates for the same age group were 15.86 and 13.40 per 100,000 person-years, respectively.

Distribution by Tumor Behavior

Most primary CNS tumors in the 0- to 84-year age group were malignant (60%), and the overall incidence rate for malignant tumors for all ages was 5.64 per 100,000 person-years. The incidence rates for tumors of benign and uncertain behavior were 2.78 and 0.79 per 100,000 person-years, respectively. Tumors of malignant behavior decreased in proportion with increasing age, while tumors of benign behavior increased in proportion (Fig. 2). Within the malignant group, the astrocytomas in those 0–14 years of age were mainly low grade (WHO grade I and II), and those in the 25- to 84-year age group were high grade (WHO grade III and IV), while in those 15–24 years of age there was an equal proportion of low- and high-grade astrocytomas.

Distribution by Site

The distribution of tumors by primary site within the CNS for age groups 0–14 years, 15–24 years, and 25–84 years is shown in Fig. 3. Tumors located in infratentorial brain decreased in proportion with increasing age, while tumors located in supratentorial brain and meninges increased in proportion. Tumors of the pituitary and pineal glands and of the craniopharyngeal duct were relatively higher in proportion in the 15- to 24-year age group than at other ages.

Distribution by Histology

The distribution of tumors by main histology groups within the CNS for age groups 0–14 years, 15–24 years, and 25–84 years is shown in Fig. 4. Tumors of neuroepithelial tissue decreased in proportion with increasing age, while meningeal and unspecified tumors increased in proportion.

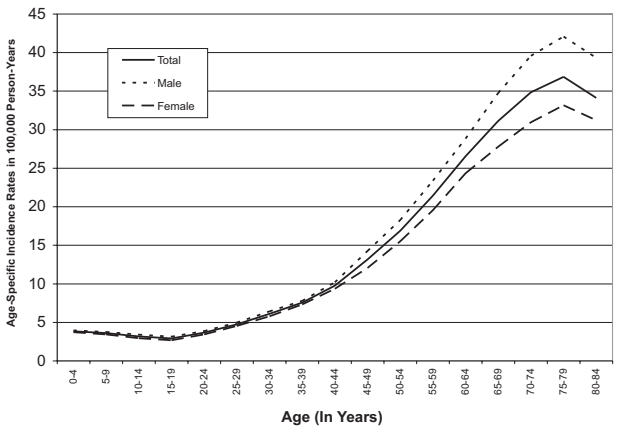

Fig. 1. Age- and sex-specific incidence rates of primary CNS tumors: England, 1995–2003.

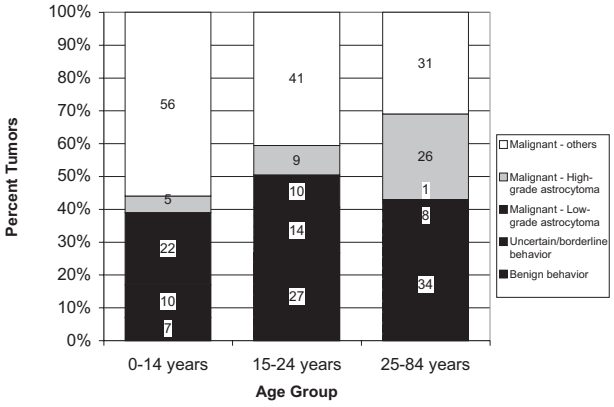

Fig. 2. Distribution of primary CNS tumors by behavior (low-grade astrocytoma, WHO grade I and II; high-grade astrocytoma, WHO grade III and IV): England, 1995–2003.

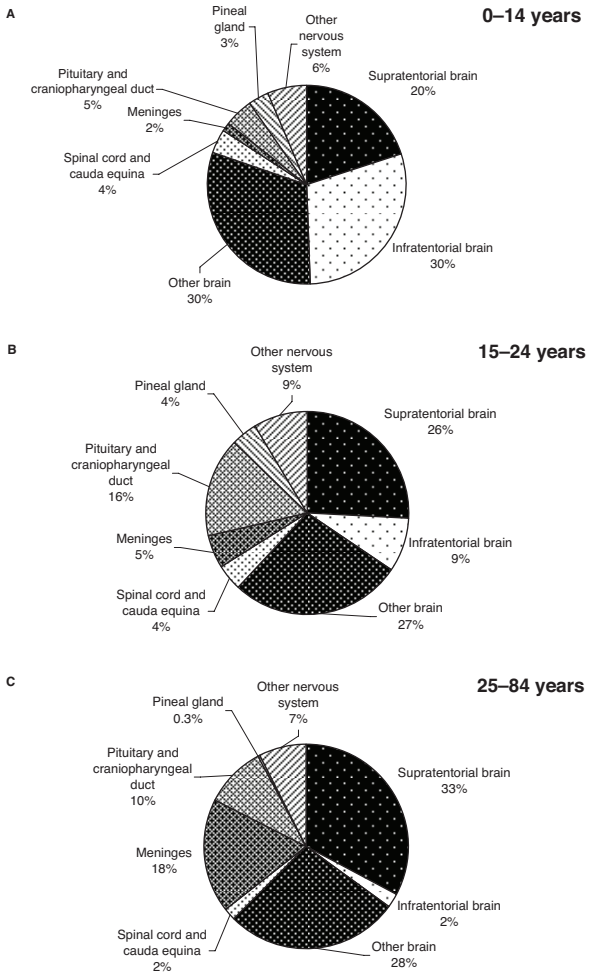

Fig. 3. Distribution of primary CNS tumors by site: England, 1995–2003.

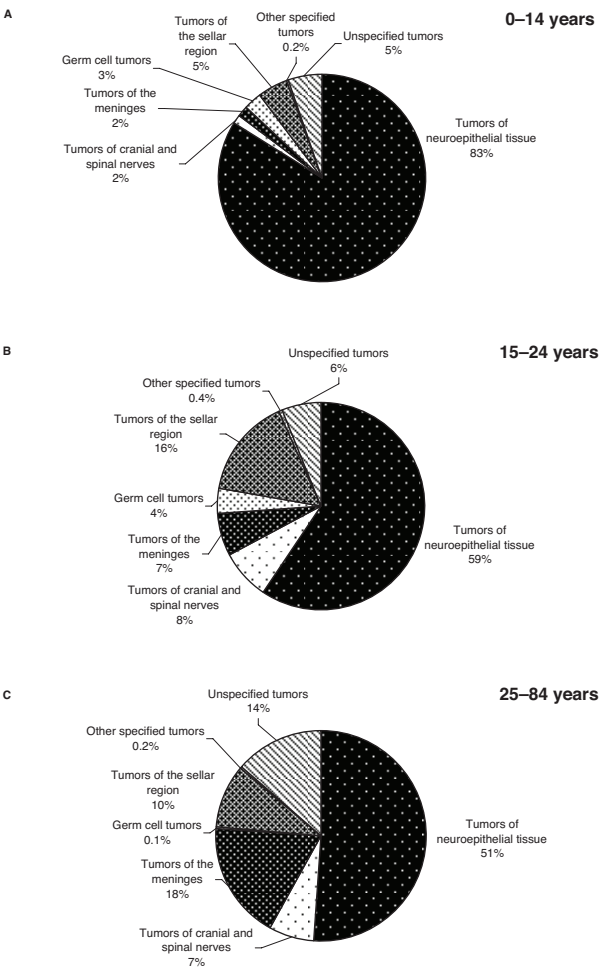

Fig. 4. Distribution of primary CNS tumors by main histology groups: England, 1995–2003.

The data on median age at diagnosis, incidence rates, and male-to-female ratio are shown in Tables 1 and 2. There was an overall male preponderance, but meningiomas showed a strong female preponderance ($p < 0.0001$), and they were twice as common in adult females compared with adult males. The most common specified tumors registered in the 0- to 14-year age group were pilocytic astrocytomas, medulloblastomas, and ependymal tumors. Craniopharyngioma was the most common nonneuroepithelial primary CNS tumor in children. Tumors with their peak incidence rates in those younger than 1 year of age were choroid plexus tumors, gangliogliomas, supratentorial primitive neuroectodermal tumors, and teratomas (data not shown). Tumors with their peak incidence rates in those 1–14 years of age were pilocytic astrocytomas, subependymal giant cell astrocytomas, anaplastic ependymomas (some of them may actually be ependymoblastomas, because they have the same morphological code, 9,392/3[17]), medulloblastomas, and craniopharyngiomas. The most common specified tumors registered in the 15- to 24-year age group were pituitary tumors, pilocytic astrocytomas, and nerve sheath tumors, while tumors with their peak incidence rates in that age group were pleomorphic xanthoastrocytomas, neurocytomas, and germinomas. Overall, the most common specified tumors registered in the 25- to 84-year age group were glioblastoma multiforme, meningiomas (94.5% nonmalignant), and pituitary tumors. Neuroepithelial tumors peaking in this age group were specified diffuse astrocytomas (peak incidence rate at 50–54 years of age), anaplastic astrocytomas, glioblastoma multiforme (peak incidence rate at 65–69 years of age), oligodendrogliomas (peak incidence rate at 50–54 years of age), anaplastic oligodendrogliomas (peak incidence rate at 55–59 years of age), mixed gliomas (peak incidence rate at 50–54 years of age), myxopapillary ependymomas, and subependymomas. Nonneuroepithelial tumors peaking in this age group included nerve sheath tumors (peak incidence rate at 60–64 years of age), meningiomas (peak incidence rate at 80–84 years of age), pituitary tumors (peak incidence rate at 65–69 years of age), and hemangioblastomas.

Table 1. Median age at diagnosis (years), incidence rates (age-standardized rate [ASR] in 100,000 person-years), and percentage of all CNS tumors by histology and sex: England, 1995–2003

	Total				Male		Female	
Histology	**No.**	**Median Age**	**ASR**	**Percent**	**ASR**	**Percent**	**ASR[a]**	**Percent**
Tumors of neuroepithelial tissue	28,814	57	5.24	53.0	6.26	59.8	4.29**	45.7
Astrocytic tumors	19,139	58	3.42	35.2	4.14	40.6	2.74**	29.5
Specified diffuse astrocytoma	399	41	0.08	0.7	0.10	0.9	0.07**	0.6
Anaplastic astrocytoma	970	50	0.18	1.8	0.21	2.0	0.16**	1.6
Glioblastoma	11,829	62	1.89	21.8	2.40	25.8	1.41**	17.5
Pilocytic astrocytoma	915	10	0.31	1.7	0.31	1.6	0.32	1.7
Other specified astrocytoma variants	65	15	0.02	0.1	0.02	0.1	0.02	0.1
Astrocytoma not otherwise specified	4,961	52	0.94	9.1	1.11	10.3	0.78**	7.9
Oligodendroglial tumors	6,632	64	1.03	12.2	1.22	13.1	0.86**	11.2
Oligodendroglioma	1,103	46	0.21	2.0	0.24	2.2	0.18**	1.8
Anaplastic oligodendroglioma	395	52	0.07	0.7	0.09	0.8	0.06**	0.6
Glioma not otherwise specified	5,134	68	0.75	9.4	0.89	10.1	0.63**	8.8
Mixed gliomas	425	46	0.08	0.8	0.09	0.8	0.08	0.8
Ependymal tumors	1,070	40	0.25	2.0	0.29	2.2	0.21**	1.7
Choroid plexus tumors	100	9	0.03	0.2	0.03	0.2	0.03	0.2
Glial tumors of uncertain origin	53	42	0.01	0.1	0.01	0.1	0.01	0.1
Neuronal and mixed neuronal-glial tumors	344	27	0.09	0.6	0.10	0.7	0.08*	0.6
Pineal parenchymal tumors	208	40	0.05	0.4	0.05	0.4	0.04	0.4
Embryonal tumors	843	10	0.28	1.6	0.33	1.8	0.23	1.3
Medulloblastoma	583	9	0.20	1.1	0.24	1.3	0.15**	0.8
Supratentorial primitive neuroectodermal tumors	259	14	0.08	0.5	0.08	0.5	0.08**	0.5
Other embryonal tumors	1	2	<0.01	<0.1	0.00	0.0	<0.01	<0.1
Tumors of cranial and spinal nerves	3,716	53	0.66	6.8	0.67	6.5	0.66	7.2
Nerve sheath tumors	3,716	53	0.66	6.8	0.67	6.5	0.66	7.2
Tumors of the meninges	9,134	62	1.38	16.8	0.96	10.7	1.78**	23.4
Meningioma	8,619	63	1.28	15.9	0.84	9.6	1.69**	22.5
Primary melanocytic lesions	12	51	<0.01	<0.1	<0.01	<0.1	<0.01	<0.1
Hemangioblastoma	503	46	0.10	0.9	0.11	1.0	0.08**	0.8
Germ cell tumors	203	17	0.06	0.4	0.09	0.5	0.03**	0.2
Tumors of the sellar region	5,310	54	0.94	9.8	0.98	9.9	0.91**	9.7
Craniopharyngioma	515	41	0.12	0.9	0.12	1.0	0.11	0.9
Pituitary tumors	4,795	55	0.82	8.8	0.86	8.9	0.80**	8.7
Miscellaneous tumors	117	55	0.02	0.2	0.02	0.2	0.02	0.2
Blood and lymphatic vessel tumors	69	51	0.01	0.1	0.01	0.1	0.01	0.1
Chordoma	48	61	0.01	0.1	0.01	0.1	0.01	0.1
Unspecified tumors	7,042	72	0.90	13.0	0.99	12.4	0.82**	13.6
Total	54,336	59	9.21	100.0	9.96	100.0	8.52**	100.0

[a] p-Values for variability in incidence by sex: *$p < 0.05$, **$p < 0.0001$

Discussion

We believe that this large, comprehensive, and up-to-date analysis of incidence data accurately reflects the incidence of primary CNS tumors in England. A total of 54,336 CNS tumors of benign, uncertain, and definite malignant behavior were registered across the whole of England from 1995 through 2003. The incidence rate for all ages (0–84 years) was 9.21 per 100,000 person-years.

Traditionally, the epidemiology of CNS tumors has been characterized for children and adults of all ages separately in recognition of the differences in pathology and etiology. It is now recognized that the epidemiology of tumors in adolescents is quite distinct from that of older adults,[3,4,18] and hitherto, the incidence of CNS tumors by morphological type has not been described in this age group. The age structure of a population can affect the crude incidence rates. Adjusting to world standard population (as has been done here) allows compari-

Table 2. Average annual number of cases (AAN), incidence rates standardized for world population (age-standardized rate [ASR], in 100,000 person-years), and male to female ratio (M:F) for each histology group for age groups 0–14 years, 15–24 years, and 25–84 years: England, 1995–2003

	0–14 Years			15–24 Years			25–84 Years		
Histology	**AAN**	**ASR**	**M:F**	**AAN**	**ASR**	**M:F**	**AAN**	**ASR**	**M:F**
Tumors of neuroepithelial tissue	276	3.01	1.10	116	1.94	1.32	2,809	7.68	1.57
Astrocytic tumors	132	1.42	0.93	64	1.07	1.37	1,930	5.40	1.64
Specified diffuse astrocytoma	4	0.04	1.76	4	0.06	0.98	37	0.12	1.61
Anaplastic astrocytoma	5	0.05	1.10	5	0.08	1.21	98	0.29	1.38
Glioblastoma	11	0.12	0.65	12	0.20	1.46	1,291	3.51	1.75
Pilocytic astrocytoma	69	0.75	0.85	16	0.27	1.75	17	0.06	1.08
Other specified astrocytoma variants	4	0.03	2.12	2	0.03	0.79	2	0.01	0.40
Astrocytoma not otherwise specified	40	0.42	1.06	26	0.43	1.30	485	1.42	1.51
Oligodendroglial tumors	38	0.41	1.07	16	0.26	1.57	683	1.66	1.46
Oligodendroglioma	2	0.02	3.21	5	0.09	1.64	115	0.36	1.30
Anaplastic oligodendroglioma	1	0.01	1.04	1	0.02	1.32	41	0.13	1.59
Glioma not otherwise specified	35	0.38	1.02	9	0.15	1.57	527	1.17	1.51
Mixed gliomas	2	0.02	0.48	2	0.04	1.07	43	0.14	1.13
Ependymal tumors	23	0.26	1.34	10	0.16	1.03	86	0.27	1.48
Choroid plexus tumors	6	0.08	1.29	1	0.01	0.70	4	0.01	0.63
Glial tumors of uncertain origin	1	0.01	2.49	1	0.02	0.64	4	0.01	0.98
Neuronal and mixed neuronal-glial tumors	9	0.10	1.13	8	0.14	1.35	21	0.07	1.28
Pineal parenchymal tumors	5	0.06	1.26	3	0.05	1.80	15	0.04	1.07
Embryonal tumors	59	0.66	1.48	12	0.19	1.13	23	0.08	1.44
Medulloblastoma	44	0.49	1.73	7	0.11	1.04	14	0.05	1.70
Supratentorial primitive neuroectodermal tumors	15	0.17	0.99	5	0.08	1.27	9	0.03	1.11
Other embryonal tumors	<1	<0.01	0.00	0	0.00		0	0.00	
Tumors of cranial and spinal nerves									
Nerve sheath tumors	5	0.05	0.64	15	0.25	1.06	393	1.17	1.03
Tumors of the meninges	5	0.05	0.94	13	0.22	0.78	996	2.56	0.53
Meningioma	4	0.04	1.19	9	0.15	0.80	944	2.40	0.49
Primary melanocytic lesions	<1	0.01	1.09	<1	<0.01	0.00	1	<0.01	2.04
Hemangioblastoma	1	0.01	0.16	4	0.06	0.75	51	0.16	1.50
Germ cell tumors	9	0.09	2.15	7	0.13	8.41	6	0.02	1.86
Tumors of the sellar region	15	0.15	1.08	31	0.51	0.59	544	1.56	1.14
Craniopharyngioma	13	0.13	1.14	6	0.11	0.94	38	0.12	1.17
Pituitary tumors	3	0.02	0.84	24	0.40	0.52	506	1.45	1.14
Miscellaneous tumors	1	<0.01	0.17	1	0.01	2.61	12	0.03	1.06
Blood and lymphatic vessel tumors	<1	<0.01	0.67	1	0.01	4.25	7	0.02	0.90
Chordoma	<1	<0.01	0.00	<1	<0.01	1.01	5	0.01	1.45
Unspecified tumors	18	0.2	0.94	12	0.20	0.94	752	1.55	1.24
Total	329	3.56	1.10	196	3.26	1.14	5,512	14.57	1.18

son between registries in different countries because it is independent of the effects of age. The major category of CNS tumors excluded from this analysis is primary CNS lymphoma, which is usually defined as extranodal lymphoma confined to the CNS without evidence of systematic disease.[15] The reliability of this diagnosis depends on the comprehensiveness of staging, and in several studies the diagnosis of primary CNS lymphoma has been revised to systemic non-Hodgkin's lymphoma with possible secondary CNS disease on further investigation.[19–22]

Previously published age-standardized incidence rates of primary CNS tumors (based on ICD-O site and not morphological type) in England are 6.5–7.7 per 100,000 person-years in males and 4.5–4.9 per 100,000 person-years in females[1,23] and are lower than incidence rates from this study. These figures significantly underestimated the true burden of CNS tumors because they included only malignant tumors located in the brain[23] or in the brain and spinal cord.[1] They excluded tumors located in the pituitary gland, craniopharyngeal duct, and pineal gland, as well as all nonmalignant tumors.

The reported incidence of CNS tumors in the United States of 14.8 per 100,000 person-years[14] is higher than that given here, while that from Norway, 9.53 per 100,000 person-years,[8] is similar to ours. The reasons for the higher incidence rate in the United States are threefold. First, U.S. age-adjusted rates are standardized to the U.S. 2000 population where children younger than 15 years comprised 21.5%, and adults older than 70 years, 9.2% of the total age distribution.[14] These contrast to the world standard population where children younger than 15 years comprise 31%, and adults older than 70 years, 4% of the total age distribution.[1] Standardizing with a population that has relatively older individuals will increase the overall incidence rates because CNS tumors are far more common in these age groups. After adjusting to the world standard population, the overall incidence rate for the United States is 11.61 per 100,000 person-years. Second, there is considerable variation in reporting of nonmalignant (benign and uncertain) tumors in the United States, and the percentage varies from 27% to 60% between different U.S. states.[14] In our data, 31% of CNS tumors were nonmalignant, and if we consider U.S. states with similar percentages of nonmalignant tumors (Connecticut, 40% nonmalignant; North Carolina, 38%), their incidence rates (Connecticut, 13.61; North Carolina, 11.43) are well below the overall figure of 14.8 per 100,000 person-years reported by CBTRUS. Finally, we have excluded CNS lymphomas from our analysis, which account for 3% of the incidence in the United States. Thus, one can conclude that the incidence of CNS tumors in the United States is actually not very different from that in the United Kingdom and Europe. These caveats also explain the higher incidence of CNS tumors in females in the United States compared to England and elsewhere,[8,24] which is caused by increased registration of nonmalignant tumors, especially meningiomas (57%), which are more common in females (74%).

The incidence rate of 3.56 per 100,000 person-years seen in children in our study is similar to the incidence rate of 3.3 per 100,000 person-years reported by ACCIS for England and Wales for 1993–1996.[25] Corresponding rates for the rest of Europe vary from 4.0 to 5.0 per 100,000 person-years for Iceland, Norway, Finland, and Denmark and between 2.0 and 3.0 per 100,000 person-years for Germany and the Netherlands.[25] Data on the incidence of primary CNS tumors for adolescents is scanty. Our previous report showed that the overall incidence rate for malignant CNS tumors in those 15–24 years of age registered in England from 1979 through 1997 is 1.65 per 100,000 person-years.[3] The U.S. Surveillance, Epidemiology, and End Results (SEER) program data, which also report only malignant tumors, give an incidence rate of 2.26 per 100,000 person-years for the 15- to 29-year age group.[18] After accounting for the slightly higher rates contributed by the 25- to 29-year age group in those data, this is closer to our rate of 1.94 per 100,000 person-years for malignant CNS tumors in those 15–24 years of age in a more recent time period. Further comparisons by histological group are not possible because the SEER report uses the ICCC rather than WHO 2000 classification. The 2008 CBTRUS report, which uses the WHO 2000 classification, is also unsuitable for comparison because the age groups are different (0–19 years, 20–34 years, and so on).[26]

With increasing age, not only does the proportion of benign CNS tumors increase but there is also a shift in the spectrum of malignant primary CNS tumors. Pilocytic astrocytoma and embryonal tumors form the bulk of malignant tumors in children. Pilocytic astrocytoma is a WHO grade I astrocytoma, and although regarded as a benign tumor by many,[27] it is classified as malignant in the ICD-O first and second editions[28,17] (ICD-O1 and ICD-O2, respectively). However, in the recent ICD-O third edition[29] (ICD-O3), pilocytic astrocytoma is classified as uncertain (morphological code 9421/1) rather than malignant in behavior. Future analysis of epidemiology of childhood CNS tumors may show an artificial rise in the proportion of nonmalignant CNS tumors because of this. Embryonal tumors are the second largest group, with 74% medulloblastomas and 26% supratentorial primitive neuroectodermal tumors. Absent among this group are ependymoblastomas (because they share the same morphological code, 9392/3,[17] with anaplastic ependymomas and will have been included there) and atypical teratoid/rhabdoid tumors, which have been recognized as a distinct entity only in ICD-O3.[29] Based on a series of cases from single institutions, the incidence of atypical teratoid/rhabdoid tumors is thought to be around 1%–2% of pediatric CNS tumors and at least 10% of all CNS tumors in infants. With increasing use of ICD-O3, incidence data for this group of tumors should be available in the future.[30] The incidence of medulloblastoma in childhood from this study is 0.49 per 100,000 person-years and is similar to that reported elsewhere.[15,31] But there is much more variability in the proportion of supratentorial primitive neuroectodermal tumors.[15,32] McNeil et al.[32] found that supratentorial primitive neuroectodermal tumors, which had not been described until the 1980s, accounted for up to one-third of all embryonal CNS tumors from 1993 through 1998 in the SEER database. Also seen in infancy are benign tumors of mixed cellular-lineage, such as desmoplastic infantile astrocytoma/ganglioglioma and dysembryoplastic neuroepithelial tumors, which have been traditionally difficult to categorize and are now included in neuronal and mixed neuronal-glial tumors.[30] Because these pathological entities have been defined only in ICD-O3, it is not possible to comment on their occurrence in our study.

In adolescents, not only is there a transition from the typical childhood tumor pattern to a distribution more typical of older adults, but there are certain features unique to this age group. First, tumors from the sellar region form a significant proportion (16%) and while in those 0–14 years of age 87% of these tumors are craniopharyngiomas, in those 15–24 years of age 78% are pituitary tumors. Also, this age group has a female preponderance for pituitary tumors, which has been previously reported.[33,34] This is due to prolactinomas and clinically nonfunctioning pituitary adenomas, which are more frequent in females.[35] The explanation for this

gender-related difference is not clear, but the role of estrogen in tumor promotion and a greater inclination in females to seek medical attention for hypogonadal symptoms has been suggested.[35] Second, germ cell tumors peak in incidence in this age group, and germinomas account for the majority of these. They have previously been noted to show a strong male preponderance at the pineal site,[36] and this is also seen in our study, where germ cell tumors were eight times more common in males than in females ($p < 0.0001$).

The data reported here on primary CNS tumors in older adults, including specified diffuse astrocytomas,[14] anaplastic astrocytomas,[14] glioblastoma multiforme,[14,15] oligodendrogliomas,[12,37] anaplastic oligodendrogliomas,[14] mixed gliomas,[14,38] certain ependymal tumors[14,15,39] (myxopapillary ependymomas[1] and subependymomas[15,40]), nerve sheath tumors,[14,15,41–43] meningiomas,[14,15,44] hemangioblastomas,[14] and pituitary tumors,[14,45] are generally similar to data from other studies. There are, however, a few obvious differences, particularly compared with the data from CBTRUS,[14] for reasons discussed above. A final point of note is that astrocytomas NOS and gliomas NOS constituted 18.5% of all primary CNS tumors in our series, and another 13% are of unspecified histology. This is because only 71%–73% of CNS tumors in all ages are microscopically verified.[1] The proportion of tumors with unspecified histology in our series increased with increasing age (Fig. 4), with a median age at diagnosis of 72 years, which suggests that younger individuals are more likely to undergo extensive investigation to achieve specific diagnoses, although this attitude toward the elderly may be changing.[46] Moreover, it has been shown that, over time, the advances made in neuroimaging, neurosurgery, and neuropathology and improvements in quality of registrations are reducing the incidence of NOS and unspecified tumors.[47]

Little is known about the etiology of primary CNS tumors, and the only proven causes (hereditary syndromes and radiation) account for a small proportion of cases.[48] The heterogeneous pathologies grouped under CNS tumors further limit our ability to study the etiology of the disease. Analyzing the pattern of these pathologies with age and sex (as has been done here) allows us to speculate about the etiopathogenesis. A nadir in the incidence of CNS tumors at ages 15–19 years and a peak at 75–79 years suggest that both genetic and environmental factors have a role, with the environment being the larger contributor. An increasing incidence of high-grade astrocytoma with increasing age along with a decreasing incidence of low-grade astrocytoma supports the suggestion that malignant transformation of astrocytic cells is a multistep process with sequential acquisition of genetic alterations with age.[15] The peak of CNS embryonal tumors in early childhood and of CNS germ cell tumors in those 15–24 years of age is similar to the incidence pattern seen in non-CNS embryonal tumors (nephroblastoma, neuroblastoma) and gonadal germ cell tumors. This implies that the etiologies for CNS or non-CNS tumors that share the same tissue of origin are likely to be related.

It would also be of interest to analyze the variation in epidemiology by race and ethnicity, as has been done by CBTRUS.[26] Currently, the individual-level cancer registration data obtained from the Office of National Statistics is anonymized and does not include information on ancestry/ethnicity. In the future, it may be possible to get such data, and then such an analysis can be done. Moreover, the minority ethnic population in England comprises 7.9%[49] (4% Asian or Asian British, 2% black or black British, 1.2% mixed, and 0.8% others), which is much less than the 26% in the United States (13.4% black or African-American, 4.4% Asian, 2% mixed, and 6.2% others).[50] Thus, the incidence rates for England are relatively less likely to be affected by ethnic variation.

Conclusion

In summary, we present a large, comprehensive, and up-to-date analysis of incidence data of primary CNS tumors in the world England that has been obtained from a high-quality national cancer registration system. We have described the epidemiology across the whole of England from 1995 through 2003 for all ages and focused on the changing patterns in children, adolescents, and older adults. The overall incidence is similar to that reported elsewhere in the world but higher than that reported in Britain before. We have also described sex-specific, age-specific, and tumor-behavior–specific standardized incidence rates for all histology groups according to the WHO 2000 classification. We hope this allows other studies to make relevant and meaningful comparisons with our data and that it provides a baseline for secular trend analysis.

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Appendix A. CNS tumor classification based on histology adapted from the WHO 2000 classification.[15] Any departures from the WHO 2000 classification are in bold and italicized.

Histology	Histology Code
Tumors of Neuroepithelial Tissue	
Astrocytic Tumors	
Specified diffuse astrocytoma	9410, 9411, 9420
Anaplastic astrocytoma	9401
Glioblastoma	9440, 9441, 9442
Pilocytic astrocytoma	***9380 (Site code restrictions 192.0, 225.1 – ICD9; C72.3, D33.3, D43.3 – ICD10),*** 9421
Other specified astrocytoma variants	9384, ***9422, 9423,*** 9424, ***9443***
Astrocytoma NOS	***9400***
Oligodendroglial tumors	
Oligodendroglioma	9450
Anaplastic oligodendroglioma	9451, ***9460***
Glioma NOS	***9380 (Site code restrictions except 192.0, 225.1 – ICD9; C72.3, D33.3, D43.3 – ICD10)***
Mixed gliomas	9382
Ependymal tumors	9383, 9391–9394
Choroid plexus tumors	9390
Glial tumors of uncertain origin	9381, 9430
Neuronal and mixed neuronal-glial tumors	8680, 8681, ***8690, 8693, 8700, 8711,*** 9492, 9505, 9506
Neuroblastic tumors	***Not included***
Pineal parenchymal tumors	***9360,*** 9361, **9362** ***(Site code restrictions 194.4, 227.4, 237.1 – ICD9; C75.3, D35.4, D44.5 – ICD10 Except 9350, 9060–9102)***
Embryonal tumors	
Ependymoblastoma	***Included in ependymal tumors***
Medulloblastoma	***9363, 9364, 9473, 9490, 9503 (T-Code restrictions 191.6 ICD9; C71.6 ICD10),*** 9470, 9471, 9472
Supratentorial primitive neuroectodermal tumor	***9363, 9364,*** 9473, 9490, ***9503 (T-Code restrictions 191.0–191.5, 191.7–192.9 – ICD9; C70.0-C72.9 except C71.6 – ICD10)***
Other embryonal tumors	9501, 9508
Tumors of Cranial and Spinal Nerves	
Nerve Sheath Tumors	9540, ***9541,*** 9550, 9560, ***9561, 9562,*** 9570
Tumors of the Meninges	
Meningioma	9530, 9531, 9532, 9533, 9534, ***9536,*** 9537, 9538, 9539
Mesenchymal, non-meningothelial tumors	***Not included***
Primary melanocytic lesions	8720, ***8726, 8740***
Hemangioblastoma	9161, ***9535***
Lymphomas and Haemopoietic Neoplasms	***Not included***
Germ Cell Tumors	
Germ Cell Tumors	***9060, 9061,*** 9064, 9070, 9071, ***9072, 9073,*** 9080, ***9081, 9082, 9083,*** 9084, 9085, ***9090, 9091, 9093, 9100***
Tumors of the Sellar Region	
Craniopharyngioma	9350
Pituitary tumors	***Site Code restrictions 194.3, 227.3, 237.0 – ICD9; C75.1, C75.2, D35.2, D35.3, D44.3, D44.4 – ICD10 except 9350, 9060-9102***
Metastatic Tumors	***Not included***
Other Specified Tumors	
Blood and Lymphatic Vessel Tumors	***9120, 9121, 9122, 9123, 9130, 9131, 9150, 9160, 9170, 9173***
Chordoma	***9370***
Miscellaneous Tumors	
Unspecified intracranial and intraspinal neoplasms	***8000-8004, 8010, 9990***

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6.3 Are reported increases in incidence of primary CNS tumours real? An analysis of longitudinal trends in England, 1979-2003

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Are reported increases in incidence of primary CNS tumours real? An analysis of longitudinal trends in England, 1979–2003

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ABSTRACT

Reported increases in the incidence of CNS tumours in the developed world in the 1970s to 1990s have been a cause for concern and debate. It still remains to be adequately answered whether these increases are true or an artefact of changes in diagnostic and registration practices. Using high-quality national cancer registration data, we have analysed incidence trends for each major histological subgroup of CNS tumour (2000 World Health Organisation (WHO) classification) registered in those aged 0–84 years for the whole of England during the period 1979 through 2003. 134,509 primary CNS tumours of malignant, benign and uncertain behaviour located in the brain, meninges, spinal cord, cranial nerves, other parts of the central nervous system and in the pituitary and pineal glands were registered. In summary, we present the single largest nationwide study on the longitudinal incidence trends of CNS tumours. The increase in incidence observed in the 1970s and 1980s was mainly in the young and the elderly and has now plateaued and may even be decreasing. There is however variation in trends by histology. The incidence of some histological subgroups has continued to increase until the most recent period of analysis. Much of the initial increase can be attributed to the emergence of much more widely available neuroimaging, while the most recent incidence changes for specific sub-groups of CNS tumours appear to be due to greater diagnostic specificity leading to a shift in registered categories. However, the trends for high-grade astrocytomas and other gliomas need further observation and investigation.

1. Introduction

According to global estimates, central nervous system (CNS) tumours account for 1.7% of all new cancers and 2.1% of all cancer deaths worldwide.[1] The highest incidence rates are in the developed world (Australia/New Zealand, Europe and North America) and lowest in Africa which suggests that availability of diagnostic facilities may influence recorded incidence rates in developing countries.[2] There are more than 100 distinct pathological entities reported for the CNS

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tumours. Around 60% of them are malignant in behaviour[3] although even this proportion depends on registration practices which vary in the extent to which registration of non-malignant tumours occurs in each country.[4,5] Even histologically non-malignant tumours can be life-threatening as a result of their space-occupying effects, degree of local infiltration and, the tendency for some low-grade astrocytomas to undergo malignant transformation, particularly those which have received irradiation.[6]

In late 1980s and early 1990s there were several reports of increasing incidence of CNS tumours, mainly in the elderly, from Europe,[7,8] North America[9,10] and Oceania.[11] By the mid to late 1990s there were similar reports of increasing incidence of CNS tumours in children, initially from Britain[12,13] followed by other parts of Europe[14,15] and North America.[16,17] Recently studies from Asia,[18] Europe[19,20] and North America[21,22] have shown that the increasing incidence of CNS tumours overall (including children and the elderly) may be levelling off and may actually be falling.

It is generally accepted that some of the increase in incidence was not real but a result of advances in neuroimaging[23–26] and better registration of non-malignant CNS tumours.[27,28] However, there is a debate as to whether in all cases, the increases can be attributed to such an artefact of changes in diagnostic and registration practices.[29,30] This is because the incidence increases started prior to the introduction of computerised tomography (CT) scanning.[7] In addition there was not only an increase in the incidence of radiologically diagnosed CNS tumours, but also of those, albeit smaller, diagnosed clinically.[10,31] Alternate explanations proposed for the increases include greater availability of neurologists,[23] attitudinal change in the delivery of healthcare to the elderly[23,25] and increased availability of alternative imaging procedures like arteriography prior to the advent of CT.[11] The case for an artefactual increase seen elsewhere is supported by the observation of no such change in the incidence of CNS tumours in the population of Rochester, Minnesota in United States of America (USA) for the era 1935–1997 although the number of CNS tumours diagnosed over this period was relatively small (373).[32,33] Rochester, which has one of the highest reported incidence rates of CNS tumours in USA, has historically had near-complete case ascertainment, registration of benign tumours, a high autopsy rate to confirm diagnosis, greater than 95% histological confirmation of tumour type, and easy access to neurological and neurosurgical expertise. In such a setting, the effect of any artefact on incidence patterns is likely to be minimal.

Furthermore, no new environmental risk factors have been identified nor has there been an increase in any existing environmental risk factor whose presence could explain the rise in the observed incidence. So far, no consistent evidence linking exposure to mobile phones, extremely low frequency electromagnetic fields, infections and pesticides to CNS tumour development has been identified.[34,35] The heterogeneous pathologies grouped under the term CNS tumours further limit our ability to study the aetiology of individual tumour types. The recent levelling off would suggest that either the exposure to the, as yet unidentified risk factor(s), has reached its peak or that the rise in incidence was indeed artefactual.

Using high quality national cancer registration data, we present here incidence trends of primary CNS tumours in children (0–14 years), adolescents and young adults (15–24 years), older adults (25–64 years) and for the elderly (65–84 years) covering the whole of England during the period 1979 through 2003 with the aim to explore the incidence trend patterns in comparison with those seen elsewhere. Importantly, we analyse the trend for each major histological subgroup of CNS tumours (malignant and non-malignant) using the 2000 WHO classification[6] for each of the four age groups. Much of the published literature lacks such detailed information on specific histologies. The only other study which has applied the detailed 2000 WHO classification in the analysis of trends, looked at 25,258 primary CNS tumours over a shorter time period (1985–1999).[26]

2. Materials and methods

2.1. Source of data

Cancer registration in England is carried out by a network of eight population-based regional registries and the national data are collated by the Office for National Statistics in London.[36] Anonymised individual patient level national cancer registration data were obtained from the Office for National Statistics on all CNS tumours (tumour at any of the following sites: brain, meninges, spinal cord, cranial nerves, other parts of the central nervous system and pituitary and pineal glands) of malignant, benign and uncertain behaviour, newly diagnosed between 1979 and 2003. National population estimates by single year of age, gender and calendar year were supplied by the Population Estimates Unit, Office for National Statistics.

2.2. Classification

The data obtained were classified into diagnostic groups according to the WHO 2000 classification on the basis of ICD-oncology second edition (ICD-O2) morphology codes[37] and International Classification of Diseases 10th revision (ICD-10) topography codes.[38] In addition pituitary tumours and not otherwise specified/unspecified CNS tumours were also included. Metastatic tumours and those where it was uncertain if they were primary or metastatic were excluded. Also excluded were CNS lymphomas, haemopoietic neoplasms, mesenchymal non-meningothelial tumours and olfactory tumours. Details of our classification including morphology and site code allocations have been published elsewhere.[3]

2.3. Statistical methods

Age and sex specific incidence rates were calculated and expressed per 100,000 person years. All rates were adjusted to the world standard population[2] using direct methods except where specifically stated. To assess the variation in the longitudinal trends with age, the total time period was divided into five quinquennia 1979–1983, 1984–1988, 1989–1993, 1994–1998 and 1999–2003. Average annual percentage change (AAPC) along with the 95% confidence intervals (CIs) was calculated

for the entire period from 1979 to 2003 for four different age groups (0–14, 15–24, 25–64 and 65–84 years) and for each of the histological sub-groups. Those above the age of 85 were excluded because of possible under-ascertainment and often lower specificity in diagnosis. *p*-Values for variability in incidence trends by sex within each age group as well as variability among the four age groups were also calculated. SPSS, R[39] and Microsoft Excel were used for analysing the data and producing tables and graphs.

3. Results

During the period 1979 through 2003, 134,509 primary CNS tumours of malignant, benign and uncertain behaviour located in the brain, meninges, spinal cord, cranial nerves, other parts of the central nervous system, and in the pituitary and pineal glands were diagnosed and registered in England in those aged 0–84 years. The population covered, equated to 1.18 billion person years. About 69,408 of the tumours were in males (51.6%) and 65,101 in females. The overall age-standardised incidence rate steadily increased from 7.41 per 100,000 person years in 1979 to 9.73 in 1992 but has not subsequently increased (Fig. 1). Indeed, there seems to be some decrease in overall incidence since 2001. Both benign and malignant tumours show an increase in incidence while those of uncertain/borderline behaviour have decreased (Fig. 2).

Table 1 shows the incidence rates (adjusted to the standard world population) in each quinquennium for all the histological sub-groups in the WHO 2000 classification. Four main patterns have been identified:

(i) No change in incidence throughout the period – specified diffuse astrocytomas (WHO grade II – fibrillary, protoplasmic and gemistocytic), pineal parenchymal tumours, medulloblastomas, hemangioblastomas, craniopharyngiomas and chordomas.
(ii) Increasing incidence throughout each of the quinquennia – anaplastic astrocytomas (WHO grade III), glioblastomas (WHO grade IV), pilocytic astrocytomas (WHO

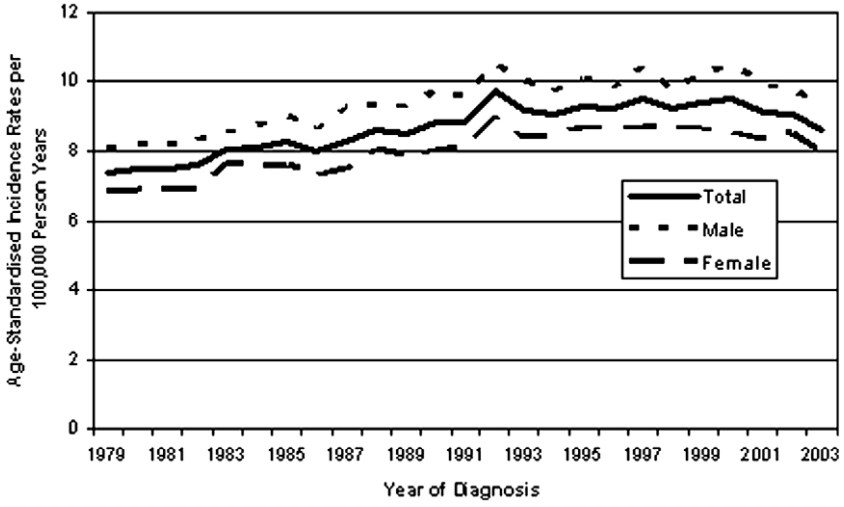

Fig. 1 – Trends in age-standardised incidence rates of primary CNS tumours in England, 1979–2003.

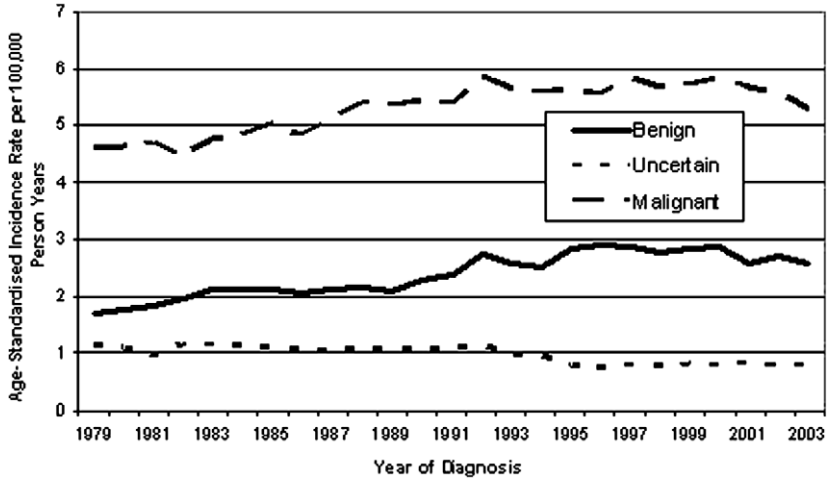

Fig. 2 – Trends in age-standardised incidence rates of primary CNS tumours in England, 1979–2003 by behaviour.

Table 1 – Incidence of primary CNS tumours in those aged 0–84 years in England from for the five quinquennia from 1979 to 2003.

	Number of cases	Age-standardised incidence rates[a] in 100,000 person years					*p*-Value
		1979–1983	1984–1988	1989–1993	1994–1998	1999–2003	
Total CNS tumours	**134,509**	**7.61**	**8.27**	**8.99**	**9.24**	**9.13**	**0.00001**
Tumours of neuroepithelial tissue (total)	**70,048**	**4.16**	**4.55**	**4.68**	**5.26**	**5.22**	**0.00001**
Astrocytic tumours	**40,327**	**2.04**	**2.21**	**2.65**	**3.33**	**3.48**	**0.00001**
Specified diffuse astrocytoma	1036	0.08	0.07	0.09	0.08	0.09	0.3
Anaplastic astrocytoma	1689	0.02	0.07	0.14	0.17	0.19	0.00001
Glioblastoma	18,309	0.47	0.53	0.82	1.60	2.05	0.00001
Pilocytic astrocytoma	1553	0.08	0.12	0.13	0.27	0.33	0.00001
Other specified astrocytoma variants	91	0.00	0.00	0.00	0.01	0.02	0.00001
Astrocytoma NOS	17,649	1.38	1.42	1.48	1.20	0.80	0.00001
Oligodendroglial tumours	**3082**	**0.17**	**0.19**	**0.19**	**0.26**	**0.30**	**0.00001**
Oligodendroglioma	2557	0.16	0.18	0.17	0.21	0.21	0.00001
Anaplastic oligodendroglioma	525	0.01	0.01	0.02	0.05	0.09	0.00001
Glioma NOS	**20,041**	**1.45**	**1.61**	**1.25**	**0.92**	**0.64**	**0.00001**
Mixed gliomas	**765**	**0.03**	**0.04**	**0.05**	**0.06**	**0.10**	**0.00001**
Ependymal tumours	**2380**	**0.17**	**0.19**	**0.20**	**0.23**	**0.25**	**0.00001**
Choroid plexus tumours	**215**	**0.02**	**0.02**	**0.02**	**0.03**	**0.03**	**0.0001**
Glial tumours of uncertain origin	**198**	**0.03**	**0.02**	**0.01**	**0.01**	**0.01**	**0.00001**
Neuronal and mixed neuronal-glial tumours	**475**	**0.01**	**0.01**	**0.02**	**0.08**	**0.09**	**0.00001**
Pineal parenchymal tumours	**543**	**0.05**	**0.04**	**0.04**	**0.06**	**0.04**	**0.67**
Embryonal tumours	**2022**	**0.21**	**0.22**	**0.23**	**0.28**	**0.28**	**0.00001**
Medulloblastoma	1707	0.21	0.21	0.22	0.20	0.20	0.65
Supratentorial primitive neuroectodermal tumour	314	0.00	0.01	0.01	0.08	0.08	0.00001
Tumours of cranial and spinal nerves							
Nerve sheath tumours	8709	0.49	0.55	0.61	0.70	0.63	0.00001
Tumours of the meninges (total)	**21,062**	**1.03**	**1.13**	**1.17**	**1.33**	**1.39**	**0.00001**
Meningioma	19,721	0.94	1.04	1.07	1.24	1.29	0.00001
Primary melanocytic lesions	28	0.001	0.003	0.002	0.004	0.003	0.27
Hemangioblastoma	1313	0.08	0.09	0.09	0.09	0.10	0.15
Germ cell tumours							
Germ cell tumours	488	0.04	0.04	0.06	0.06	0.06	0.00001
Tumours of the sellar region (total)	**13,497**	**0.78**	**0.86**	**1.04**	**1.04**	**0.85**	**0.00001**
Craniopharyngioma	1484	0.13	0.14	0.12	0.14	0.10	0.07
Pituitary tumours	12,013	0.65	0.72	0.91	0.90	0.75	0.00001
Miscellaneous tumours (total)	**485**	**0.05**	**0.04**	**0.03**	**0.02**	**0.02**	**0.00001**
Blood and lymphatic vessel tumours	346	0.04	0.03	0.02	0.01	0.01	0.00001
Chordoma	139	0.01	0.01	0.01	0.01	0.01	0.25
Unspecified tumours							
Unspecified tumours	20,220	1.06	1.09	1.41	0.83	0.95	0.00001

[a] Adjusted to world standard population.

grade I), anaplastic oligodendrogliomas (WHO grade III), mixed gliomas, neuronal and mixed neuronal-glial tumours and meningiomas.

(iii) Initial increase in incidence followed by stabilisation – oligodendrogliomas (WHO grade II), ependymal tumours, choroid plexus tumours, supratentorial primitive neuroectodermal tumours (PNETs), nerve sheath tumours, germ cell tumours and pituitary tumours.

(iv) Initial increase in incidence followed by decrease – astrocytomas not otherwise specified, gliomas not otherwise specified and unspecified tumours.

Age specific incidence rates for ages 0–4 years, and five-year age groups up to 80–84 years for each quinquennium are shown in Fig. 3. The increase in the incidence of primary CNS tumours was seen mainly in the young and the elderly and had been relatively stable for those aged 25–64 years. Within the young, the increase in incidence was the highest in the youngest (38%, 31%, 27%, 26% and 11% for 0–4, 5–9, 10–14, 15–19 and 20–24 year age groups, respectively, between the period 1979–1983 and the period 1999–2003). Among the elderly, the incidence change increased with age (15%, 24%, 54%, 115% and 176% for 60–64, 65–69, 70–74, 75–79 and 80–84 year age groups, respectively). Because of this, the age of peak incidence rate for CNS tumours shifted from 65–69 years in 1979–1983 to 75–79 years in 1999–2003.

Table 2 shows the AAPC for four different age groups (0–14, 15–24, 25–64 and 65–84 years) and for each of the histological sub-groups of the WHO 2000 classification. Overall the incidence significantly increased in all age groups with the highest increases in those aged 0–14 years and 65–84 years. Analysis by histology, however, revealed different patterns. Firstly, for those CNS tumours where incidence had not changed over 25 years (see above), there was also little or no change in each of those four age groups. Secondly, for those CNS tumours where incidence had steadily increased in 25 years or had increased and stabilised, the change was either seen in all age groups (anaplastic astrocytomas, glioblastomas, anaplastic oligodendrogliomas, mixed gliomas, neuronal and mixed neuronal-glial tumours and supratentorial PNETs) or mainly in the elderly (oligodendrogliomas, ependymal tumours, nerve sheath tumours, meningiomas and pituitary tumours) or mainly in the young (pilocytic astrocytomas, other specified astrocytoma variants including pleomorphic xanthoastrocytomas, choroid plexus tumours and germ cell tumours).

4. Discussion

This analysis of 134,509 primary CNS tumours across the whole of England from 1979 through 2003 is the single largest reported study of longitudinal trends in CNS tumour incidence. Availability of such large numbers of cases derived from a high quality national cancer registration system allows us to study in detail the variation in incidence trends by sex, age, tumour behaviour and histology. Overall, the incidence of CNS tumours in England gradually increased from 1979 until 1992 and then levelled-off. Indeed since 2001, there seems to be a slight downturn in incidence and future studies will have to establish whether this decline continues.

This increase in overall incidence was mainly due to increases in the incidence in the young (0–24 years) and the elderly (65–84 years), but in both these age groups the incidence has been stable over the last ten years of the analysis period. Looking beyond the overall trend, there are still some CNS tumours which show an increase in incidence in all age groups (anaplastic astrocytomas, glioblastomas, anaplastic oligodendrogliomas, mixed gliomas and neuronal and mixed neuronal-glial tumours); in those 0–24 years of age (pilocytic astrocytomas); and in those 25–84 years of age (meningiomas) up to and including the most recent time period.

The variation in temporal trends by age and by histology suggests that no single carcinogen (or lack of protective factor) can explain the rise and the subsequent stabilisation in

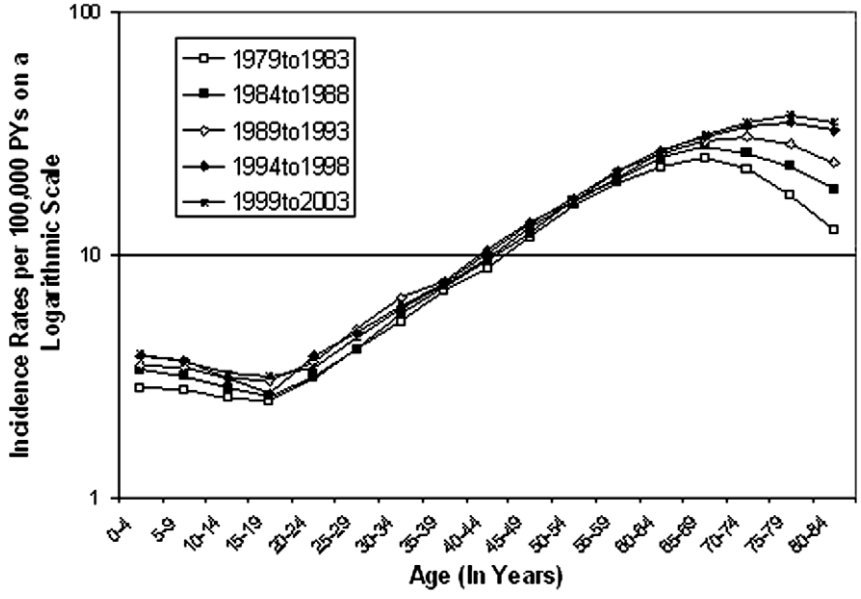

Fig. 3 – Age-specific logarithmic incidence curves of primary CNS tumours in England from 1979 to 2003.

Table 2 – Average annual percentage change (AAPC) of primary CNS tumours in England from 1979 to 2003 across four different age groups.[a, b].

	Number of cases	Average annual percentage change				
		0–14 years	15–24 years	25–64 years	65–84 years	
Total CNS tumours	**134,509**	**1.3 (1.0, 1.6)**	**0.9 (0.6, 1.3)**	**0.4 (0.3, 0.5)**	**2.5 (2.3, 2.6)**	[c]
Tumours of neuroepithelial tissue	70,048	**2.2 (1.8, 2.6)**	**1.6 (1.1, 2.1)**	**0.4 (0.3, 0.5)**	**2.9 (2.7, 3.1)**	[c]
Astrocytic tumours	40,327	**3.0 (2.4, 3.6)**	**2.2 (1.5, 3.0)**	**2.3 (2.1, 2.5)**	**6.2 (5.9, 6.5)**	[c]
Specified diffuse astrocytomas	1036	1.2 (−1.5, 4.1)	**4.3 (1.0, 7.7)**	0.2 (−0.8, 1.2)	−1.0 (−3.6, 1.7)	
Anaplastic astrocytoma	1689	**8.9 (5.3, 12.7)**	**12.2 (8.0, 16.5)**	**7.7 (6.8, 8.7)**	**8.7 (6.9, 10.4)**	
Glioblastoma	18,309	**6.5 (4.2, 8.8)**	**5.6 (3.6, 7.6)**	**7.8 (7.5, 8.1)**	**11.8 (11.4, 12.3)**	[c]
Pilocytic astrocytoma	1553	**8.4 (7.4, 9.5)**	**8.4 (6.4, 10.5)**	**4.5 (2.6, 6.3)**	−0.4 (−4.4, 3.9)	[c]
Other specified astrocytoma variants	91	**19.5 (11.5, 28.0)**	**22.0 (11.3, 33.6)**	2.8 (−2.5, 8.5)	16.7 (−3.7, 41.4)	[c]
Astrocytoma NOS	17,649	**−1.7 (−2.5, −1.0)**	**−1.2 (−2.1, −0.3)**	**−2.7 (−3.0, −2.5)**	**−1.0 (−1.4, −0.6)**	[c]
Oligodendroglial tumours	3082	−1.6 (−4.3, 1.2)	1.6 (−0.6, 3.8)	**3.4 (2.8, 4.0)**	**5.6 (4.0, 7.2)**	[c]
Oligodendroglioma	2557	**−3.5 (−6.5, −0.5)**	0.2 (−2.1, 2.5)	**1.6 (1.0, 2.3)**	**3.3 (1.7, 5.0)**	
Anaplastic oligodendroglioma	525	**10.8 (1.9, 20.5)**	**16.3 (6.8, 26.6)**	**14.8 (12.7, 16.9)**	**18.8 (13.3, 24.5)**	
Glioma NOS	20,041	**1.2 (0.2, 2.2)**	**−4.0 (−5.4, −2.6)**	**−6.1 (−6.4, −5.8)**	**−1.1 (−1.3, −0.8)**	[c]
Mixed gliomas	765	3.4 (−1.2, 8.3)	**8.3 (3.7, 13.1)**	**6.3 (5.0, 7.7)**	**8.3 (4.9, 11.8)**	
Ependymal tumours	2380	0.8 (−0.4, 2.0)	1.56 (−0.2, 3.4)	**2.8 (2.1, 3.6)**	**5.7 (3.8, 7.6)**	[c]
Choroid plexus tumours	215	**6.7 (3.6, 9.8)**	2.5 (−4.2, 9.7)	0.2 (−2.9, 3.3)	−0.3 (−7.7, 7.7)	[c]
Glial tumours of uncertain origin	198	−3.5 (−8.0, 1.1)	**7.2 (0.5, 14.5)**	**−9.5 (−12.2, −6.9)**	−1.1 (−6.7, 4.8)	[c]
Neuronal and mixed neuronal-glial tumours	475	**14.6 (10.8, 18.6)**	**14.2 (10.4, 18.2)**	**11.3 (8.9, 13.8)**	**9.1 (3.3, 15.2)**	
Pineal parenchymal tumours	543	0.1 (−2.4, 2.6)	−2.2 (−5.1, 0.7)	0.0 (−1.7, 1.7)	**4.4 (1.1, 7.8)**	
Embryonal tumours	2022	**1.4 (0.6, 2.1)**	**2.1 (0.4, 3.8)**	**2.8 (1.3, 4.3)**	**8.2 (1.5, 15.3)**	
Medulloblastoma	1707	−0.2 (−1.0, 0.6)	−0.9 (−2.7, 0.9)	0.5 (−1.1, 2.1)	2.5 (−5.4, 11.2)	
Supratentorial primitive neuroectodermal tumour	314	**16.6 (13.1, 20.2)**	**20.4 (14.0, 27.2)**	**13.5 (9.3, 18.0)**	**17.3 (4.3, 32.0)**	
Other embryonal tumours	1					
Tumours of cranial and spinal nerves						
Nerve sheath tumours	8709	**−4.6 (−6.2, −3.0)**	0.4 (−0.9, 1.8)	**2.2 (1.8, 2.6)**	**1.5 (0.9, 2.2)**	[c]
Tumours of the meninges	21,062	1.8 (−0.8, 4.5)	−0.6 (−0.9, 2.1)	**1.2 (1.0, 1.5)**	**2.9 (2.6, 3.3)**	[c]
Meningioma	19,721	1.0 (−1.8, 3.9)	0.9 (−0.9, 2.8)	**1.3 (1.0, 1.5)**	**3.0 (2.7, 3.3)**	[c]
Primary melanocytic lesions	28	8.4 (−2.8, 20.8)		−3.9 (−10.6, 3.3)	**24.3 (−2.1, 57.9)**	
Hemangioblastoma	1313	4.2 (−3.6, 12.6)	−0.3 (−3.0, 2.5)	0.6 (−0.2, 1.5)	0.4 (−1.4, 2.3)	
Germ cell tumours						
Germ cell tumours	488	**3.0 (1.0, 5.1)**	**6.0 (3.5, 8.6)**	0.3 (−2.2, 2.9)	−1.4 (−7.5, 5.1)	[c]
Tumours of the sellar region	13,497	−0.2 (−1.5, 1.2)	−0.2 (−1.2, 0.7)	**0.5 (0.2, 0.8)**	**3.1 (2.6, 3.6)**	[c]
Craniopharyngioma	1484	−0.4 (−1.8, 1.1)	**−2.1 (−4.0, 0.0)**	−0.8 (−1.8, 0.2)	0.9 (−1.0, 2.9)	
Pituitary tumours	12,013	0.7 (−2.6, 4.2)	0.3 (−0.8, 1.4)	**0.6 (0.3, 0.9)**	**3.3 (2.8, 3.8)**	[c]
Miscellaneous tumours	485	**−6.39 (−11.3, −1.2)**	**−10.3 (−14.8, −5.6)**	**−4.3 (−5.8, −2.7)**	−1.9 (−4.6, 0.8)	
Blood and lymphatic vessel tumours	346	**−11.9 (−18.0, −5.4)**	**−12.2 (−17.4, −6.6)**	**−4.8 (−6.6, −3.0)**	−3.3 (−6.8, 0.2)	
Chordoma	139	**14.8 (−0.8, 33.0)**	−5.0 (−13.5, 4.4)	−2.7 (−5.7, 0.3)	0.1 (−4.0, 4.5)	
Unspecified tumours						
Unspecified tumours	20,220	**−2.5 (−3.6, −1.5)**	−0.7 (−2.0, 0.6)	**−1.9 (−2.2, −1.6)**	**1.4 (1.1, 1.6)**[c]	[c]

[a] AAPC was not reported for groups of insufficient size.

[b] Statistically significant AAPC are in bold ($p < 0.05$) and 95% CI are given in parentheses.

[c] The difference in AAPC across the four age groups is statistically significant ($p < 0.05$).

incidence. Prolonged exposure to radiofrequency signals from mobile phones or occupational electric and magnetic fields, which have been under investigation,[34,35] are unlikely to have contributed in a major way specifically to the increase of incidence seen only in the elderly or the young. If the increase in incidence in the young is the result of exposure to a tumourigenic factor in pregnancy or early childhood then the latent period would have to be very short to produce such an effect. Studies which have looked at maternal occupation during pregnancy, paternal occupation during peri-conceptional period, maternal exposure to tobacco smoke, N-nitroso compounds in household water during pregnancy and proximity of home address at birth to high voltage power lines have not found a consistent link or a dose-risk relationship.[40–47] Clearly the aetiology of the majority of CNS tumours is still unknown and these arguments will need to be revisited as our understanding increases.

In the absence of an identifiable causative factor, is there an alternative explanation for the continuing rise of some CNS tumours? Some of the answer probably lies in the observation of a decrease in incidence in the last ten years of CNS tumours characterised by lack of specificity for behaviour (CNS tumours of unknown/borderline behaviour, Fig. 2) or histology (e.g. unspecified CNS tumours, and gliomas not otherwise specified, Table 1). This would suggest that improvements in neurosurgical techniques and developments in neuropathology have enabled more specific diagnosis to be made leading to a shift of tumours previously diagnosed as "not otherwise specified" or "unspecified" to more specific histologies and registered as such. Data on CNS tumours from the European Automated Childhood Cancer Information System show an increasing proportion of microscopically verified CNS tumours over time leading to a decrease in the "not specified" category.[48] Included among tumours that are now being increasingly recognised, are oligodendroglial tumours and mixed gliomas (using 1p/19q chromosomal loss as a diagnostic tool)[49] and neuronal tumours like central neurocytomas where diagnosis is assisted by electron microscopy and immunohistochemistry.[50] However, there is an increase in astrocytic tumours overall and shift alone from astrocytoma not otherwise specified to anaplastic astrocytoma or glioblastoma cannot explain the increase.

There is another interesting facet to the trends of these groups of less specific CNS tumours. As seen in Table 1 their incidence actually increased for the initial period of the analysis (along with most other histological sub-groups of CNS tumours) before declining. This would imply that the initial increase was a result of a factor which affected all groups. It has been proposed elsewhere that a steep increase in the use of CT scan imaging of the head, particularly in the elderly, accounted for a large part of the observed increase in incidence seen in the USA and Nordic countries during the 1970s and 1980s.[23,25,31,51] Our observations support this, as elderly patients with an underlying primary CNS tumour who present with focal neurological symptoms or after accidents are far more likely previously to have been clinically (mis)diagnosed as having cerebrovascular disease or transient ischaemic attack without the benefit of neuroimaging.[52] This argument can be extrapolated to low-grade astroglial and neuronal tumours as well. Smith et al. have attributed the increase in incidence seen in low-grade glial lesions in the brain stem in children to changes in detection and/or reporting of childhood CNS tumours during the mid-1980s in USA.[24] Another consequence of the widespread availability and use of improved neuroimaging has been the diagnosis of slow growing low-grade CNS tumours at an earlier age. In our study the median age at diagnosis for pilocytic astrocytoma decreased from 13 years in the period 1979–1983 to 10 years from 1999 to 2003 (data not shown).

The increase in high-grade astrocytomas (anaplastic astrocytomas and glioblastomas) and high-grade gliomas (anaplastic oligodendrogliomas) is more difficult to interpret. The increase is not restricted to children or the elderly but has happened across all age groups (Table 2) and so cannot be simply attributed to increased availability of neuroimaging or a change in attitude towards the elderly. Due to the aggressive nature and poor outlook of these tumours, they are unlikely to be under diagnosed or picked up coincidentally. As distinct and well-recognised malignant pathological entities, the incidence of this group of CNS tumours is unlikely to be affected by changes in classification or registration practices, although advances in neurosurgery and neuropathology would lead to increased specificity and some shift between tumour categories.

Studies from Europe[19,20] and USA[53] have reported continuing increase of high-grade astrocytomas and gliomas in the 1990s and early part of the 21st century. Lönn et al. reported that the increase in the incidence of glioblastoma from 1993 to 1998 seen in the Nordic countries was confined to those aged 60–79 years with no change in those aged 20–59 years.[19] On the other hand, the increase in incidence of high-grade astrocytomas in Netherlands from 1989 to 2003 was seen in those aged 15–44 years as well as those above 65 years of age with no significant change in adults aged 45–64 years.[20] Finally, McCarthy et al., have recently reported continuing increases in the incidence of anaplastic oligodendroglioma in those aged 20–64 years from USA.[53] Our analysis shows that the increase of high-grade astrocytomas and gliomas in the most recent period is not restricted to those aged 65–84 years (Fig. 4). All these factors make it difficult to dismiss the increase in incidence in high-grade astrocytomas and other gliomas as an artefact. This is a group of tumours for which aetiological studies may yet yield some clues to their changing incidence.

5. Conclusion

In summary, we present the single largest study on the longitudinal trends of CNS tumours derived from data obtained from a high quality national cancer registration system. The overall increase of incidence seen in CNS tumours in England in 1970s and 1980s was mainly in the young and the elderly and has now levelled off and may be decreasing. There is however variation in these trends by histology and the incidence of some histological sub-groups has continued to increase until the most recent period of analysis. Much of the initial increase can be attributed to the emergence of widely available neuroimaging, while more recent changes in trends

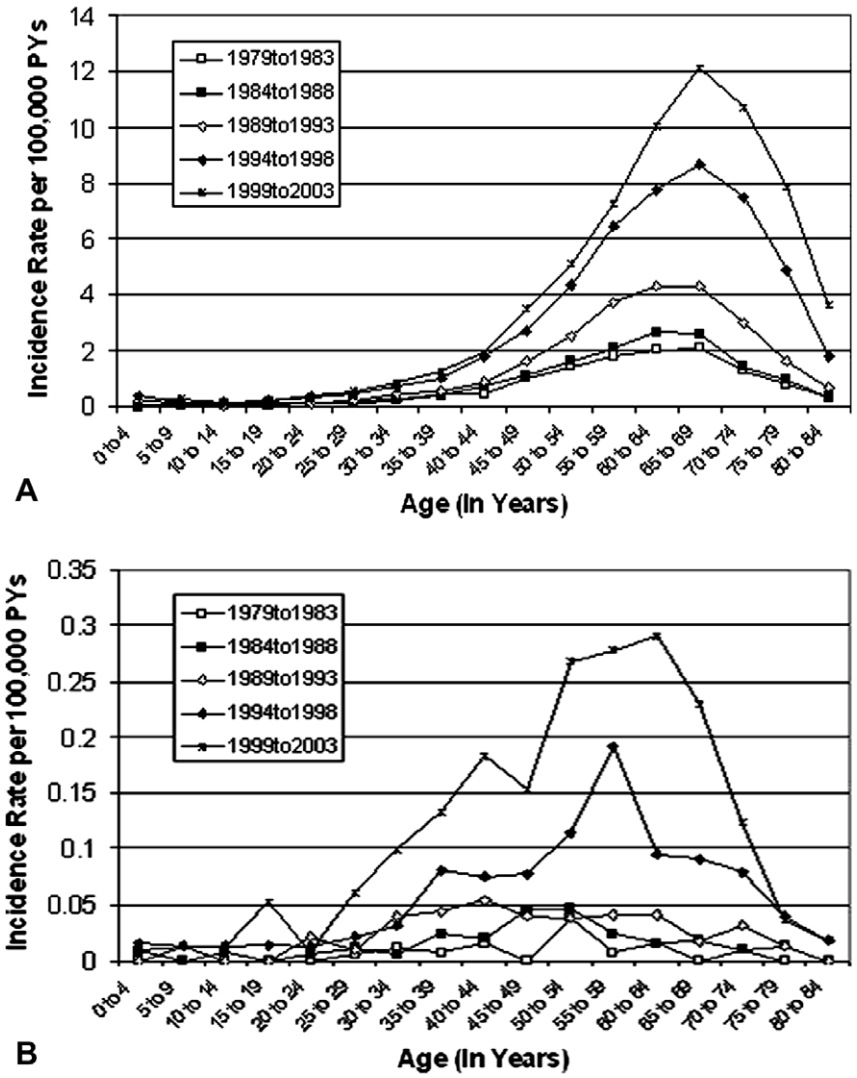

Fig. 4 – Age-specific incidence curves of (A) high-grade astrocytomas, and (B) high-grade oligodendrogliomas in England from 1979 to 2003.

of specific sub-groups of CNS tumours is likely to be as a result of increased specificity of diagnosis leading to a shift in registered categories. However, the trends of high-grade astrocytomas and gliomas as well as pilocytic astrocytomas need further observation and investigation.

Conflict of interest statement

None declared.

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6.4 Comparative incidence patterns and trends of gonadal and extragonadal germ cell tumours in England, 1979 to 2003

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Condensed Abstract

Malignant germ cell tumours, which display heterogeneity by histology and site, occur at all ages with incidence peaks in infancy and young adulthood. Regardless of site, the similarity in shapes of the age-incidence curves of germ cell tumours, suggests a common initiation of these tumours in embryonic/foetal life with variable rates of tumour progression as a result of local factors or events during postnatal and pubertal period.

Abstract

Background - Gonadal and extragonadal germ cell tumours (GCT) are thought to arise from primordial germ cells and could have similar aetiopathogenesis. Unlike testicular GCT, there has been limited comprehensive population-based analysis of ovarian and extragonadal GCT.

Methods - All malignant GCT and benign and uncertain behaviour central nervous system (CNS) GCT registered in England in the age group 0-84 years from 1979-2003 were included. Incidence rates were calculated and adjusted to world standard population.

Results – There were 33364 GCT (92.5% testes, 3.9% ovary, 3.2% extragondal) in persons aged 0-84 years. CNS was the most common extragonadal site. An initial peak in incidence at 0-4 years of age of non-germinomas was seen at all sites except ovary. Second incidence peaks between ages of 10-39 years, which was more marked in males, were also seen at all sites. The age at this incidence peak varied by site and was 10-14 years (CNS), 15-19 years (ovary), 25-29 years (other extragonadal sites), and 30-34 years (testes). A significant increase in incidence with time was seen in germinomas (testes, CNS) and non-germinomas (testes, ovary).

Conclusions – These age-incidence patterns suggest a common initiation of GCT in embryonic/foetal life with variable rates of tumour progression as a result of subsequent events which may be site-specific. Future genetic studies need to consider GCT from all sites to enable a better understanding of their aetiology.

Keywords

Germ Cell Neoplasms; Testicular Neoplasms; Ovarian Neoplasms; Central Nervous System Neoplasms; Mediastinal Neoplasms; Incidence; Longitudinal Trends; England

Introduction

Malignant germ cell tumours (GCT), which display heterogeneity by histology and site, occur at all ages with incidence peaks in infancy and young adulthood. 3.3% of all cancers in 0 to 14 year olds are malignant GCT while in the 15 to 24 year age group the proportion increases to 13.8%.[1,2] Testicular tumours, most of which are GCT, are the most common malignancy in young men aged 15 to 44 years[3] and the incidence of these cancers is estimated to have doubled in the last 40 years.[4] In contrast to testicular GCT, ovarian GCT represent only 3% of all malignant ovarian tumours with ovarian carcinoma predominating. They are however the most common malignant ovarian tumour in females aged less than 20 years of age.[5,6]

Whereas the epidemiology of testicular GCT has been the subject of extensive research, there has been limited population based analysis of ovarian GCT and none for extragonadal GCT. Knowledge of extragonadal GCT has been derived from retrospective reviews of hospital cases or those on clinical trials[7-10] and such information is likely to be affected by hospital referral patterns and clinical trial registration practices. The secular trends in the incidence of GCT of the ovary, CNS and other extra-gonadal sites, in contrast to the well documented trends for testicular GCT, are so far largely unexplored.

The initiation and promotion of testicular, ovarian and extragonadal GCT could be due to exposure to similar endogenous and/or exogenous causative factors perhaps acting at different sites and at different stages of life. Analysing and contrasting the variation in incidence patterns of GCT across different sites by age, sex and histology could provide a greater understanding of factors critical in tumourigenesis. In order to address this, we present here detailed incidence patterns and trends of gonadal and

extragonadal GCT for the whole of England during the period 1979 through 2003 using high quality national cancer registration data.

Methods

Source of Data

Cancer registration in England is carried out by a network of eight population-based regional registries. These regional registries collect data on cancers registered to residents of their areas, and submit a standard dataset on these registrations to Office for National Statistics (ONS) in London.[11] Anonymised, national cancer registration data on individual patients of all ages newly diagnosed between 1979 and 2003 were obtained from the ONS. Information supplied included year of diagnosis, age at diagnosis, sex of patient, primary site, morphology and behaviour codes.

National population estimates by single year of age, sex and calendar year were supplied by the Population Estimates Unit, ONS. Annual mid-year estimates of population in England are based on census data together with information on births, deaths and migration.[12]

Categorisation of Tumours

Cases of all malignant GCT (morphology codes 9060-9090 with behaviour code '3') based on the International Classification of Diseases for Oncology 1st and 2nd edition (ICD-O1 and ICD-O2) morphology codes were selected.[13,14] In addition, GCT with the above morphology codes located in the central nervous system (CNS) but with benign or uncertain behaviour code (0 and 1 respectively) were also selected. GCT were grouped by histology into germinomas (morphology codes 9060-9064), non-germinomas (9071,

9080-9084, 9090) and other & mixed GCT (9070, 9072, 9073, 9085, 9101-9102) based on the ICD-O1 and ICD-O2 morphology codes.

In addition to grouping by histology, GCT were also grouped by site into

1. Testicular (International Classification of Diseases 9th revision (ICD-9) site codes[15] 186.0-187.9 and International Classification of Diseases 10th revision (ICD-10) site codes[16] C62.0-63.9),
2. Ovarian (ICD-9 site code 183.0 and ICD-10 site code C56.0),
3. Extragonadal – These were further divided into four subgroups based on site
    a. CNS (ICD-9 site codes 191.0-192.9, 194.3, 194.4, 225.0-225.9, 227.3, 227.4, 237.0, 237.1, 237.5, 237.6 and ICD-10 site codes C71.0-C72.9, C75.1-C75.3, D33.0-D33.9, D35.2-35.4, D43.0-43.9, D44.3-D44.5)
    b. Mediastinum & thorax (ICD-9 site codes 162.0-165.9, 171.4, 195.1 and ICD-10 site codes C33.9-C39.9, C49.3, C76.1)
    c. Abdomen & pelvis (ICD-9 site codes 151.0-159.9, 171.5, 171.6, 179.0-185.0, 188.0-189.9, 195.2, 195.3 and ICD-10 site codes C16.0-C26.9, C48.0-C48.8, C49.4, C49.5, C51.0-C58.9 [except C560], C61.9, C64.9-C68.9, C76.2, C76.3)
    d. Other specified (ICD-9 site codes 140.0-150.9, 193.0 and ICD-10 site codes C00.0-C15.9, C73.0)
4. Unspecified (ICD-9 site codes 171.0-171.3, 171.8, 171.9, 172.0-173.9, 195.0, 195.4-199.1 and ICD-10 site codes C44.0-C44.9, C49.0-C49.2, C49.6-C49.9, C76.7-C80.0)

Statistical Methods

Age, sex, site and histology specific incidence rates were calculated and expressed per million person years. All rates were adjusted to the world standard

population using direct methods.[17] To assess the variation in the longitudinal trends with age, the total time period was divided into five quinquennia 1979-1983, 1984-1988, 1989-1993, 1994-1998 and 1999-2003. Average annual percentage change (AAPC) along with the 95% confidence intervals were then calculated for the entire period from 1979-2003. P-values for variability in incidence trends by age group (0-9, 10-49 and 50-84 years), sex, site and histology were also calculated using Poisson regression. Those above the age of 85 were excluded because of possible under-ascertainment and often less specificity of diagnosis. SPSS, R and Microsoft Excel were used for analyzing the data and producing tables and graphs.

Results

Overall Incidence

During the period 1979 through 2003, 33364 GCT (31740 males and 1624 females) were registered in England for those aged 0 to 84 years and the overall age-adjusted incidence rate was 26.44 per million person years. GCT comprised 0.7% of all cancers overall and 11.2% in persons under 30 years of age. The population covered, equated to 1.18 billion PYs. The distribution of GCT in gonadal and extragonadal sites is shown in figure 1. There were 30875 testicular and 1316 ovarian GCT. The age-adjusted incidence rates of testicular and ovarian GCT were 48.37 and 2.34 per million person years respectively. 1060 of the total GCT (3.2%) were extragonadal in location and the age-adjusted incidence rate was 1.05 per million person years.

Although the majority of GCT were located in the gonads in both sexes, there was variation in location by age (figure 2). 42% of all GCT in both male and female children

0 to 14 years of age were extragonadal. The proportion of extragonadal GCT was highest in girls aged 0 to 4 years (figure 2A) and the most common location was abdomen and pelvis (including sacrococcygeal). In boys the proportion of extragonadal GCT was highest at ages 5 to 14 years (figure 2B) and the most common location was CNS.

Age-Specific Incidence Patterns

The age-specific incidence rates for gonadal and extragonadal GCT are shown in figure 3 and 4 respectively. In males, there was a smaller incidence peak at 0 to 4 years of age at most sites followed by a larger peak of incidence in adolescence and young adulthood in GCT at most sites. There was variation in the age when this latter peak was achieved - CNS (10-14 years), mediastinum & thorax (25 to 29 years), abdomen & pelvis (25 to 29 years) and testes (30 to 34 years). In contrast, in females the dominant peak incidence at 0 to 4 years at all extragonadal sites exceeded that in males with the maximum differential in abdomen & pelvis, but was absent in ovarian GCT. The ovarian GCT peak in incidence was at 15 to 19 years. This pubertal peak was also seen in CNS GCT at 10 to 14 years of age but was not well-defined in other extragonadal sites in females.

Distribution and Incidence Patterns by Site and Histology

CNS was the most common location for extragonadal GCT in both males and females followed by mediastinum & thorax in males and abdomen & pelvis in females (Figure 1 and Table I). Germinoma (seminoma) was the most common histology in testicular GCT whilst non-germinoma was most common in ovarian and extragonadal GCT. This pattern was true for most extragonadal sites with the exception of the pineal gland where germinomas exceeded non-germinomas.

Detailed age-incidence patterns for GCT by histology and each of the gonadal and extragonadal sites are shown in figure 5 and 6 and a summary of the observations is in Table II.

Longitudinal Incidence Trends

For the period 1979 to 2003, there was a statistically significant increase in the incidence of GCT overall as well as for testicular, ovarian and CNS GCT but not in GCT of mediastinum & thorax and of abdomen & pelvis (table III). The overall increase was seen in germinomas and non-germinomas but this varied by site. There was significant increase in incidence of testicular seminomas and, to a lesser extent, of non-seminomas. In ovarian GCT the increase was exclusively from non-dysgerminomas with no change in dysgerminomas. In CNS GCT the increase was entirely due to an increase in the incidence of germinomas. Most of this increase was seen in the above tumour groups in the 10 to 49 year age group. There was also a significant increase in the incidence of non-germinomas of the abdomen & pelvis in the 0 to 9 year age group.

Discussion

This analysis of 33364 cases of gonadal and extragonadal GCT across the whole of England from 1979 through 2003 is the first comprehensive review on incidence patterns and longitudinal trends of these tumours. The large difference in the incidence of testicular and ovarian/extragonadal GCT seen in this analysis is likely to be related to the lower number of susceptible germ cells surviving in non-testicular sites by the time of puberty. After initial multiplication by mitosis, the primordial germ cells (oogonium) in the ovary peak in numbers (around 7 million) at 16-20 weeks of gestation after which

they enter meiotic arrest (now called oocyte) and then steadily decline in numbers so that by birth 1-2 million oocytes are left and by puberty only 300,000.[18] While the number of primordial germ cells in extragonadal locations is not known, like their counterparts in the ovary, they also enter meiotic arrest in foetal life and undergo apoptosis.[19,20] In contrast, the mitotic proliferation of spermatogonal germ cells continues throughout adult reproductive life.

The published literature is dominated by studies on testicular GCT with limited population-based information on ovarian[5,21,22] and CNS GCT[23,24], and none on GCT located at other extragonadal sites. Consequently, there are no previous studies contrasting the incidence patterns of gonadal and extragonadal GCT. Such an analysis is important in gaining a better understanding of the aetiopathogenesis of these tumours which show considerable heterogeneity by site and histology, but are regarded as one disease entity.[25] The heterogeneity is thought to be a reflection of the developmental potential of germ cells at different stages of maturation and with different imprinting status.[25] The primordial germ cells, which form in the wall of the yolk sac during the fourth week of embryogenesis and migrate into the developing gonads, are considered to be the cell of origin of gonadal (testicular and ovarian) GCT. Extragonadal GCT are also thought to arise in the same primordial germ cells which have migrated aberrantly along the midline to the CNS, mediastinum and other para-axial sites.[26] The remarkably similar shape of the age-incidence curves (with some variations which are further explored below) of these tumours regardless of site, as summarised in Table II, is consistent with a common cell of origin and possibly a common initiation.

It is probable that subsequent to the migration of primordial germ cells to the respective gonadal and extragonadal sites, there are further critical events during foetal and/or postnatal life which determine the promotion of tumourigenesis and the rate at which this happens. Based on some of the epidemiological observations in our analysis, it is likely that these events vary among the different sites where GCT will eventually develop. Firstly, there is variation in the age of peak incidence of GCT by site in adolescents and young adults. Secondly, while the peak incidences of germinoma and non-germinoma are seen at the same age at extragonadal sites, this is not true for germinomas of the gonads which peak in incidence 5 to 10 years after the non-germinoma peak. Thirdly, the longitudinal trends of testicular, ovarian and extragonadal GCT are dissimilar.

The observed differences by site in the incidence patterns and longitudinal trends of GCT can also provide clues to the exposures associated with GCT. The incidence of testicular GCT has doubled in the last 40 years and an annual increase of 3-6% is reported for Caucasian populations.[27,28] No definitive causative factors have been found to explain this rise in incidence, although there is a strong birth cohort effect and exposure to endogenous maternal estrogens in-utero has been suggested.[27-29] There is a paucity of epidemiological studies on prenatal and postnatal risk factors associated with ovarian and extragonadal GCT which address similar questions. Our analysis confirms the rise in incidence of testicular seminomas and non-seminomas. But, lack of a similar parallel increase in GCT of ovarian and extragonadal sites suggest that the hypothesized hormonal factors may have a lesser role in the aetiopathogenesis of GCT located at these sites.

In summary, the remarkable similarity between the shapes of age-incidence curves of GCT suggests a common initiation of these tumours. This is likely to happen early in the embryonal period prior to migration of primordial germ cells into the genital ridges or ectopic sites. However, the variation in peak incidence and longitudinal trends by site suggests that progression of tumourigenesis is influenced by events during the foetal and/or postnatal period which are likely to be site-specific. Future genetic and epidemiological studies need to consider GCT at all sites rather than be restricted to testicular and ovarian GCT to enable a better understanding of the biology and aetiology of these tumours.

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Figure 1 Distribution of GCT in Gonadal and Extragonadal Sites in England, 1979 to 2003

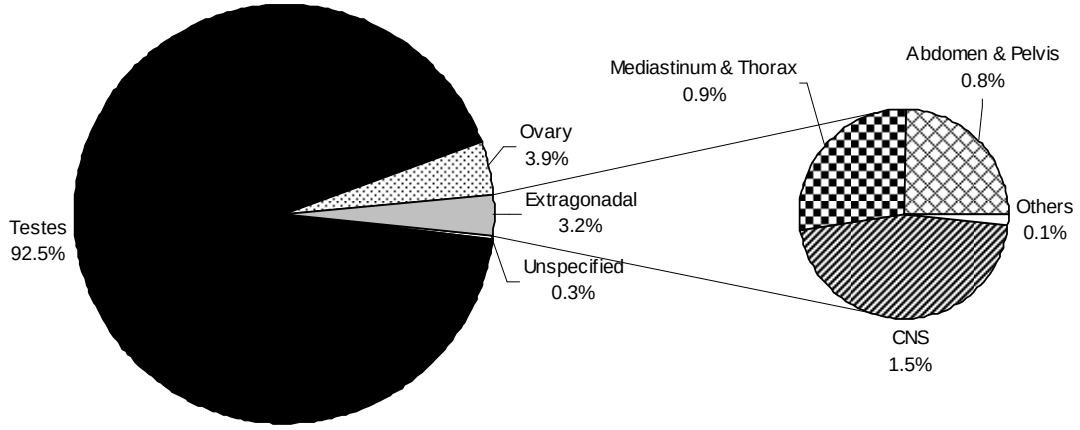
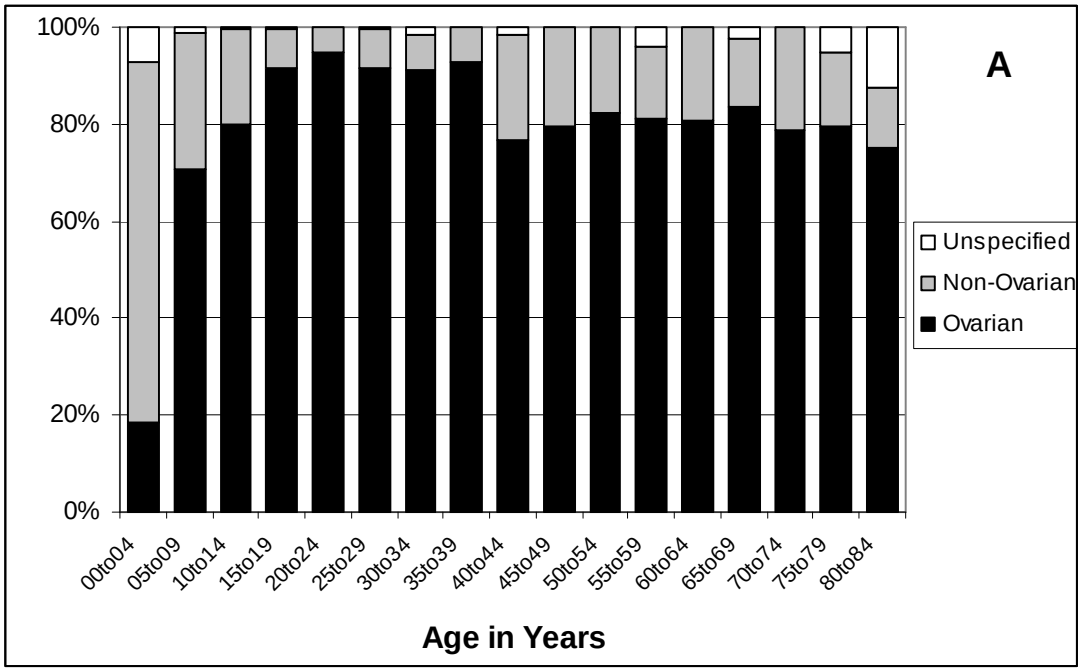


Figure 2 Age Related Variation in the Proportion of Gonadal and Extragonadal GCT in (A) Females, and (B) Males



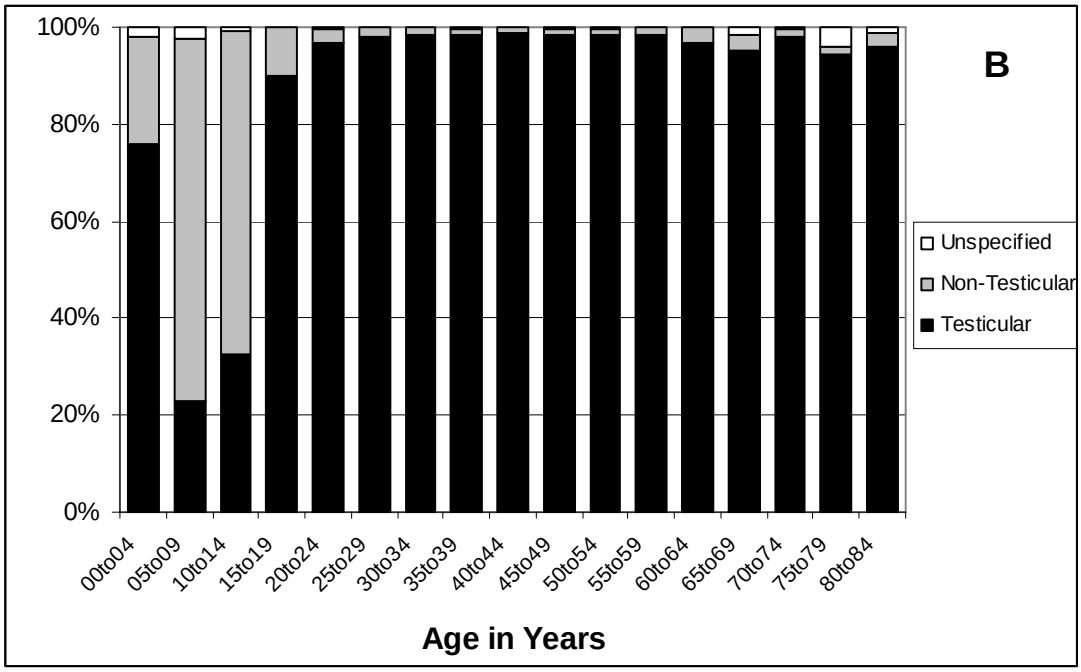


Figure 3 Age- and Sex-Specific Incidence Patterns of Gonadal GCT in England, 1979 to 2003

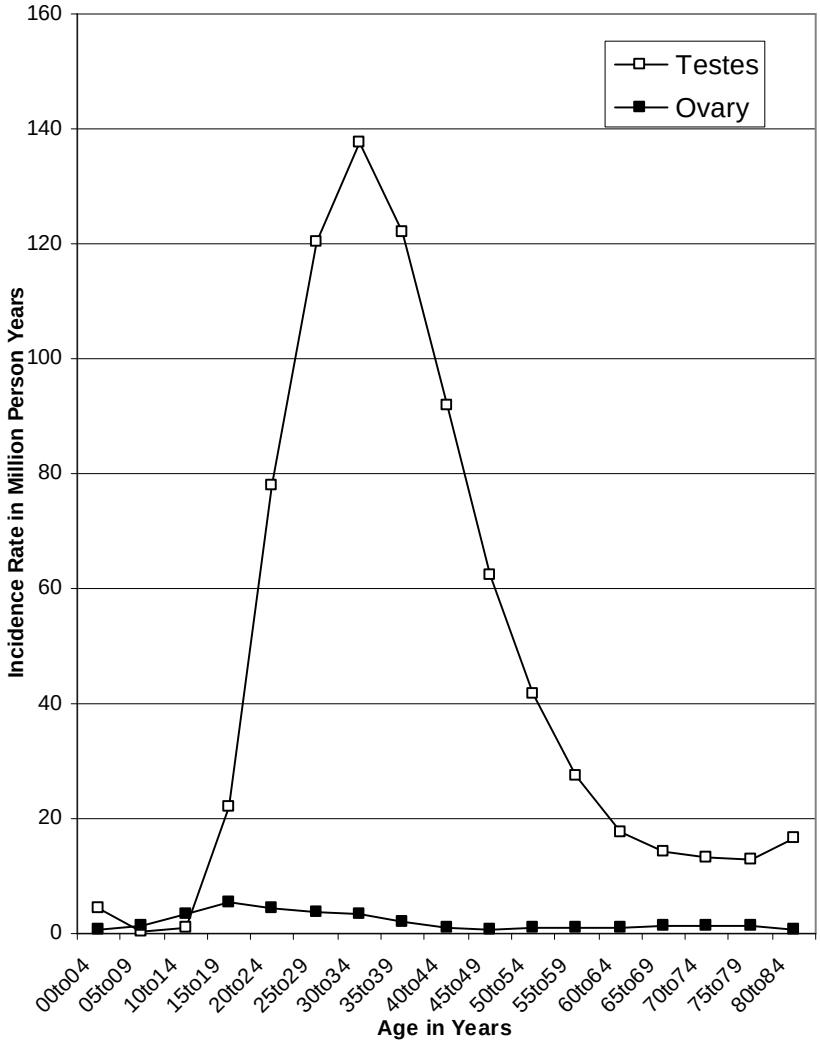


Figure 4 Age- and Sex-Specific Incidence Patterns of Extragonadal GCT in England, 1979 to 2003

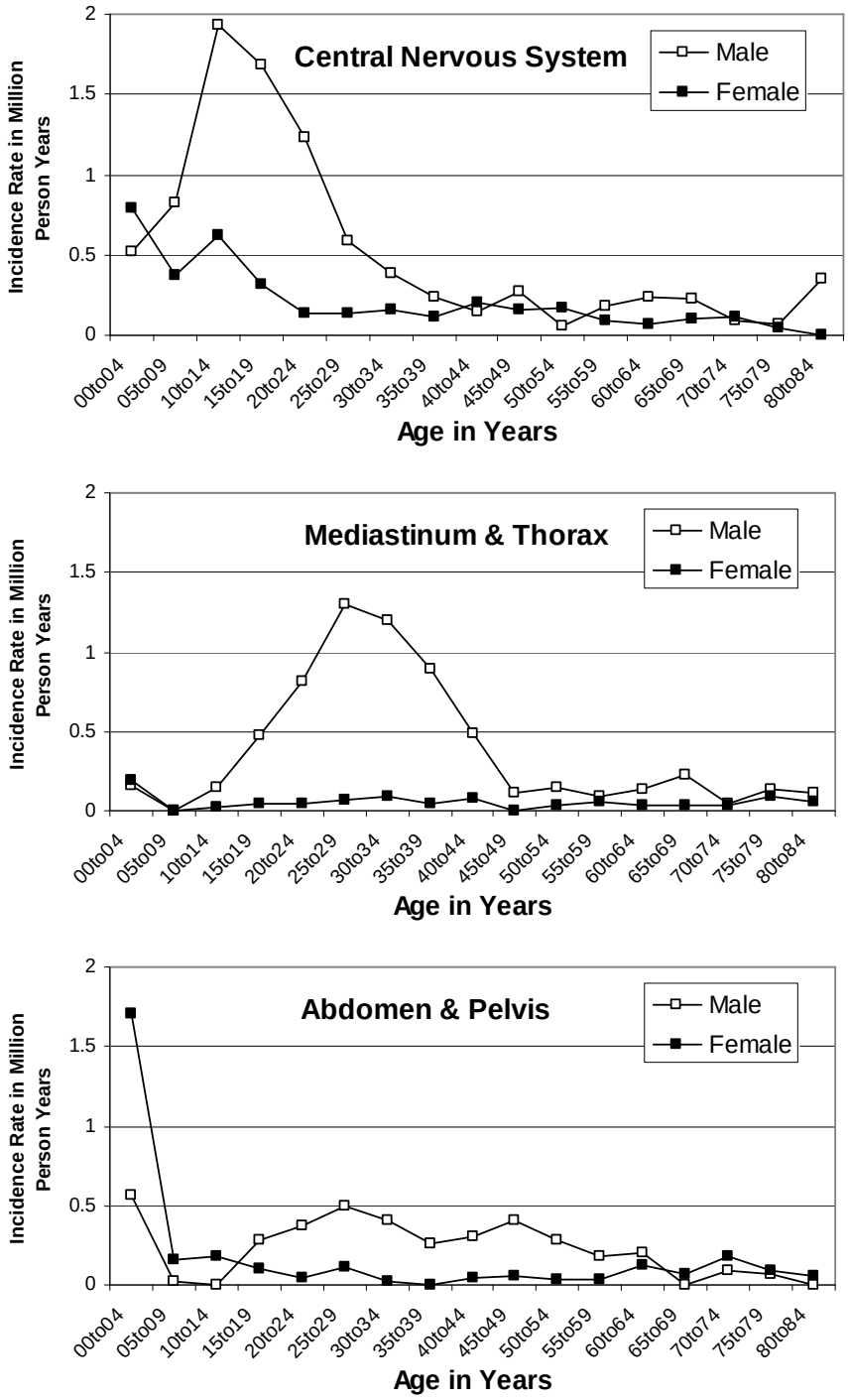
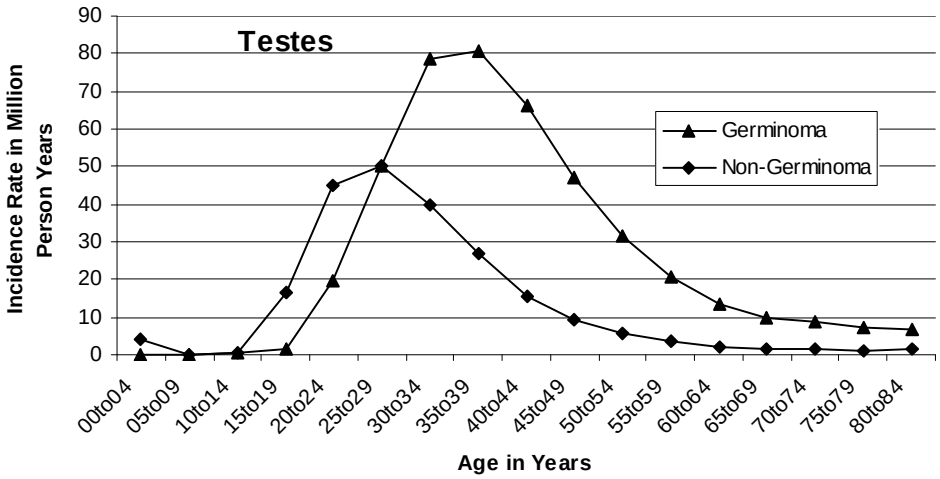


Figure 5 Age- and Histology-Specific Incidence Rate Patterns of Gonadal GCT in England, 1979 to 2003 (Note different scales on the Y-axis)



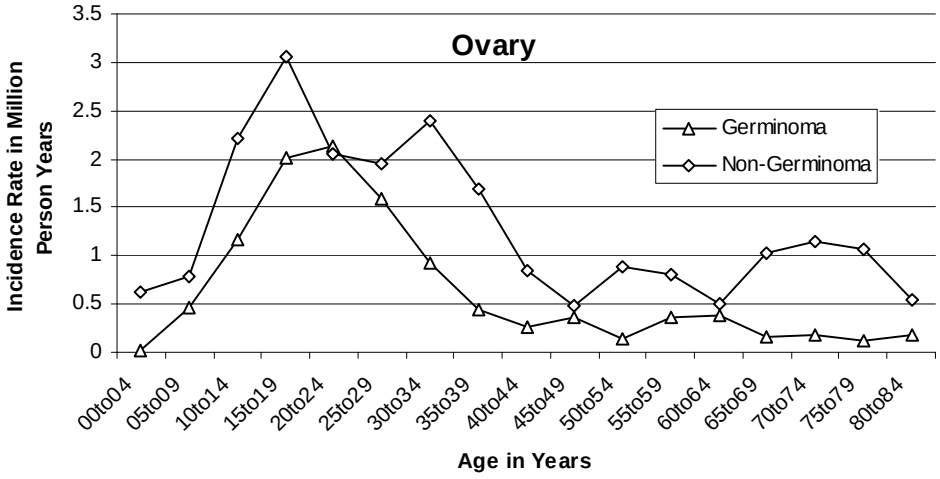


Figure 6 Age- and Histology-Specific Incidence Rate Patterns of Extragonadal GCT in England, 1979 to 2003

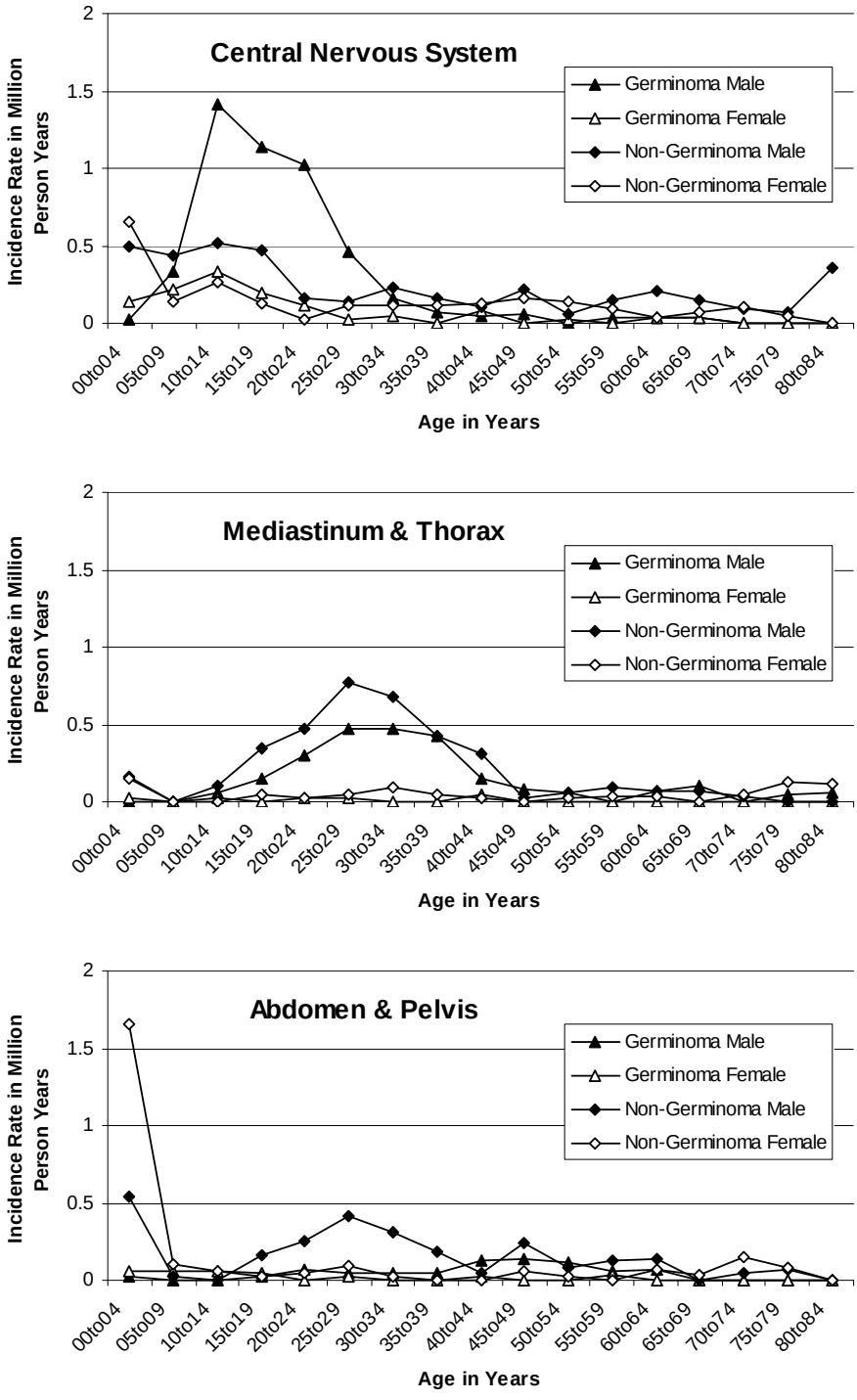


Table I Distribution of Gonadal & Extragonadal GCT by Site and Histology in England, 1979 to 2003

	Germinoma	Non-Germinoma	Mixed GCT	Unspecified Histology	Total	Incidence rate*
Testes	**17202**	**9353**	**2556**	**1764**	**30875**	**48.37**
Ovary	**433**	**836**	**47**	**0**	**1316**	**2.34**
All Non Gonadal	**394**	**605**	**61**	**0**	**1060**	**1.05**
Male	**329**	**403**	**45**	**0**	**777**	**1.45**
CNS	200	141	9	0	**350**	**0.71**
Pineal	168	40	4	0	**212**	
Non-Pineal	32	101	5	0	**138**	
Mediastinum & Thorax	99	149	12	0	**260**	**0.43**
Abdomen & Pelvis	29	104	21	0	**154**	**0.28**
Others	1	9	3	0	**13**	**0.03**
Female	**65**	**202**	**16**	**0**	**283**	**0.65**
CNS	48	86	2	0	**136**	**0.3**
Pineal	22	8	0	0	**30**	
Non-Pineal	26	78	2	0	**106**	
Mediastinum & Thorax	6	25	2	0	**33**	**0.06**
Abdomen & Pelvis	11	87	10	0	**108**	**0.28**
Others	0	4	2	0	**6**	**0.01**
Unspecified Site	47	55	11	0	**113**	**0.09**

*Expressed per million person years.

GCT – Germ Cell Tumours, CNS – Central Nervous System

Table II Summary of Incidence Peaks Seen in Gonadal and Extragonadal GCT

Site	Histology	0 to 4 Years Age Incidence Peak	Adolescent & Young Adult Incidence Peak
Testes	Germinoma	No	Yes (peak at 35 to 39 year of age)
	Non-Germinoma	Yes	Yes (peak at 25 to 29 year of age)
Ovary	Germinoma	No	Yes (peak at 20 to 24 year of age)
	Non-Germinoma	No	Yes (peak at 15 to 19 year of age)
Central Nervous System	Germinoma	No	Yes (peak at 10 to 14 year of age and male > female)
	Non-Germinoma	Yes (female > male)	Yes (peak at 10 to 14 year of age and male > female)
Mediastinum & Thorax	Germinoma	No	Yes (peak at 25 to 29 year of age and male > female)
	Non-Germinoma	Yes (female = male)	Yes (peak at 25 to 29 year of age and male > female)
Abdomen & Pelvis	Germinoma	No	No
	Non-Germinoma	Yes (female > male)	Yes (peak at 25 to 29 year of age and male > female)

Table III Age-Adjusted Incidence Rates of GCT by Histology and Site for Successive Five Year Periods in England, 1979-2003

	Age-Adjusted Incidence Rate in Million Person Years					Average Annual Percentage Change (95% Confidence Interval)*			
	1979-1983	1984-1988	1989-1993	1994-1998	1999-2003	0 to 84 yrs	0 to 9 yrs	10 to 49 yrs	50 to 84 yrs
Overall	19.83	24.58	28.35	31.75	34.76	2.67 (2.51,2.83)	1.05 (-0.23,2.35)	2.91 (2.73,3.08)	1.35 (0.92 1.78)
Germinoma	10.46	12.61	14.32	18.00	20.48	3.43 (3.21,3.65)	8.92 (4.36,13.67)	3.67 (3.43,3.91)	2.14 (1.61,2.67)
Non-Germinoma	8.16	9.17	8.79	10.38	8.83	0.56 (0.29,0.83)	0.2 (-1.18,1.6)	0.71 (0.42,0.99)	-1.08 (-2.08,-0.07)
Testes	36.25	45.34	52.58	58.99	65.21	2.78 (2.61,2.94)	-2.66 (-4.66,-0.62)	2.95 (2.77,3.13)	1.88 (1.42,2.33)
Germinoma	19.92	24.10	27.35	34.36	39.46	3.47 (3.24,3.69)		3.7 (3.46,3.95)	2.32 (1.78,2.86)
Non-Germinoma	13.95	15.70	14.83	18.03	15.13	0.58 (0.29,0.87)	-2.74 (-4.85,-0.59)	0.64 (0.34,0.95)	0.67 (-0.6,1.96)
Ovary	1.92	2.01	2.02	2.52	2.51	1.36 (0.59,2.14)	3.07 (-0.22,6.48)	2.64 (1.75,3.55)	-4.83 (-6.64,-2.98)
Germinoma	0.71	0.76	0.64	0.80	0.71	-0.03 (-1.35,1.31)	6.18 (-0.96,13.86)	0.5 (-0.94,1.96)	-6.68 (-10.73,-2.46)
Non-Germinoma	1.14	1.25	1.34	1.61	1.61	1.65 (0.68,2.63)	2.06 (-1.84,6.12)	3.5 (2.32,4.69)	-4.72 (-6.78,-2.62)
Central Nervous System	0.31	0.33	0.50	0.50	0.53	2.94 (1.64,4.26)	1.77 (-1.12,4.75)	3.8 (2.25,5.38)	-1.02 (-5.01,3.12)
Germinoma	0.11	0.09	0.27	0.29	0.35	6.88 (4.92,8.89)	6.95 (0.94,13.32)	7.31 (5.19,9.49)	
Non-Germinoma	0.21	0.23	0.22	0.19	0.17	-1.11 (-2.91,0.71)	-0.57 (-3.96,2.94)	-1.76 (-4.17,0.7)	0.08 (-4.28,4.66)
Mediastinum & Thorax	0.21	0.23	0.32	0.27	0.19	-0.15 (-1.76,1.48)		0.37 (-1.38,2.16)	-5.52 (-10.29,-0.5)
Germinoma	0.07	0.06	0.09	0.13	0.09	2.35 (-0.42,5.2)		2.67 (-0.25,5.7)	
Non-Germinoma	0.14	0.16	0.22	0.13	0.09	-1.66 (-3.73,0.44)		-1.11 (-3.38,1.2)	-9.38 (-16.09,-2.14)
Abdomen & Pelvis	0.19	0.28	0.22	0.26	0.26	0.49 (-1.22,2.24)	5.87 (2.64,9.19)	-1.72 (-4.11,0.73)	-3.4 (-7.53,0.9)
Germinoma	0.02	0.04	0.03	0.04	0.05	1.92 (-2.48,6.54)		0.47 (-4.87,6.13)	
Non-Germinoma	0.15	0.21	0.16	0.21	0.17	-0.19 (-2.19,1.85)	4.88 (1.65,8.23)	-3.91 (-6.92,-0.8)	-4.91 (-10.41,0.93)

* Average Annual Percentage Change was not reported for groups of insufficient size

6.5 The Contrasting Age-Incidence Patterns of Bone Tumours in Teenagers and Young Adults: Implications for Aetiology

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Manuscript in Preparation

TITLE PAGE

Manuscript Category

Original Article (Epidemiology)

Title

The Contrasting Age-Incidence Patterns of Bone Tumours in Teenagers and Young Adults: Implications for Aetiology

Running Title

Bone Tumour Incidence Patterns

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Condensed Abstract

Incidence patterns of osteosarcoma and Ewing sarcoma during adolescence points towards a link with puberty. The variation in these patterns with site suggests pubertal bone growth to be a key factor in osteosarcoma while different biological pathways, which may be unrelated to growth, could also be relevant for Ewing sarcoma.

Abstract

Background – Nearly 6% of malignant tumours in teenagers and young adults (TYA) aged 15 to 24 years are bone tumours, although their contribution to cancer-related mortality is disproportionately higher in this age group. Studies suggest a link between osteosarcoma and Ewing sarcoma and puberty although the biological pathways have not yet been fully elucidated.

Methods - Using the national cancer registration data for England, we have analysed incidence patterns and analysed variation with age, sex, morphology and site.

Results - During the period 1979 through 2003, 1185 bone tumours (12.9% of all bone tumours) were registered in TYA. Nearly 85% of these were osteosarcoma and Ewing sarcoma both of which peak in adolescence. The peak incidence of osteosarcoma of the

long bones of the lower limb more than six times larger than that at any other site. In contrast, peak incidence of Ewing sarcomas located in the central axis exceeded those in the long bones of the lower limb. Less than 10% of bone tumours in TYA were chondrosarcomas and the incidence was highest for central axis chondrosarcomas followed by those in the long bones of the lower limb.

Conclusions – These patterns suggest that puberty plays a role in the development of osteosarcoma and Ewing sarcoma but not chondrosarcoma. Variation in these patterns with site suggests pubertal bone growth to be a key factor in osteosarcoma while different biological pathways which may be unrelated to bone growth could also be relevant for Ewing sarcoma.

Keywords

Bone Neoplasms; Osteosarcoma; Ewing Sarcoma; Chondrosarcoma; Incidence; Longitudinal Trends; Adolescents; Young Adults; England

Introduction

In England, only 0.2% of all primary cancers (excluding non-melanoma skin cancers) arise in bone.[1] However, the proportion varies with age and is 3.8% in children aged 0 to 14 years of age and 5.7% in teenagers and young adults (TYA) aged 15 to 24 years.[1-3] Bone tumours contribute disproportionately to cancer-related mortality in TYA and are third only to leukaemias and central nervous system tumours.[4]

Overall, osteosarcoma is the most common primary malignant tumour of the bone (35%) followed by chondrosarcoma (25%) and Ewing sarcoma (16%).[5] Other rare tumour types each comprise less than 10%. Osteosarcoma and Ewing sarcoma have a peak in incidence in adolescence while chondrosarcoma is seen mainly at an older age. Clinical studies show that long bones of the lower limb and pelvic bones are the most common site of occurrence of these tumours.[6] There is however little information on the variation in site distribution of these tumours by age. The published literature is similarly deficient in population-based data on the variation in age-incidence patterns of these tumours by site.[7]

We present here detailed incidence patterns and trends for osteosarcomas, Ewing sarcomas, chondrosarcomas and other tumours of the bone across all ages for the whole of England during the period 1979 through 2003 using high quality national cancer registration data. Elucidating the variation of age-incidence patterns of these tumours with site will assist in understanding the possible aetiological relationship between critical periods of growth and age of onset for each of these tumours and at different site groups. Such information will be valuable in the context of the suggested link between growth and bone tumours.[8,9]

Methods

Source of Data

Anonymised, national cancer registration data for England on individual patients of all ages newly diagnosed between 1979 and 2003 were obtained from the Office for National Statistics (ONS). Information supplied included year of diagnosis, age at diagnosis, sex of patient, primary site code, morphology code and behaviour code.

National population estimates by single year of age, sex and calendar year were supplied by the Population Estimates Unit, ONS. Annual mid-year estimates of population in England are based on census data together with information on births, deaths and migration.[10]

Categorisation of Tumours

Malignant bone tumours were selected from the dataset. These were grouped by histology based on the International Classification of Diseases for Oncology 1st and 2nd edition (ICD-O1 and ICD-O2) morphology codes[11,12] into osteosarcomas (morphology codes 9180-9190), Ewing sarcoma (9260, 9362, 9470-9473), chondrosarcomas (9220-9240) and others. Extra-skeletal Ewing sarcoma cases were also included.[3] This is in recognition of the presence of the common *EWS/Fli-l* fusion gene in these tumours and difficulties in ascertaining whether some tumours are arising in bone and invading soft tissue or vice versa.[3,13]

For analysis by site, two major groups were defined:

1. Bone (International Classification of Diseases 9th revision (ICD-9) site codes[14] 170.0-170.9 and International Classification of Diseases 10th revision (ICD-10) site codes[15] C40.0-C41.9). These were further sub-classified into six site sub-groups:
    a. Long bones of the lower limb (ICD-9 site codes 170.7 and ICD-10 site codes C40.2)
    b. Scapula and long bones of the upper limb (ICD-9 site code 170.4 and ICD-10 site code C40.0)
    c. Short bones of the upper and lower limb (ICD-9 site code 170.5, 170.8 and ICD-10 site code C40.1, C40.3)
    d. Bones of cranium and face including mandible (ICD-9 site code 170.0, 170.1 and ICD-10 site code C41.0, C41.1)
    e. Bones of central axis including vertebral column, sternum, clavicle, pelvic bones, sacrum and coccyx (ICD-9 site code 170.2, 170.3, 170.6 and ICD-10 site code C41.2-C41.4), and
    f. Unspecified site (ICD-9 site code 170.9, 195.0-195.8, 199.0-199.2 and ICD-10 site code C40.8, C40.9, C41.8, C41.9, C76.0-76.8, C80.0)
2. Extra-skeletal (ICD-9 site code 140.0-165.9, 171.0-194.9 and ICD-10 site code C00.0-C39.9, C43.0-C75.9)

Statistical Methods

Age, sex, site and histology-specific incidence rates were calculated and expressed per million person years. All rates were adjusted to the world standard population using direct methods.[1] SPSS and Microsoft Excel were used for analyzing the data and producing tables and graphs.

Results

During the period 1979 through 2003, 9146 bone tumours were registered in England in persons aged 0 to 84 years and the overall age-adjusted incidence rate was 7.19 per million person years. The population covered, equated to 1.18 billion person years. Osteosarcoma was the most common primary malignant tumour of the bone with 3124 cases (34.2%) followed by chondrosarcoma with 2485 cases (27.2%), Ewing sarcoma with 1764 cases (19.3%) and 1773 (19.4%) were other bone tumours (chordoma 4.4%, giant cell tumour 2.0%, other specified 0.3% and unspecified 12.7%). Sex-specific age-adjusted incidence rates for these tumours are shown in Table I.

18.64% of Ewing sarcomas were of extraskeletal origin while this proportion was much smaller for osteosarcoma (0.3%) and chondrosarcoma (4.4%). The most common extraskeletal sites for each of these bone tumours were: breast for osteosarcoma; connective tissue (mainly lower limb and pelvis), nasal cavity and larynx for chondrosarcoma; and connective tissue (mainly lower limb and thorax) for Ewing sarcoma.

There was variation in the distribution of bone tumours by age (Figure 1). Ewing sarcoma was most common in those aged 0 to 9 years while osteosarcoma was the predominant bone tumour at ages 10 to 29 years. Chondrosarcoma was the most common bone tumour at ages of 30 years and above. 1535 bone tumours (16.3% of all bone tumours) were seen in children aged 0 to 14 years and the relative proportion of osteosarcoma, Ewing sarcoma and chondrosarcoma was 46.0%, 44.3% and 2.5% respectively. 1185 bone tumours (12.9%) were seen in TYA aged 15 to 24 years and the

relative proportions of osteosarcoma, Ewing sarcoma and chondrosarcoma in this age group were 50.7%, 33.8% and 8.0% respectively.

Osteosarcoma and Ewing sarcoma showed distinct peaks of incidence at 10 to 14 years of age in females and at 15 to 19 years of age in males with the incidence peak greater in males (Figure 2). Osteosarcoma also showed a second but smaller peak of incidence at older ages. The incidence of chondrosarcoma and other bone tumours increased steadily with age with the incidence slightly higher in males.

Incidence Patterns by site

Figure 3 to 5 show age-incidence patterns of osteosarcoma, Ewing sarcoma and chondrosarcoma for the six site sub-groups of bone as well as those with extraskeletal location. Osteosarcoma at all sites (except those located in the cranial and facial bones) showed an initial incidence peak at 15 to 19 years of age with the peak of osteosarcoma of the long bones of the lower limb more than six times larger than that at any other site in this age group. Osteosarcoma at all sites had minimum incidence at 45 to 54 years of age with increasing rates thereafter. In the older age groups the incidence of osteosarcoma at the central axis matched that of the long bones of the lower limb.

The peak incidence of Ewing sarcoma at all sites was between 10 to 19 years of age, and peak incidence of Ewing sarcomas located in the central axis exceeded those in the long bones of the lower limb. Subsequently incidence rates declined and were very low after the age of 34 years and close to zero after 54 years of age. The incidence of chondrosarcoma at all sites did not show an adolescent peak, but steadily increased with age. The incidence was highest for central axis chondrosarcomas followed by those in the long bones of the lower limb.

Longitudinal incidence trends

For the period 1979 to 2003, the incidence of osteosarcoma and chondrosarcoma was stable (Figure 6). The incidence of Ewing sarcoma was stable until the mid-1990s before rising sharply and remaining stable at a higher rate over the most recent period of analysis. The increase in incidence of Ewing sarcoma located in extraskeletal sites was responsible for the overall increase in incidence (Figure 7). The incidence of Ewing sarcoma of bone remained stable throughout the period.

Discussion

This analysis of 9146 primary malignant bone tumours across the whole of England from 1979 through 2003 is to date the single largest reported population-based study of these tumours. Overall eight out of ten primary malignant bone tumours are osteosarcomas, chondrosarcoma or Ewing sarcomas, and the relative frequency of these tumours seen in our study is similar to that reported in previous smaller population- and hospital-based series.[6,7,16]

Longitudinal trends over the 25 year period of analysis show a stable incidence of Ewing sarcoma of the bone, osteosarcoma and chondrosarcoma. The step increase in incidence of Ewing sarcoma at extraskeletal sites is likely to be related to improved diagnosis. Advances in diagnostics, including identification of the t(11;22) chromosomal translocation and characterisation of *EWS-FLI1* gene fusions[17,18] leading to their more accurate categorization could be responsible for this increase.[13]

The peak of incidence of osteosarcoma and Ewing sarcoma in adolescence, which is larger and later in adolescent males than females, points to a link with puberty. Despite

this similarity, marked variations by primary site between the two tumours may provide clues to the critical pathways in tumourigenesis. The adolescent incidence peak of Ewing sarcoma of bone is seen at all sites but the incidence peak of tumours of the central axis exceeds that in long bones of the lower limb. This pattern broadly correlates with the structure of the adult human skeleton, which by weight at 29 to 39 years of age, is made up of bones of the central axis (29%), long bones of the lower limb (25%), skull and facial bones (21%), long bones of the upper limb (15%), and short bones of the upper and lower limbs (9%).[19] Although such data, which are obtained from studies on skeletal samples either prepared in anatomy laboratories or derived from cemeteries, are not available for children or adolescents, we know from the ratio of sitting height and leg length that children and adolescents will have a larger proportion of bones of the central axis, skull and face in comparison to long bones of the lower limb.[20]

In contrast to Ewing sarcoma, tumours of the long bones of upper and lower limb are markedly over-represented in the adolescent peak of osteosarcoma. These are the bones which have the greatest increase in length during the pubertal growth spurt as a result of growth of cartilage at the epiphyseal plate, as well as endochondral ossification of this cartilage. These observations suggest that bone growth during puberty may be one key step in the evolution of an osteosarcoma cell. Further indirect evidence of the importance of bone growth is provided from a reported association of greater height at diagnosis among patients with osteosarcoma which is stronger and more consistent in comparison to Ewing sarcoma.[8,9,21-24]

While the link between pubertal growth and osteosarcoma onset has biological plausibility, its basis has still not been determined. Pubertal growth mediators,

particularly IGF-1[25,26] and sex steroids[27,28] are candidates of interest but their role may be in the promotion rather than initiation of tumourigenesis. Our current level of knowledge is also insufficient to comment on the significance of antenatal and childhood extrinsic and intrinsic exposures and growth patterns on the development of these bone tumours. Evolution of a malignant cell is a multi-step process and preceding pre-malignant changes might occur during other periods of rapid growth, e.g. in foetal life, during infancy and/or during the mid-childhood growth spurt.

The adolescent incidence peak of Ewing sarcoma remains unexplained. Unlike osteosarcoma, bone growth during puberty would be a less likely major mechanism. If one considers the primitive tissue of origin of this tumour and the nearly zero incidence in older adults, it has similarities with the embryonal tumours[2] of childhood although the incidence peak in Ewing sarcoma is later than for them. The striking racial variation in the distribution of this tumour[29], and reported associations with congenital hernias[22], rib anomalies[30], low birth weight[31] and parental occupation in agriculture during the peri-conception period[32] suggest a stronger prenatal component to the aetiology of Ewing's sarcoma.

Less than 10% of bone tumours in TYA at ages 15 to 24 years in our analysis were chondrosarcoma. Of the 146 chondrosarcomas in this age group, 31.5% were in long bones of the lower limb and 28.8% in bones of the central axis. This is different to the overall distribution of chondrosarcomas which are most common in bones of the central axis. This age-related difference could be due to chance (because of relatively small number of cases) or from misclassification of chondroblastic osteosarcoma, which have peak incidence in adolescence and can be difficult to distinguish from

chondrosarcoma.[33] However, if this age-related difference is true, the role of genetic susceptibility in tumours in this age group must be considered as TYA are not likely to have had the same length of lifestyle-related exposures compared to older people. Patients who develop chondrosarcoma secondary to enchondromas (seen in syndromes like Ollier disease and Maffucci syndrome) are generally younger than those with primary chondrosarcoma.[34] Clinical series of chondrosarcomas in children and young people have not shown a particularly high proportion of chondrosarcomas secondary to these syndromes.[35,36]Additionally, a range of cytogenetic changes have been seen in chondrosarcoma but there is no description of high-penetrance mutations in those with chondrosarcomas at a younger age.[34]

In summary, incidence patterns of osteosarcoma and Ewing sarcoma during adolescence point towards a link with puberty. The variation in these patterns with site suggests pubertal bone growth to be a key factor in osteosarcoma while different biological pathways which may be unrelated to growth could be relevant for Ewing sarcoma. Chondrosarcoma is relatively infrequent in TYA and it is yet not established whether chondrosarcomas in this age group are epidemiologically and genetically different from those which develop in older adults.

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Table I Overall, Sex- and Site-Specific Incidence Rates (in Million Person Years) for Osteosarcoma, Ewing Sarcoma and Chondrosarcoma at Ages 0 to 84 Years in England, 1979 to 2003

TUMOUR / SITE	Osteosarcoma				Ewing Sarcoma				Chondrosarcoma			
	Total Number	Age-Adjusted Incidence			Total Number	Age-Adjusted Incidence			Total Number	Age-Adjusted Incidence		
		Total	Male	Female		Total	Male	Female		Total	Male	Female
Overall	**3124**	**2.65**	3.06	2.26	**1764**	**1.84**	2.06	1.61	**2485**	**1.56**	1.86	1.27
Bone	**3083**	**2.62**	3.03	2.24	**1352**	**1.44**	1.65	1.22	**2316**	**1.45**	1.73	1.17
Skull & Face	**179**	**0.12**	0.14	0.11	**41**	**0.04**	0.07	0.02	**192**	**0.13**	0.12	0.15
Central Axis	**487**	**0.31**	0.33	0.3	**505**	**0.53**	0.58	0.48	**833**	**0.52**	0.66	0.37
Short Bones	**85**	**0.07**	0.09	0.05	**61**	**0.07**	0.07	0.06	**234**	**0.14**	0.16	0.11
Long Bones Upper Limb	**354**	**0.3**	0.35	0.25	**163**	**0.18**	0.21	0.15	**266**	**0.17**	0.21	0.13
Long Bones Lower Limb	**1745**	**1.66**	1.93	1.39	**413**	**0.44**	0.52	0.37	**531**	**0.34**	0.4	0.28
Unspecified	**263**	**0.18**	0.21	0.15	**257**	**0.26**	0.29	0.23	**319**	**0.19**	0.23	0.17
Extraskeletal	**11**	**0.01**	0.01	0.01	**324**	**0.31**	0.32	0.3	**110**	**0.07**	0.09	0.06

Figure 1 Age Related Variation in the Proportion of Osteosarcoma, Ewing Sarcoma and Chondrosacoma

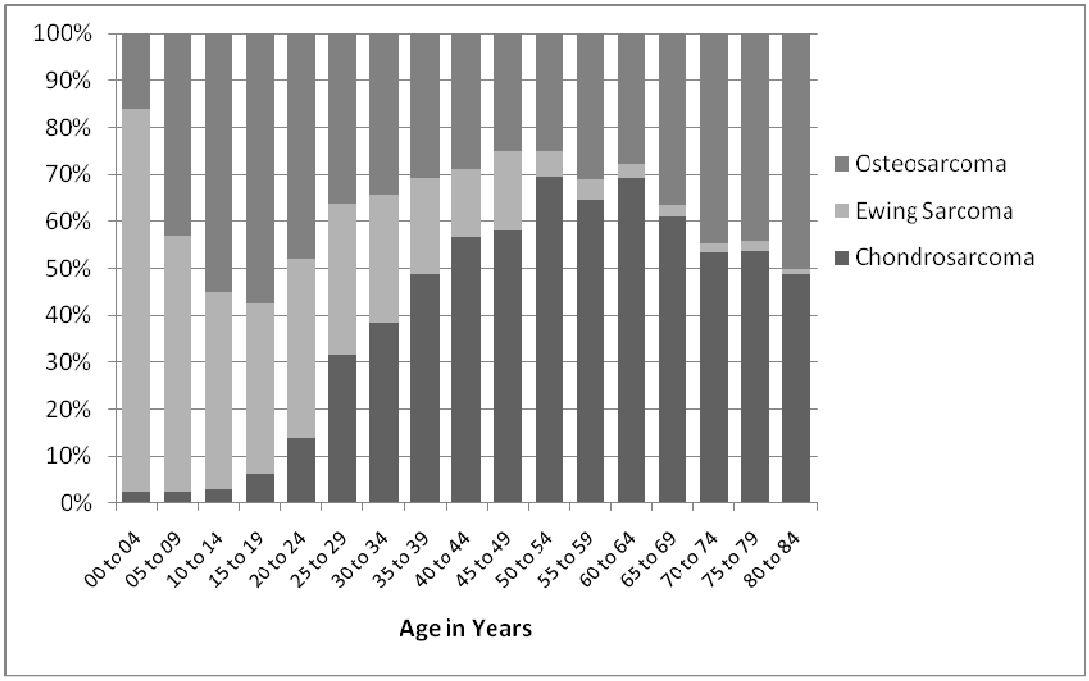
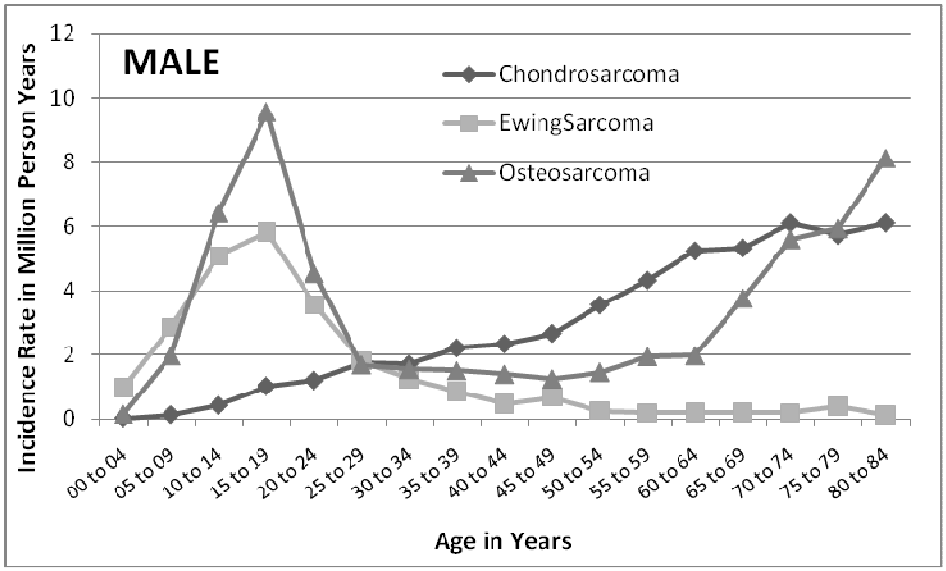


Figure 2 Age-Specific Incidence Rate Patterns of Osteosarcoma, Ewing Sarcoma and Chondrosacoma in Males and Females in England, 1979 to 2003



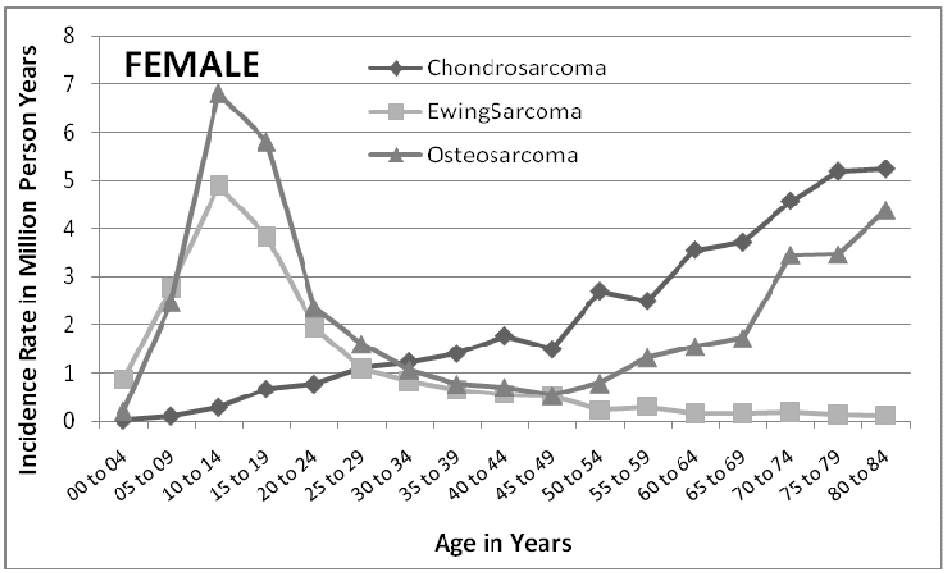


Figure 3 Age- and Site-Specific Incidence Rate Patterns of Osteosarcoma in England, 1979 to 2003

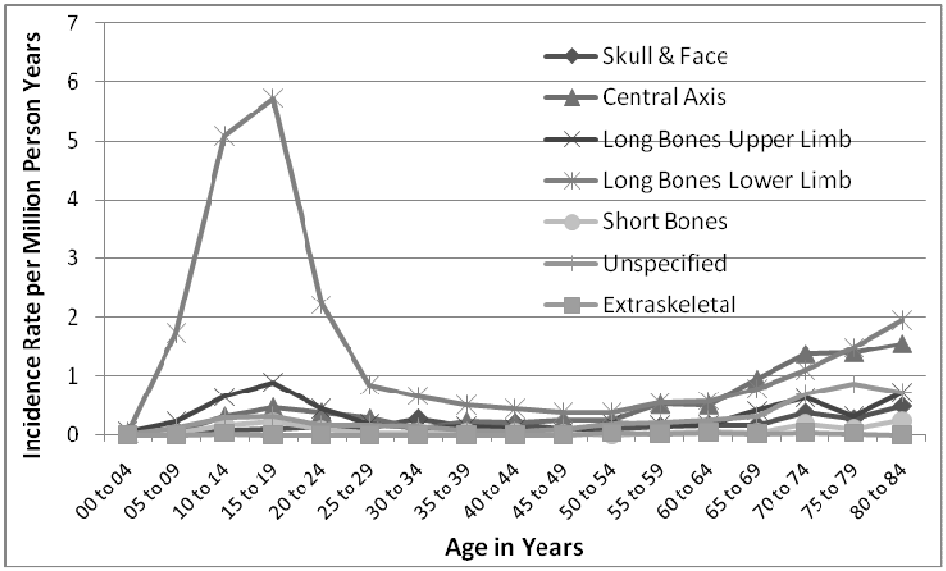


Figure 4 Age- and Site-Specific Incidence Rate Patterns of Ewing Sarcoma in England, 1979 to 2003

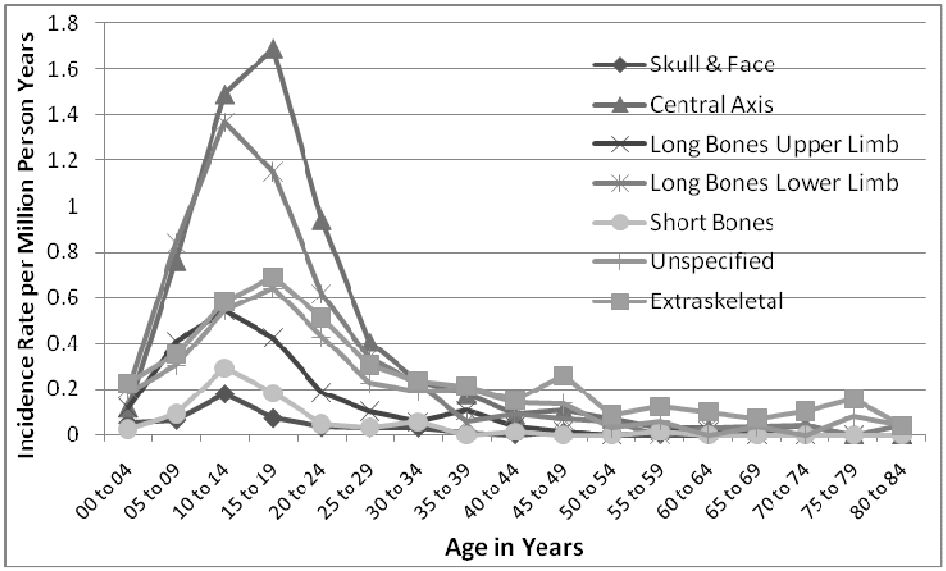


Figure 5 Age- and Site-Specific Incidence Rate Patterns of Chondrosarcoma in England, 1979 to 2003

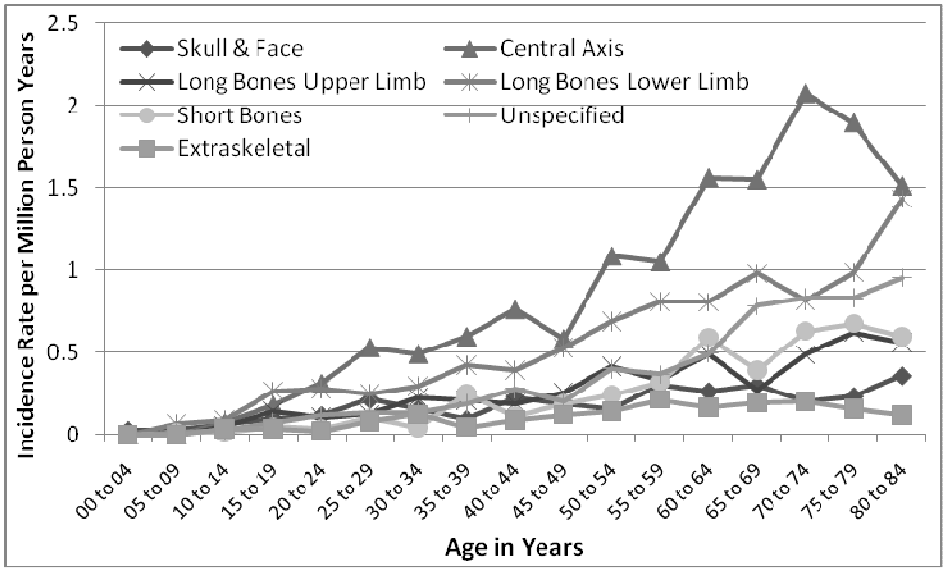


Figure 6 Trends in Age-Standardised Incidence Rates of Osteosarcoma, Ewing Sarcoma and Chondrosacoma in England, 1979 to 2003

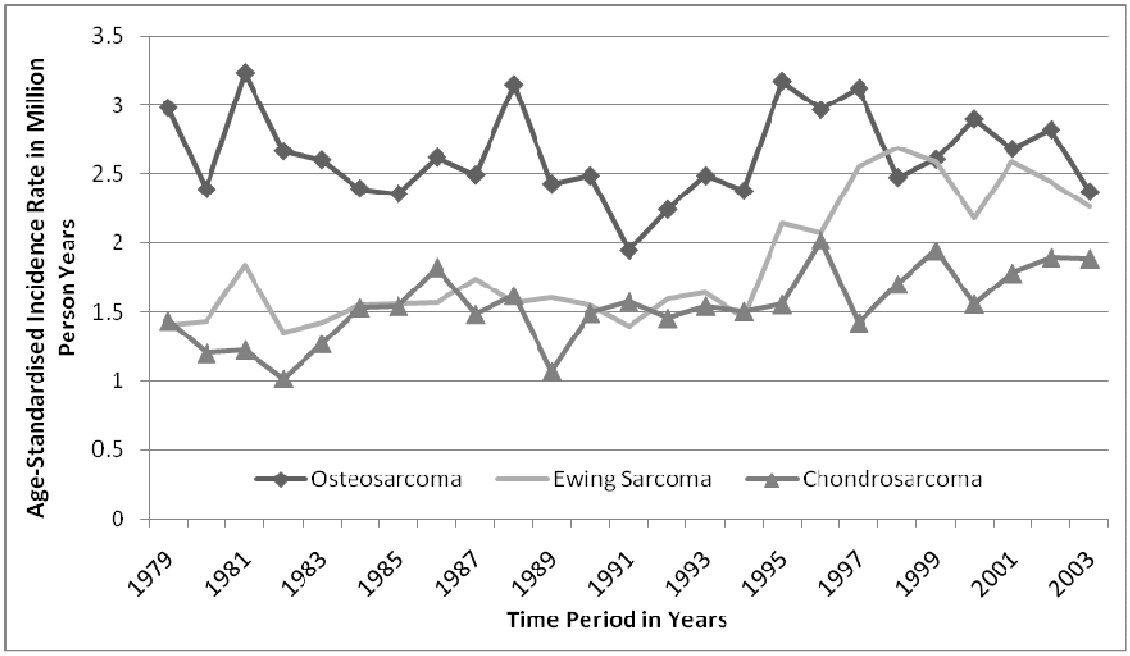
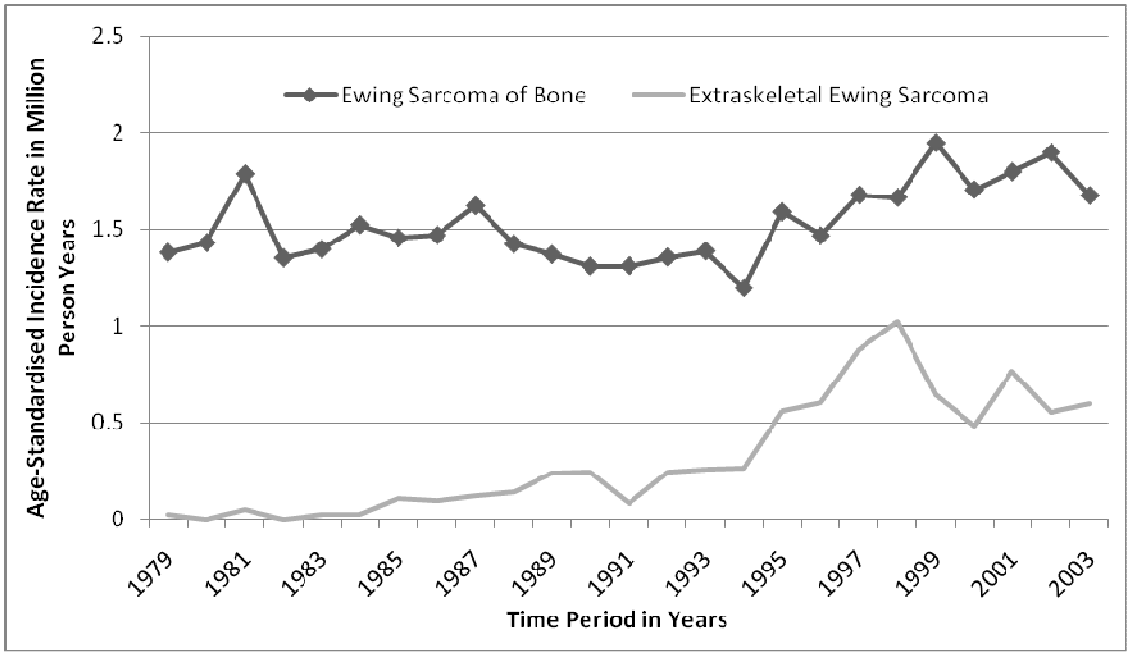


Figure 7 Trends in Age-Standardised Incidence Rates of Ewing Sarcomas of Bone and Extraskeletal Sites in England, 1979 to 2003



6.6 Relationship between height at diagnosis and bone tumours in young people: A meta-analysis

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Manuscript Under Review – Cancer Causes and Control

Title

Relationship between height at diagnosis and bone tumours in young people: A meta-analysis

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Abstract

Objective - Some evidence exists that patients with osteosarcoma and Ewing sarcoma are taller than the general population. However, previous studies are under-powered, lack comprehensive data and show inconsistencies.

Methods - Random-effects meta-analyses were undertaken on identified studies linking osteosarcoma and Ewing sarcoma with height at diagnosis. Outcomes in individual studies were reported as standard deviation (SD) scores or percentages of study population with height at diagnosis above the median of the reference population. A separate meta-analysis for each outcome and tumour type was performed.

Results – 14 studies examined the height of patients with osteosarcoma or Ewing sarcoma. Meta-analyses on SD scores found patients with osteosarcoma were 0.260 SD (95%CI: 0.088-0.432) taller than the reference population (five studies). A meta-analysis on percentages found 62% (95%CI: 57%-67%) of patients were estimated to have a height above the median (six studies).Patients with Ewing sarcoma were 0.096 SD (95%CI 0.004-0.188) taller (four studies). Only one available Ewing sarcoma study reported percentages and a meta-analysis was not possible.

Conclusion - The average height of patients with osteosarcoma was significantly above the average height of the reference population. The association of greater height with Ewing sarcoma was also significant but much weaker.

Keywords

Osteosarcoma, Ewing Sarcoma, Growth, Body Height, Meta-analysis

Introduction

Osteosarcoma and Ewing sarcoma are the two most common malignant bone tumours in children, teenagers and young adults aged 0 to 24 years.[1,2] Relatively little is known about the aetiology of these tumours. Less than 10% of all osteosarcoma cases can be attributed to well-recognised risk factors including ionising radiation, chemotherapy, cancer predisposition syndromes, Paget's disease and fibrous dysplasia. Even less is known about the causation of Ewing sarcoma although associations have been seen with parental occupation related to agriculture and with congenital hernias.[3] The biological basis of these associations remains to be explained.

An interesting link seems to exist between growth, particularly in adolescence, and both osteosarcoma and Ewing sarcoma. In 1953 Johnson suggested that a particular bone tumour of a given cell type usually arose in the field where the homologous cells were most active and so osteosarcoma arose in the metaphysis which had abundant osteoclasts whereas round cell tumours (Ewing sarcoma) develop in the bone-free marrow cavity of the mid-shaft (diaphysis).[4] Further studies on human and canine osteosarcoma suggested a link between growth and occurrence of these tumours.[5-8] Price observed that there was an overall preponderance of osteosarcoma in males, with the mean age of occurrence later than in females.[5] There was also a predilection of osteosarcoma for long bones of the lower limb with the mean age of occurrence later than osteosarcoma in the upper arm. In dogs, where osteosarcoma is 40 to 50 times more common than in humans,[6] an increasing risk of osteosarcoma had been seen with increasing weight and increasing height of the dog which was present even after adjusting for the breed size.[7,8] Exploring this link further, Fraumeni in 1967 showed that human

males and females with osteosarcoma (and Ewing sarcoma to a lesser degree) were significantly taller at diagnosis than controls.[9] Subsequently several other studies have yielded conflicting results.[10-12]

The aim of this study is to explore the strength of association between height at diagnosis and onset of osteosarcoma and Ewing sarcoma. Specific objectives are to identify relevant studies and to perform a meta-analysis where feasible. By these means we aim to identify areas for future research.

Materials and Methods

A comprehensive literature search of Medline (1950 to 2009) was undertaken with no language restriction. Search strategy included combining keywords "osteosarcoma", "Ewing sarcoma", "bone neoplasms", "epidemiology", "risk factors", "aetiology" and "genetics". There was further emphasis on the literature exploring links between growth and development of osteosarcoma and Ewing sarcoma by combining keywords "growth", "height", "length", "stature", and "puberty". Reference lists of relevant studies were also searched for additional studies.

Identified relevant studies were critically appraised and data on outcomes relating to an association with height at diagnosis were extracted. Three categories of outcome data were identified:

1. Mean standard deviation score (SDS) of height at diagnosis in the study population,
2. Percentage of study population with height at diagnosis above the median,
3. Other (e.g. mean height of study population and of control population)

Random-effects meta-analyses were undertaken using the Restricted Maximum Likelihood method (REML)[13] if there were adequate number of studies with outcomes reported in the first two categories specified above. Results were displayed by using forest plots.[14] Each study is represented by a block (the area of the block indicates the weight assigned to that study) at the point estimate of grouped effect with a horizontal line (depicting 95% confidence intervals) extending either side of the block. The overall estimate from the meta-analysis and its confidence intervals are put at the bottom, represented as a diamond. The centre of the diamond represents the pooled point estimate, and its horizontal tips represent the 95% confidence intervals.

The presence of heterogeneity was assessed by p-value of Cochran's Q on the basis of inverse variance weights and its magnitude estimated using I^2.[15] The between study variance, tau^2, was also calculated as an estimate of the degree of heterogeneity.[16] The number of studies included in our meta-analyses failed to reach the threshold used in standard methods for assessing publication bias[17].

Results

A total of 14 relevant studies were identified (Table I). Of these six included patients with osteosarcoma and Ewing sarcoma, six studies with osteosarcoma only, and two studies with Ewing sarcoma only. For ten of these studies, it was feasible to extract the data required for inclusion in a meta-analysis. For the other four, the results have been summarised in Table II.

Meta-analysis for Osteosarcoma

Five studies reported their results using mean SDS for height at diagnosis in osteosarcoma study populations and were included in the first meta-analysis (Figure 1). In this analysis, patients with osteosarcoma were estimated to be 0.260 standard deviations (95%CI: 0.088 to 0.432) taller than the reference population (heterogeneity I^2=83%, tau^2=0.03). Six studies used the second category of outcome data (percentage of study population with height at diagnosis below/above the median) to report results on osteosarcoma which were included in the second meta-analysis (Figure 2). 62% (95%CI: 57% to 67%) of patients with osteosarcoma were estimated to have a height above the median for the reference population (heterogeneity I^2= 39%, tau^2=0.006). Longhi et al[12] reported outcomes for both the above categories and so these were included in each of the meta-analyses.

Meta-analysis for Ewing sarcoma

Four studies on Ewing sarcoma study populations reported results under the first category of outcome data (mean SDS of height at diagnosis in the study population). These were included in the third meta-analysis (Figure 3). Patients with Ewing sarcoma were estimated to be 0.096 standard deviations (95%CI 0.004 to 0.188) taller than the reference population (heterogeneity I^2=0%, tau^2=0). Since the REML estimated tau^2 to be zero, the method was reduced to a fixed-effects approach. Therefore, we conducted a sensitivity analysis with the widely used DerSimonian-Laird (DL) method[18] and estimated patients to be 0.112 standard deviations taller than the reference population. However, the effect was not significant (95%CI -0.029 to 0.252). Heterogeneity with the DL method was not estimated to be negligible: I^2=43%, tau^2=0.009.

There was only one study[9] for the second category of outcome data (percentage of study population with height at diagnosis below/above the median) which showed that 61% of the patients with Ewing sarcoma were taller than the median.

Discussion

The epidemiological observation of peak incidence of osteosarcoma and Ewing sarcoma at 15 to 19 years of age in males and 10 to 14 years of age in females, along with the suggested link of tall stature with these tumours would imply that growth, and in particular pubertal growth, plays a critical role in tumourigenesis. Since Fraumeni's initial report,[9] several other studies, which have subsequently looked at the association, have yielded conflicting results.[10-12,19-28] This is partly because of methodological limitations including small study samples, sub-optimal data collection methods (parental recall of height at diagnosis on telephone interviews) and lack of uniformity in reporting results. This meta-analysis is an opportunity to settle controversies arising from conflicting results.

We found that the average height of patients with osteosarcoma was significantly above the average height of the reference population on meta-analysis using either of the outcome data categories. In all ten studies, the point estimate of effect is in favour of greater height, and in seven out of the ten studies, the 95% confidence intervals imply statistical significance, which suggests the presence of a strong and consistent association. Moreover, the magnitude of the estimated effect from the meta-analysis of percentage of study population with height at diagnosis above the median SD scores (62%) is similar to the magnitude of the estimated effect from the meta-analysis of SD

scores (0.26 SD which would equate to 60% study population having height at diagnosis above the median).

Although the average height of patients with Ewing sarcoma was also found to be significantly above that of the reference population, the magnitude of the estimated effect was smaller. However, the finding was not verified by our sensitivity analysis with the DL method.[18] Although the effect estimate was similar in size, it was found not to be significant at the 95% level. Both methods (REML & DL) provide very wide confidence intervals for the effect estimate which reflect the small numbers of patients in the included studies. Finally, three other published studies (Table II) do not show a significant association of height at diagnosis with Ewing sarcoma, highlighting the inconsistent and weak association.

These observations lead to two key questions. What does having a greater height at diagnosis than the reference population signify? And why is this association much stronger with osteosarcoma in comparison to Ewing sarcoma? During adolescence (when the incidence of these tumours peak), the height is a function of childhood growth and pubertal growth spurt. Is the above-average height in osteosarcoma patients due to taller children with normal pubertal growth spurt, or to children of average height but with a faster/greater pubertal growth spurt, or to a combination of the two? Rapid bone growth during adolescence may create a vulnerable period when cells are more likely to become transformed into overt malignancy. However, evolution of a malignant cell is a multi-step process and preceding pre-malignant changes might occur during other periods of rapid growth, e.g. in foetal life, during infancy and/or during the mid-childhood growth spurt. The challenge is to try to identify intrinsic (e.g.. hormonal and genetic) factors and

extrinsic environmental factors (e.g.. viruses, diet, physical exercise, toxic chemicals, radiation) which bring about changes in target cells eventually leading to cancer formation.

The variation in the magnitude of association of osteosarcoma and Ewing sarcoma with height at diagnosis is not surprising when one considers the anatomical distribution of these tumours, both of which peak in adolescence. In our recent analyses of population-based data of 9424 primary bone tumours from England diagnosed during the period 1979 to 2003, we show that Ewing sarcomas of the central axis (vertebral column, ribs, sternum, clavicle, pelvic bones, sacrum and coccyx) and long bones of the lower limb have nearly equal incidence peaks (Arora et al, in preparation). This pattern broadly co-relates with the structure of the adult human skeleton, which at 29 to 39 years of age, is made up of bones of the central axis (29%), long bones of the lower limb (25%), skull and facial bones (21%), long bones of the upper limb (15%), and short bones of the upper and lower limbs (9%).[29]

In contrast, peak incidence of osteosarcoma of long bones of the lower limb, which is a metaphyseal tumour, is six times more than that at any other site. These are the bones which have the greatest increase in length during the pubertal growth spurt as a result of growth of cartilage at the epiphyseal plate, as well as endochondral ossification of this cartilage. Further support for this argument is provided by the observation of Cotterill et al[11] that those patients with femoral osteosarcoma were not only significantly taller at diagnosis than the reference population but also taller than those with non-femur osteosarcoma. Such an observation was not made with Ewing sarcoma.

In summary, clinical observations and epidemiological incidence patterns of osteosarcoma in humans and animals suggest a link with growth particularly to onset of osteosarcoma. Our meta-analyses provide further support for this link. The lack of a similar convincing association of height at diagnosis with Ewing sarcoma, which also peaks in adolescence, suggests that different biological pathways involving puberty which may be unrelated to growth could be relevant.

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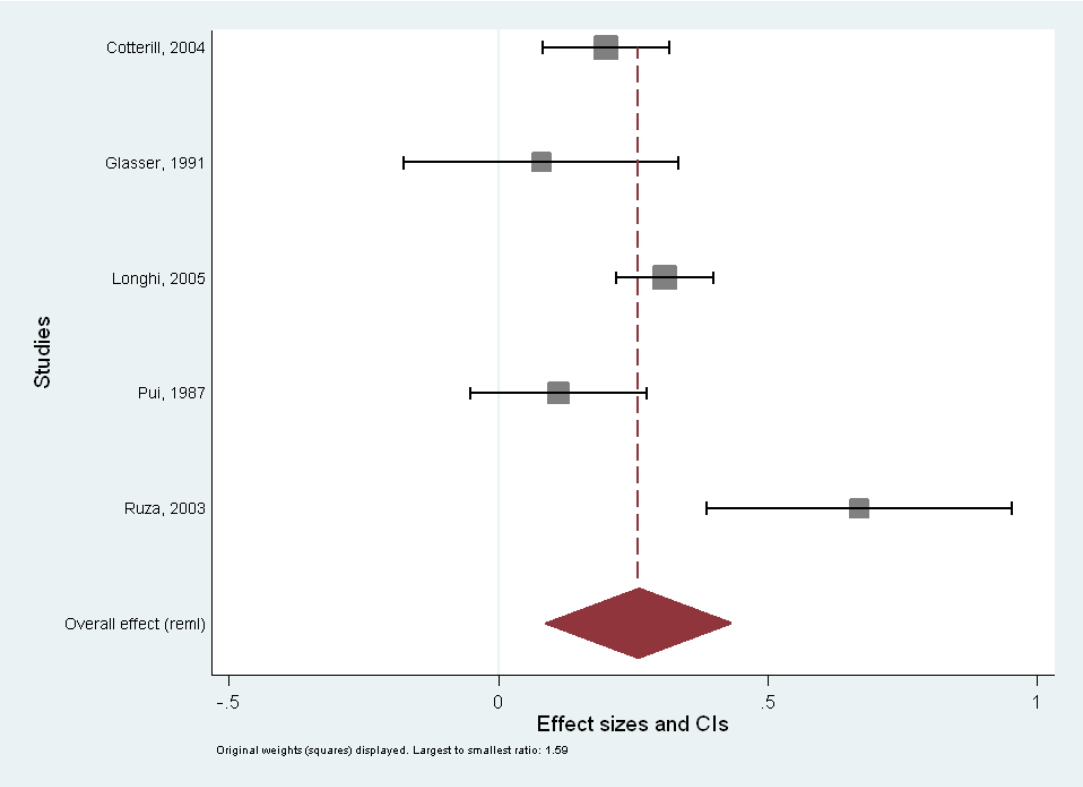
Figure 1 Forest Plot of Osteosarcoma Studies with Outcome Data Category of Mean Standard Deviation Score of Height at Diagnosis in the Study Population

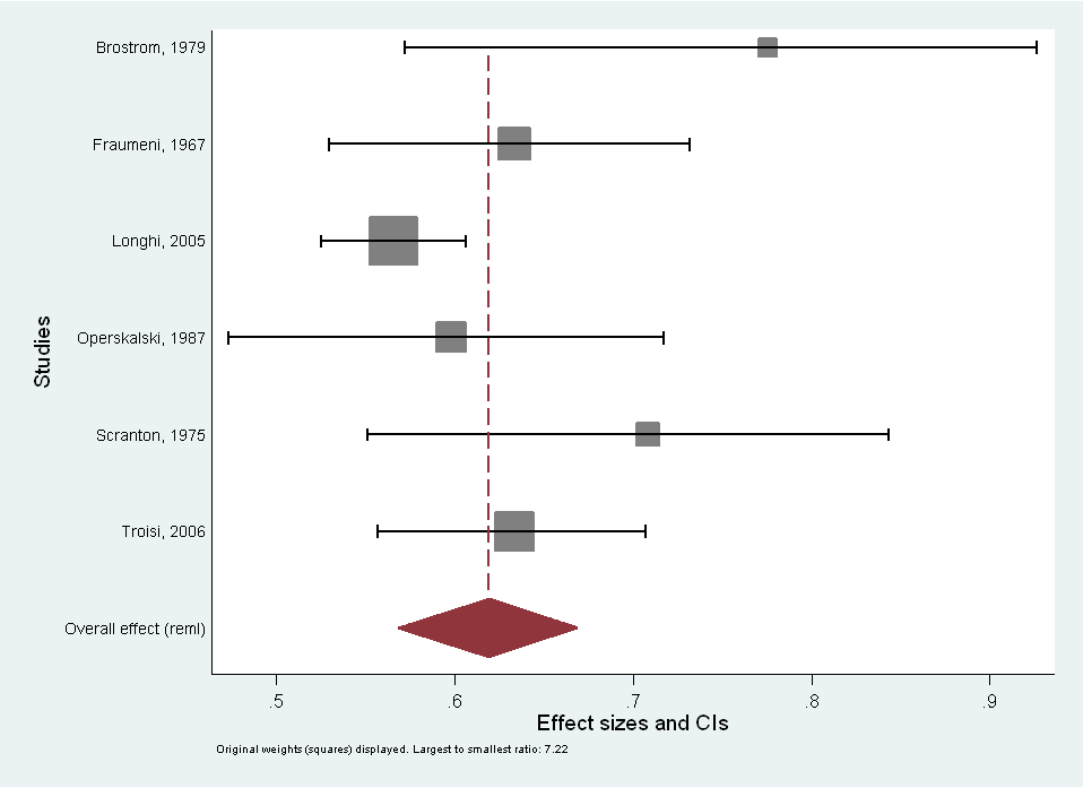


Study	Effect	[95% Conf.	Interval]	% Weight
Cotterill, 2004	0.200	0.082	0.318	23.09
Glasser, 1991	0.080	-0.175	0.335	16.49
Longhi, 2005	0.310	0.220	0.400	24.17
Pui, 1987	0.112	-0.051	0.275	21.01
Ruza, 2003	0.670	0.388	0.952	15.23
Overall effect (reml)	0.260	0.088	0.432	100.00

Heterogeneity Measures

	value	df	p-value
Cochrane Q	15.36	4	0.004
I^2 (%)	83.35		
H^2	5.01		
tau^2 est(reml)	0.030		

Figure 2 Forest Plot of Osteosarcoma Studies with Outcome Data Category of Percentage of Study Population with Height at Diagnosis Above the 50th Percentile



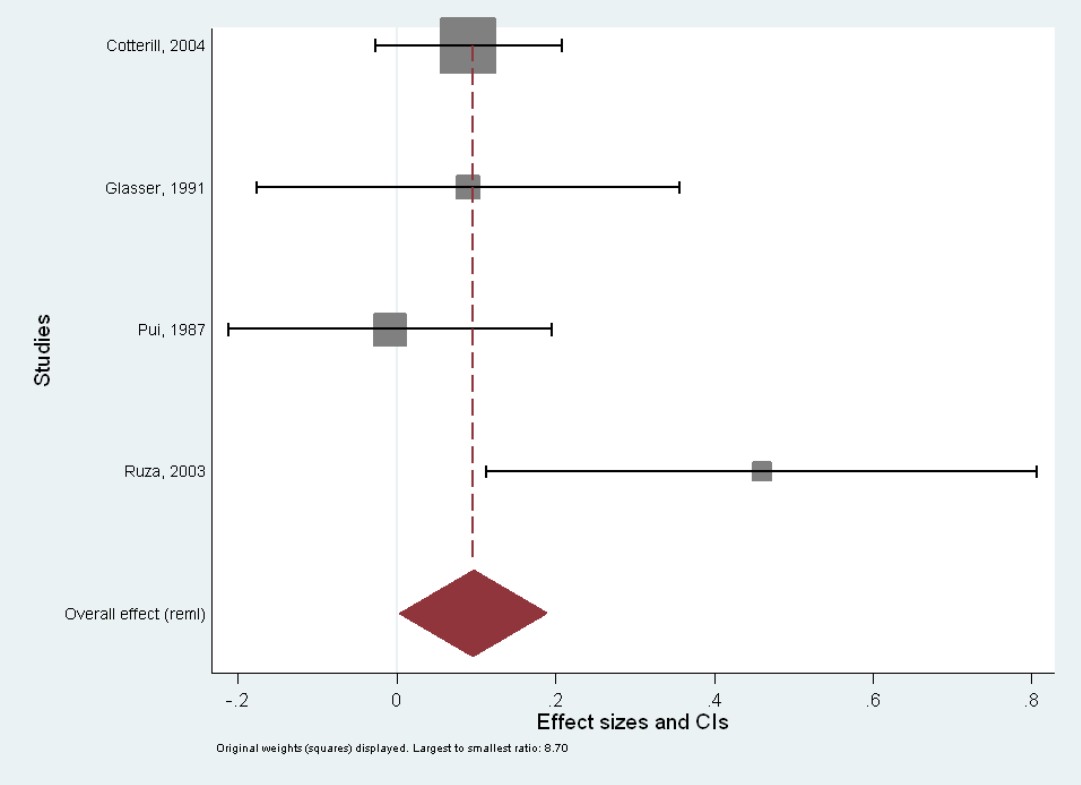
Study	Effect	[95% Conf.	Interval]	% Weight
Brostrom, 1979	2.154	1.716	2.593	4.98
Fraumeni, 1967	1.842	1.630	2.053	15.82
Longhi, 2005	1.703	1.621	1.785	35.94
Operskalski, 1987	1.769	1.518	2.020	12.45
Scranton, 1975	2.001	1.674	2.327	8.26
Troisi, 2006	1.842	1.685	1.998	22.55
Overall effect (reml)	1.812	1.708	1.915	100.00

Heterogeneity Measures

	value	df	p-value
Cochrane Q	8.63	5	0.125
I^2 (%)	39.31		
H^2	0.65		
tau^2 est(reml)	0.006		

Using the Freeman-Tukey arcsin method, reported study percentages were transformed to effects and meta-analysed. The overall effect was back-transformed to percentage and is displayed along with the original study percentages in the plot

Figure 3 Forest Plot of Ewing sarcoma Studies with Outcome Data Category of Mean Standard Deviation Score of Height at Diagnosis in the Study Population



Study	Effect	[95% Conf.	Interval]	% Weight
Cotterill, 2004	0.090	-0.028	0.208	60.89
Glasser, 1991	0.090	-0.177	0.357	11.85
Pui, 1987	-0.008	-0.212	0.196	20.27
Ruza, 2003	0.460	0.113	0.807	7.00
Overall effect (reml)	0.096	0.004	0.188	100.00

Heterogeneity Measures

	value	df	p-value
Cochrane Q	5.24	3	0.155
I^2 (%)	0.00		
H^2	0.00		
tau^2 est(reml)	0.000		

Table 1 Summary of Studies Looking at Link between Height at Diagnosis and Osteosarcoma or Ewing Sarcoma

Study ID	Number of Cases	Age Range	Source of Cases & Controls	Outcome Data Type
Brostrom 1980[19] **Sweden**	19 - Osteosarcoma	≤ 25 years	Cases from Swedish cancer registry. No controls.	Percentage with height at diagnosis below/above the 50th percentile (Reference population – Swedish childhood growth standards)
Buckley 1998[20] **USA & Canada**	152 - Osteosarcoma 153 - Ewing Sarcoma	≤ 21 years	Cases registered on Children's Cancer Group, database. Controls identified by random digit telephone dialling matched by age and race.	Mean height of cases and controls
Cotterill 2004[11] **UK**	364 - Osteosarcoma 356 - Ewing Sarcoma	≤ 40 years	Cases on national bone tumour studies. No controls.	Mean SDS of height at diagnosis (Reference population – UK national childhood growth standards)
Fraumeni 1967[9] **USA**	85 - Osteosarcoma 82 - Ewing Sarcoma	≤ 18 years	Cases at Children's Hospital Medical Centre at Boston. Controls were children <18 years with primary cancer other than osseous cancer in same centre during same period.	Percentage with height at diagnosis below/above the 50th percentile (Reference population – Control population in study)
Gelberg1997[21] **USA**	91 - Osteosarcoma	≤ 25 years	New York State cancer registry (excluding New York city). Controls were randomly selected from live birth records from the same area and were matched for sex and year of birth.	P-value for trend of height for cases and controls
Glasser 1991[22] **USA**	68 - Osteosarcoma 54 - Ewing Sarcoma	≤ 15 years	Cases at Memorial Sloan-Kettering Cancer Centre at New York. No controls.	Mean SDS of height at diagnosis (Reference population – USA childhood growth standards from NCHS)
Holly 1992[23] **USA**	43 - Ewing Sarcoma	≤ 31 years	Cases from San Francisco Bay Area cancer registry. Controls identified by random digit telephone dialling matched by sex and age.	P-value for mean height for cases and controls
Longhi 2005[12] **Italy**	567 - Osteosarcoma	Female ≤ 16 years, Male ≤ 18 years	Cases at Istituti Ortopedici Rizzoli at Bologna. No controls.	Mean SDS of height at diagnosis, AND Percentage with height at diagnosis below/above the 50th percentile (Reference population – Italian childhood

				growth standards)
Operskalski 1987[24] **USA**	60 - Osteosarcoma	≤ 25 years	Cases from Los Angeles County cancer registry. 2 controls from friends/neighbours whose biological mothers spoke English matched by sex, race and birth year (± 3 years).	Percentage with height at diagnosis below/above the 50th percentile (Reference population – USA childhood growth standards from NCHS)
Pendergrass 1984[25] **USA**	291 - Ewing Sarcoma	≤ 18 years	Cases on Intergroup sarcoma study. No controls.	Mean difference and P-value for mean height for cases and reference population (Reference population – USA childhood growth standards from NCHS)
Pui 1987[10] **USA**	150 - Osteosarcoma 113 - Ewing Sarcoma	≤ 18 years	Cases at St. Jude Children's Research Hospital. No Controls.	Mean SDS of height at diagnosis (Reference population – USA childhood growth standards from NCHS)
Ruza 2003[26] **Spain**	58 - Osteosarcoma 36 - Ewing Sarcoma	≤ 18 years	Cases at University Clinic of Navara at Pamplona. No controls.	Mean SDS of height at diagnosis (Reference population – Spanish childhood growth standards)
Scranton 1975[27] **USA**	35 - Osteosarcoma	≤ 18 years	Cases at Children's Hospital & Presbyterian-University Hospital at Pittsburgh. No controls.	Percentage with height at diagnosis below/above the 50th percentile (Reference population – USA childhood growth standards)
Troisi 2006[28] **USA**	156 - Osteosarcoma	≤ 40 years	Cases at orthopaedic departments in 10 USA medical centres. Controls were patients in same department with benign bone tumours or non-neoplastic conditions who were matched by age, sex, hospital and postal code	Percentage with height at diagnosis below/above the 50th percentile (Reference population – USA childhood growth standards from NCHS)

SDS – Standard deviation scores, NCHS – National Centre for Health Statistics

Table II Summary Results of the Studies not Included in the Meta-Analysis

Study ID	Tumour Type	Findings	Comments
Buckley 1998[20]	Osteosarcoma	152 cases, 152 controls. Mean height of cases at diagnosis and controls was not significantly different in males (p=0.43) or females (p=0.73)	Data collected by parental interview of cases and controls via telephone and thus dependant on parental recall.
	Ewing Sarcoma	153 cases, 153 controls. Mean height of cases at diagnosis and controls was not significantly different in males (p=0.87) or females (p=0.96)	
Gelberg1997[21]	Osteosarcoma	91 cases, 106 controls. A significant association of osteosarcoma with increasing height one year before diagnosis was observed (p=0.01) when data collected from all sources was included. The association showed borderline significance when heights obtained only from records were included (p=0.08).	Data collected on height one year prior to diagnosis from school records, medical records, and parental (or subject's if $\geq$ 18 years age) interview
Holly 1992[23]	Ewing Sarcoma	43 cases, 193 controls. Mean height of cases at diagnosis and controls was not significantly different in males (p=0.24) or females (p=0.81)	Data collected by parental interview of cases and controls in person or on telephone.
Pendergrass 1984[25]	Ewing Sarcoma	291 cases, no controls. No significant difference among male cases and reference population in mean heights (p=0.69) or distribution by percentile groups (p=0.12). Female cases had a lower mean height of borderline significance (p=0.06) and distribution by percentile group (p=0.08).	Data collected from the Intergroup Ewing's Sarcoma study records

7. Summary discussion of papers 1 to 6

Adult-onset cancer arises as a result of serial successive alterations to specific genes mainly in somatic cells, but may be also seen in germline cells leading to inherited or familial cancers. This multi-step process of sequential alterations in several different genes happens over time and is responsible for the well-recognised pattern of increasing incidence of cancer overall with age. The transformation of a normal cell into a malignant cell is usually a consequence of prolonged exposure to endogenous and exogenous carcinogens modified by individual susceptibility to cancer resulting from genetic polymorphisms or significant germline mutations. Worldwide 20% of cancers are considered to be associated with infection whilst environmental exposure to tobacco accounts for 30% of cancers in the developed world [1].

Unlike cancer in adults, children with cancer have not lived long enough to sustain long periods of exposure to exogenous agents and very little is known about the aetiology in this age group. Overall only about 5% of all childhood cancers can be attributed to cancer predisposition syndromes [17]. For many diagnostic groups, the occurrence of the highest incidence at an early age, the primitive cell type of origin and the association with congenital malformations strongly suggest that many childhood cancers originate in utero [12,17,49]. Exposures during conception, embryonal or foetal life may initiate genetic changes and increase the susceptibility of later overt cancer during childhood.

Little is known about the aetiology of cancer in teenagers and young adults (TYA). As this age group bridges the period between childhood and adulthood, it is logical to consider that congenital factors as well as environmental exposures preceding development of cancer might play a role. Genetic susceptibility is likely to play a

greater role in TYA cancers compared to older adults following carcinogenic exposures due to the short period available for exposure.

The objective of this thesis was to gain a better understanding of the aetiology of cancer in TYA by describing in detail the incidence patterns. To achieve this, I used different strategies and focussed on some specific cancers. Epidemiological description of the distribution of cancer and the identification of groups of individuals at different risk for development of cancer (as done in this thesis by geographical areas, age groups, primary sites and time periods) provides basic information that is required to test hypotheses concerning the causes of cancer in this age.

Based on my observations, cancers in TYA can be divided into three main groups. Firstly, there are cancers such as pilocytic astrocytoma and medulloblastoma, which have a peak incidence in early childhood and the TYA cases represent the tail end of the age distribution. There is some evidence to suggest that this tail results from underlying genetic variations with the tumours. Medulloblastoma diagnosed in older children, adolescents and young adults may be more frequently associated with the germline mutations of APC gene, while pilocytic astrocytoma in persons older than 15 years has significantly more gain of whole chromosomes in contrast to younger children [50,51].

Secondly, for high grade gliomas, chondrosarcomas and epithelial cancers of lung, breast, colo-rectum, ovary and oral cavity TYA cases represent the very beginning of the large peaks of incidence seen in the 6th, 7th & 8th decades of life. Again, there is evidence to suggest that TYA with these cancers may have a predisposing genotype. In individuals with germ-line TP53 mutations, high grade gliomas tend to arise at much earlier ages [52,53]. A high proportion of predisposing mutations in BRCA1, BRCA2 and TP53 is seen in early-onset breast cancer patients

[15], and of MSH2 and MLH1 in early-onset colo-rectal cancer patients [16]. A range of cytogenetic changes have been seen in chondrosarcoma, but there is no description of high-penetrance mutations in those with chondrosarcomas at a younger age [54] although they are seen in patients with germline TP53 mutations (JM Birch, personal communication). Similarly, the spectrum of genetic changes in young people with oral cancer is not different from that of older adults, although there is a paucity of studies focussed at younger cohorts [55].

While genetic predisposition is clearly relevant, necessary environmental exposures remain essential in the evolution of the cancer. The contrasting analysis of TYA cancers in England and India shows that cancers which are known to have a high incidence in older adults in the respective countries (epithelial cancers of lung, breast, colo-rectum and ovary in England and of oral cavity in India) are also higher in incidence in the younger age groups. Inherited differences between populations could play a role but this is not likely to be significant since frequency of high-penetrance mutations for some of the above cancers reported in Indian patients is similar to that reported in Europe and USA [56,57]. Future migrant studies looking at incidence of cancer in TYA in different ethnic groups in England will help in further understanding.

The final group of TYA cancers are those which peak in incidence in this age group. This includes osteosarcoma, Ewing sarcoma and germ cell tumours and hence the focus on them in this thesis. The incidence patterns of bone sarcomas suggest that puberty plays a role in the development of osteosarcoma and Ewing sarcoma but not chondrosarcoma. Variation in these patterns with site suggests pubertal bone growth to be a key factor in osteosarcoma while different biological pathways which may be unrelated to bone growth could also be relevant for Ewing sarcoma. Further evidence for this is provided by my meta-analysis which shows that the average height of

patients with osteosarcoma is significantly above the average height of the reference population while there is a lack of a similar convincing association in Ewing sarcoma.

GCT are a heterogeneous group of tumours. Irrespective of site, GCT show a peak in incidence between ages of 10 to 39 years and show similar genetic mutations [58-60]. This suggests a common initiation of these tumours likely to be during embryonal or foetal periods or early childhood. However, the variation in peak incidence by site (10 to 14 years in CNS, 15 to 19 years in ovarian, 25 to 29 in mediastinum & thorax and abdomen & pelvis, and 30 to 34 years in testicular GCT) suggests that progression of tumourigenesis is affected by the local macro- and micro-environment and events during the postnatal and pubertal period.

The work done in this thesis follows on from the initial descriptions of cancer in TYA over the last decade [8,10,61]. Based on the epidemiological observations made here, several hypotheses have been generated:-

1. Endogenous (hormones, growth factors) and exogenous (environmental exposures, diet) factors play a significant role in the initiation and/or promotion of cancer in TYA.
2. These factors may exert their effect in the prenatal and/or postnatal period.
3. For some TYA cancers, particularly those which represent the tail end of childhood cancers or those which have peak incidence in TYA, the initiation of tumourigenesis may be in embryonal and foetal life.
4. Puberty is an important period in the evolution of some TYA cancers. The pathogenesis may be a result of hormonal exposures and rapid cell growth (e.g pubertal growth spurt).
5. Genetic susceptibility could also play a role in TYA who develop adult-onset cancers.

6. The proportion of TYA cancers attributed to cancer predisposition syndromes is likely to be small.

Future research in TYA cancers can address some of these questions by:-

1. Contrasting incidence patterns of TYA cancers among different ethnic groups in England as has been done for children and older adults [62,63]. This will help to further elucidate the importance of environmental factors over genetic factors in the aetiology of specific cancers in this age group.
2. Undertaking multi-centre and multi-national studies into the aetiology and molecular epidemiology of TYA cancers by collecting clinical information and biological samples for genetic analysis similar to past and current studies in childhood cancer [64,65]. A pilot interview-based study on bone tumours in children and young people is currently underway in England, details of which are in the Appendix. This will be the forerunner of a major multi-centre case-control study.
3. Focussing on growth during foetal life, infancy and childhood in addition to pubertal growth along with other internal and external factors possibly linked to causation of osteosarcoma and Ewing sarcoma.

In summary, I have explored the epidemiology of cancer in TYA using some of the established methodologies which have previously been used in advancing our knowledge of childhood and older adult cancers. The observations made in this thesis have allowed formulation of several hypotheses regarding aetiology of cancer in this age group which can be tested by further research.

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9. Appendix

Pilot Study of Childhood, Teenage and Young Adult Bone Tumours

Study Protocol

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Purpose of the Investigation

We aim to ascertain and recruit a population-based sample of patients diagnosed up to 24 years of age with osteosarcoma and Ewing sarcoma; interview families, collect DNA samples and abstract relevant medical records; in order to determine the feasibility of setting up a multi-centre, international case-control study of aetiology. Specific aims of the pilot study are to:

1. Assess the proportion of regional cases treated at the specialist paediatric (age 0-14 years) and teenage and young adult (age 15-24 years, TYAs) oncology units in Manchester and Leeds.
2. Assess the recruitment, interview and DNA sample collection rates for cases, their mothers and fathers.
3. Identify and resolve any difficulties in liaising with clinic staff in the above specialist and other units in approaching and recruiting families.
4. Assess and develop further the interview questionnaires including identifying questions which present respondents with most difficulties.
5. Assess the consent rates to view and subsequent availability of obstetric, neonatal and child health records relating to index cases in relation to age of index (0-4,5-9,10-14,15-19,20-24). Also assess the quality and completeness of the records.
6. Assess the accuracy of information reported at interview compared with that abstracted from medical records.
7. Quantify the frequency of exposures of interest in the study population to assist with final questionnaire design and power calculations for the subsequent main study.
8. Optimize biological sample collection processing and storage methodologies.
9. Analyse patterns of growth including adult heights in parents, birthweights and heights in childhood and adolescence in index cases compared with population data and standard growth charts.
10. Analyse familial cancer patterns in the interviewed sample in relation to other factors of interest (congenital anomalies, known genetic and other chronic conditions). Select families for future analyses of candidate genes as appropriate.

Background

Cancer statistics for England are published annually by the Office for National Statistics (ONS) London (1). The diagnostic classification applied to these figures is based on the International Classification of Diseases (ICD) which groups cancers by primary site (2). This is satisfactory in general since 80% of all cancers are carcinomas. Carcinomas are rare in young people and presentation of statistics by primary site gives a misleading picture of cancers in the young. Patterns of cancer incidence can provide insights into possible aetiological factors but to be effective, descriptive studies must employ a diagnostic classification that relates to the cells and tissues of origin of the respective cancers. We have developed such a scheme and applied this to national data (3). The Birch classification scheme has attracted international support and has become the accepted vehicle for cancer incidence studies in TYAs (4).

We have conducted preliminary analyses of national cancer data, by morphological type across all age groups (0-79 years) to identify cancer types which show peaks of incidence in the young. Of particular interest were the age-incidence curves for individual types of bone tumours. Such information is not retrievable from standard incidence data since all bone tumours are presented together. Osteosarcoma (OS) and Ewing sarcoma (ES) account for over 90% of all bone tumours in 0-24 year olds. The median age of diagnosis for OS and ES across all ages is 22 years and 17 years respectively. In both OS and ES the main peak of incidence occurs earlier in females than males.

Much is known about aetiology of common cancers in adults (5). Carcinoma of the lung is mainly due to tobacco smoke. Breast carcinoma is linked to hormonal and reproductive factors but is also influenced by diet and lifestyle. Colorectal carcinoma is associated with a diet rich in fat, refined carbohydrates and animal protein and a lifestyle involving low physical activity. For these cancers, clinical onset follows a prolonged period of chronic exposure. It is clear in children and TYAs, there has been no opportunity for such chronic exposures. Therefore the mechanisms and the risk factors themselves may differ in their nature or their proportional contribution to cancer in these young people. It is likely that genetic susceptibility may play a greater role in this age range than for cancers in older people (6).

Embryonal malignancies in young children have a prenatal origin. It is likely that all events required for their onset occur before birth. It is possible that while one or more events leading to OS and ES occur prenatally, events which precipitate the onset of disease occur post-natally during childhood and/or adolescence. These events may occur endogenously due to chance, or could be mediated through environmental exposures e.g. viruses, toxic chemicals, leading to transformation in a pre-malignant clone of cells which has a pre-natal origin. Factors affecting growth and development including diet, physical exercise and serious illness may also influence the onset of OS and ES in older children and TYAs.

Clinical studies show that the earlier peak of onset of OS in girls, corresponds to their more advanced skeletal age and earlier adolescent growth spurt, whereas the increased risk of OS among boys may result from the larger bone volume formed during a longer growth period (7). OS has a predilection for the metaphyseal portions of the most rapidly growing bones in adolescents; the distal femur, proximal tibia and proximal humerus (8). Tumours of the humerus tend to occur at a younger age than do tumours of the femur and tibia, corresponding to the earlier growth spurt of the humerus (7). Thus, the tumour appears to occur most frequently at sites when the greatest increase in length and size of bone occurs. While ES of bone also shows an incidence peak in adolescence, which occurs earlier in girls than boys, the primary site distribution is less well-defined in terms of sites of maximal growth and tumours of the vertebral column, ribs, sternum, clavicle, pelvis, sacrum and coccyx are more common. Some evidence exists that adolescent patients with OS and ES are taller than the general population (9,10) and OS patients may be heavier at birth (11). However, these studies were under-powered and/or lacked comprehensive data and there were inconsistencies. A small pilot study of OS reported case-control differences in IGF2 receptor haplotype which may have functional significance (12).

Descriptive studies including time trends, geographical variations in incidence, clustering and ecological studies can provide pointers to possible aetiological factors. Studies of childhood bone tumours show stable incidence over time for OS (13,14). For ES the Manchester Children's Tumour Registry (MCTR), which operates a system of special diagnostic review, found stable incidence (13) but there was a slight increase in national data (14) almost certainly due to

increased recognition of ES with improved diagnosis. Space-time clustering among cases of specific disease is associated with an infectious aetiology. There was no evidence of space-time clustering among cases of OS based on MCTR data but weak evidence of this in a national dataset (15). There is little international variation in incidence of OS in children, but ES is virtually absent from black populations (16).This observation most likely has a genetic basis. In English national data on TYAs stable incidence over time has been found for both OS and ES (17). There were no significant variations in incidence by socioeconomic deprivation and geographical region (18).

These small variations in incidence suggest that environmental factors play a minor role in aetiology or exposures have been uniformly distributed over time and geographically. However, this does not exclude the possibility of the involvement of environmental exposures in the onset of bone tumours in young people. Children and adolescents, at the stage of maximum growth, may be more susceptible to such exposures than older adults. The possibility that environmental agents may target different organs and tissues in the growing child and adolescent, compared with mature adults, should be considered. The role of genetic factors in modifying risks may be greater than in older adults (6) and studies of aetiology should incorporate molecular analyses of polymorphisms in genes controlling growth factors, immune response and metabolism. In addition, it is well known that a minority of bone sarcomas occur in association with certain cancer predisposition syndromes, including Li-Fraumeni syndrome (LFS) and retinoblastoma (19,20), but the proportions of cases attributable to these mutations is uncertain, particularly in TYAs. Determination of the frequency of such high penetrance mutations is important, since the presence of germline mutations has profound implications for future clinical management, including genetic counselling.

In conclusion, although little is known about aetiology, the striking age-incidence patterns of OS and ES, the known genetic susceptibility in rare cases and the largely stable incidence patterns, allow a set of hypotheses to be formulated. Bone tumours rank 6th and 4th for mortality (14,21) in relation to other cancers, in children and TYAs respectively (14,21) and represent one of the most important causes of death in the young. It is imperative that we make the effort to identify and tackle causes of OS and ES leading to prevention. However, one of the biggest challenges is the rarity of these diseases. In order to achieve sufficient statistical power, a multi-centre international study is required. A necessary first step is a pilot study to establish feasibility.

Objectives of the study

The objectives of the full-scale study are to understand the aetiology of bone sarcomas focusing on genetic susceptibility, growth and development throughout childhood and adolescence as well as aspects of molecular epidemiology including epigenetic profiles, DNA repair capacity and mutation patterns. The main objectives of the **pilot study** are to gather sufficient information on young people with OS and ES to enable a protocol for the full-scale study to be developed and to formulate a testable set of hypotheses. The following draft set of hypotheses have been formulated:

1. Factors associated with postnatal patterns of growth influence risk of developing OS and ES.
2. An initiating event (or events) occurs earlier in childhood creating a pre-malignant clone (or clones) in the target tissue(s). The mid-childhood growth spurt will be a particularly vulnerable period.
3. The rapid growth during the adolescent growth spurt increases the chance of malignant transformation.

4. Risk factors for OS and ES which influence growth may be endogenous or exogenous
5. Endogenous factors include growth factors/hormones acting pre-natally and post-natally and genetic variation in these.
6. Exogenous factors include nutrition, physical exercise, illnesses during childhood and environmental exposures that may interact with growth, especially bone growth (including bone-seeking elements, mitogenic substances, ionizing radiation). Susceptibility to these factors may be under genetic control.
7. There will be overlap between causal factors in each of the tumour types, but the timing, route, combination and intensity of exposures coupled with individual genetic make-up will determine outcome.
8. In a small proportion of cases, the tumours will arise in association with highly penetrant mutations to cancer-associated genes.

Plan of Investigation

Professor Birch and Professor McKinney will be responsible for organising the study in Manchester and Leeds respectively, in collaboration with the lead clinicians Professor Eden and Professor Lewis. A part-time research nurse will be based in each centre.

Case Recruitment

Cases of histologically confirmed OS and ES in persons aged 0-24 years diagnosed during the period, July 2009 to August 2011, resident in the North West (NW) and Yorkshire and the Humber (YH) Strategic Health Authority areas will be eligible. Virtually all incident cases in children aged 0-14 will be treated in the regional paediatric oncology units in Leeds and Manchester. It is expected that most cases in 15-24 year olds will be treated in the respective Teenage Cancer Trusts units, but adult oncology units in Leeds and Manchester may treat some of the older patients and these will also be monitored. During this 2 year period we predict there will be about 30 cases in YH (Leeds) and 40 cases in NW. We would expect to recruit at least 75% of incident cases (minimum 50 patients) through the main oncology centres in Leeds and Manchester.

We will liaise with relevant clinic staff to identify and obtain permission to approach patients and/or their parents from the clinician in charge. Initial approach will be to the patients themselves or their parents depending on age. Informed consent will be needed from TYA patients to approach their parents. Invitation letters and information sheets will be mailed or handed to patients and/or parents in the hospital. Following consent clinical details of participating cases will be extracted from oncology records and a copy of the pathology report obtained.

Interview procedure

Following written informed consent, research nurses will conduct face to face interviews, using structured proformas with study subjects in their homes or the hospital, depending on preference. Separate interviews will be conducted with cases, their mothers and fathers as appropriate. The proformas will focus on mother's pregnancy with the index case, birth (including birthweight) and neonatal care, factors in infancy and early childhood including, nutrition, illnesses, growth and development, factors in later childhood and adolescence including illnesses and their treatment, physical activity, social habits (including smoking), growth and development, family histories of cancer, congenital anomalies and other genetically determined conditions, parental health,

including adult heights, parental smoking. Information collected from the face to face interview will be used to assess exposure prevalence.

The investigators have extensive experience of conducting interview-based studies and have previously achieved recruitment rates of over 90%. This rate should be achieved in the pilot for cases in the main oncology centres. Completeness of ascertainment and recruitment will be cross-checked with respective cancer registries.

Collection of biological specimens

Molecular genetic analysis will be an important component of the full study. In preparation, in the pilot we shall collect blood and saliva samples from cases and their parents to assess compliance rates. Methodologies and procedures for biological sample collection will be set up and optimised. Case blood samples will be obtained by arrangement with oncology staff to avoid additional procedures. The research nurses will be responsible for biosample collection from parents (blood or saliva) and saliva samples from cases (if no blood sample is possible). Biosamples will be stored in Manchester for future analysis. Samples will be labelled with study numbers including a code to indicate whether the sample is from a case, mother or father. No ID information will be included to allow future anonymised molecular analyses. It will be possible to link back to the epidemiological and clinical data via the study number but the data and laboratory results will be stored separately. Data and results will be linked only for statistical analysis in a temporary file (Data Management).

Abstraction of medical records

An important aspect of this pilot will be location and abstraction of relevant medical records including, mothers' obstetric records (gestation, birthweight, congenital anomalies, neonatal problems/care) and child health records (developmental milestones, growth, general health) using standard proformas. For some health authorities, the latter are computerised. Informed consent to access and abstract records will be obtained at interview.

Future Analysis of Biosamples

The power of the study will be too low for calculation of familial cancer risks, but families showing clustering of cancers consistent with predisposition syndromes will be selected for future analysis of candidate genes. We expect to collect samples from 50 families and would anticipate selection of about 10 families. Analyses of these genes and low-penetrance genes/polymorphisms will be conducted as part of the full-scale study and biosamples from the pilot will be incorporated into these. These analyses will be subject to separate ethical approval as part of the main study.

Data Management

Data will be coded in both centres but input, cleaned and edited centrally in Manchester. The data stored in Manchester will be split in three files to allow anonymisation as well as linkage. The following scheme will be applied.

1. File 1 (Admin File) − A password controlled computer file containing identifying and demographic details of cases will be created. This file will include variables such as dates of birth, addresses, NHS number, hospital number and "logging" of progress with interviews, records abstractions and biological samples.

2. File 2 (QUESTIONNAIRE File) − All the questionnaire data will be held in a separate password controlled file with no identifying information but with individuals allocated a study number. Data abstracted from medical records will also be held in File 2.
3. File 3 (LABORATORY File) − Each specimen from the same individual will be labelled with the study number, plus a specimen number (to allow for more than one specimen from the same person) and stored within the University of Manchester. Subsequently, and in accordance with local standard operating procedures and in compliance with the requirements of the Human Tissue Act, specimens may be dispatched to collaborating laboratories for analysis in separately funded studies with specific ethical approval. The laboratory receiving the samples will be given details of the specimen, the age and sex of the patient. Specimen details and laboratory results will be held on a third password controlled restricted access computer file. No identifying details will be held in this file.

At the time of analysis, files 1, 2 and 3 will be linked to create a temporary file to combine the clinical and epidemiological data and subsequently the laboratory results. This file will use the study number and relevant reference dates but no other identifiers. On completion of the analysis, this file will be deleted. All data will be stored on an air gap (stand alone) network. Offices have keypad locks and entry to the department is by swipe card. All members of staff sign a confidentiality agreement as part of their contract.

Time Table

Jan 2009–June 2009	Prepare study materials including leaflets, consent forms and questionnaire
	Apply for MREC approval
	Obtain NHS trust research governance approval
	Recruit staff and obtain NHS honorary contracts for study staff
	Establish collaborative links with treatment centres
	Establish laboratory procedures
July 2009-Sept 2011	Ascertain, approach and interview 50 cases
	Collect and process samples
	Abstract data from health records
	Collect and computerise data
Oct 2011–Feb 2012	Complete data collection and computerisation
	Clean, verify and edit the data
	Evaluate participation rates
	Assess exposure frequencies
	Write reports
	Prepare protocol and grant applications for full study

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CTYAB/PIS under 12
Version 2 Aug 09

Pilot Study of Childhood, Teenage & Young Adult Bone Tumours

Information Leaflet for Children (under 12 years)

What is the background to this study?
A new large study of the causes of bone tumours in children, teenagers and young adults is being planned. Scientists from different countries will work together on this large study. Before the large study can begin, we need to do a small study called a **pilot study.** Our pilot study is being done before the main project to collect important information, for example about your health, to help with the main project.

Why do you need to do a pilot study?
In the pilot study we shall try out some ways of doing the research which we hope to use in the large study. The pilot study will tell us if these work and whether we need to change anything.

Who is doing the research?
The pilot study is being carried out by teams of scientists, nurses and doctors from Manchester and Leeds.

Why have you chosen me?
We have chosen you because we know that you have had the kind of tumour we are interested in.

What will you do in the research ?
We shall be asking your parents if they would like to take part in the study by answering a lot of questions. A research nurse who is part of our team will arrange to meet with your parents to do this. We are also giving an information sheet to your parents, so you might want to talk to them about the study.

What sort of questions will they be asked?

Your parents will be asked to give some information about your early life which includes: illnesses and injuries, what happened when you were a baby, the sorts of sports you play, other things you like to do and also some general information about your family. We will also ask your mother about when she was expecting you. They do not have to answer all the questions if they, or you, do not want them to.

Will you be doing anything else ?

We should like a small blood sample or a saliva (spit) sample from you and your parents. We also want to look at your medical notes to find out more about how much you grew when you were younger and any illnesses or injuries you may have had.

Why do you need a blood or saliva sample from me?

You can take part in the study without giving blood or a saliva (spit) sample. If you are willing your doctor or nurse at the hospital will take a small sample (about 2 teaspoons) from you at the same time as a sample is being taken as part of your treatment, so there won't be any extra needles.

Instead of giving us a blood sample, you could give a saliva sample by spitting into a special little pot. The nurse will show you how to do this. The samples will be used in tests done in a laboratory, which we hope will tell us if some people are more likely to develop bone tumours than others. The samples will be kept at the University of Manchester so that they can be used for these tests in the future.

Will I find out the results on my blood or saliva sample?

No. Results on samples will not be given to those taking part in the study or their families and will not be passed on to their doctors or anybody else.

Who will be able to look at the information in the study ?

Only a small number of people working on the project all of whom know they must keep the information about you secret.

Can I see my information ?

Yes. You have a right to see all the information about you which we collected for the study.

What will happen if I do not want to take part in the research?

Nothing. If you do not want to take part, or if you do not want your parents to answer the questions, this will not affect your treatment in any way and nobody will mind.

Do I have to take part in the study?

We will try to make sure that you and your parents are happy to take part in the study. If you want to take part we shall need the consent of your parents. If after reading this information sheet, thinking it over for a few days and talking to your parents, you decide not to join the study that is OK.

What happens next ?
One of our research nurses will contact your parents soon if they are willing, to arrange to meet them to ask them the questions for our research.

How can I find out more about the study?
For advice or information about the study contact:
Professor Jill Birch
Cancer Research UK Research Group,
School of Cancer & Imaging Sciences
The Medical School, Stopford Building, Room 1.900
University of Manchester, Oxford Road
Manchester M13 9PL
TEL: 0161-275-5404
FAX: 0161-275-5348
EMAIL: jillian.birch@manchester.ac.uk

OR
Dr Richard G.Feltbower
Centre for Epidemiology & Biostatistics
Paediatric Epidemiology Group, Room 8.49J, Level 8
Worsley Building, University of Leeds
Clarendon Way, Leeds LS2 9JT
TEL/FAX: 0113 343 4841/4877
EMAIL: r.g.feltbower@leeds.ac.uk
OR
Talk to a member of your clinical team at your hospital or clinic

How can I find out more about bone tumours in children, teenagers and young adults?
The following organizations provide information:

Bone Cancer Research Trust
Suite 1d, Gledhow Mount Mansion,
Roxholme Grove, Leeds, LS7 4JJ
Tel: 0113 262 1852
Email: info@bone cancerresearch.org.uk
WEBPAGE: www.bonecancerresearch.org.uk

Children's Cancer & Leukaemia Group
University of Leicester, 3rd floor,
Hearts of Oak House, 9 Princess Road West
Leicester LE1 6TH
Tel: 0116 249 4460 Email:info@cclg.org.uk
WEBPAGE: www.cclg.org.uk

Teenage Cancer Trust
3rd Floor, 93 Newman Street,
London, W1T 3EZ
Tel: 020 7612 0370
Email: tct@teenagecancertrust.org.
WEBPAGE: www.teenagecancertrust.org

Cancer Research UK
PO Box 123, Lincoln's Inn Fields
London WC2A 3PX
Tel: 020 7242 0200
WEBPAGE: www.cancerresearchuk.org

CTYAB/PIS 12-15
Version 2 Aug 09

Pilot Study of Childhood, Teenage & Young Adult Bone Tumours

Information Leaflet for Young People (12-15 years)

What is the study about ?
A new large-scale study of the causes of bone tumours in children, teenagers and young adults is being planned. We hope that people from all over Europe will take part in the large-scale study. We shall be studying such things as nutrition, growth and development throughout childhood and adolescence, sport and exercise, viruses and other environmental exposures. Information collected from different centres will be combined and this will allow for powerful analyses of possible causes of these tumours. Before this large-scale study can go ahead, a smaller study called a **pilot study** is being done to collect information which will help with the design of the main project.

What is the aim of the pilot study?
In the pilot study we shall be trying out a questionnaire to look at the sort of answers given and whether there are any questions which people taking part find difficult to answer. We should also like to look at whether medical records that would be useful in the study are still available. It is also important to see how many people agree to take part. All these things will help us plan the main study so that it is a success.

Who is doing the pilot study ?
The pilot study is being carried out by teams of scientists, nurses and hospital doctors from Manchester and Leeds.

Why have you chosen me?
We have chosen you because we know that you have had the kind of tumour we are studying.

What will I have to do ?
We should like to arrange to carry out an interview with your parents which generally takes about 1 hour. A research nurse will arrange a time and place for the interview, so you do not have to do anything. We are also giving an information sheet to your parents, so you might want to talk to them about the study.

What sort of questions will you ask my parents ?
At the interview your parents will be asked about your health including: illnesses and injuries, where you have lived and any sports or other activities you have taken part in and also some general information about health in your family. We will also ask your mother about when she was expecting you. They do not have to answer all of the questions if they, or you do not want them to.

Do you need any other information ?
With your permission, we should like to extract details from your oncology records about the particular type of bone tumour which you developed. We should also like access to your general health records so that we can extract information about your growth and development during your childhood, including height and weight at different ages and your developmental milestones. In addition, we shall be asking your mother if we can extract information from her medical records about her pregnancy, your birth and health soon after birth, including results of scans and other tests before you were born, your birth weight, size and your general health shortly after you were born.

Does the study involve anything else ?
If you agree, we would like a small blood sample from you or a sample of saliva (spit). We would also like to look at health records for information on growth and previous illnesses.

Why do you need a blood or saliva sample from me?
You can take part in the study without giving blood or a saliva sample but if you agree, a blood sample (5-20ml of blood or 1-4 teaspoons) will be collected at the same time as a sample is being taken as part of your treatment. If this is not possible, you could give a saliva sample. All you have to do is to spit into a small pot. We should also like a blood or saliva sample from your parents which would be collected by the research nurse. The blood and saliva samples will be used to extract genetic material to look for differences which may affect the chances of developing bone tumours.

What will happen to the samples ?
The material will be stored at the University of Manchester and will be used for future analysis. The blood/saliva samples will be considered as being gifted to the University and you will have no rights over any commercial developments arising from their use in research.

Will I find out the results on my or my parents blood or saliva sample?
No. Results on samples given for research are not passed on to those who took part in the research, nor to their families, to their doctors or anybody else.

Who will look at the information ?
A very small number of staff directly working on the project will look at the information. Other staff working for the NHS and/or the University may also need to look at part of the information to make sure that the research is being carried out properly and to check

that all the information is kept secure. All staff know that the information must be kept confidential.

Can I look at the information ?
Yes. You have a right to see all the information about you collected by us at interview and from your medical records.

What will happen if I do not want to take part in the research?
Nothing. This research is entirely voluntary and this will NOT affect your medical care in any way.

How do I know if your work is ethical?
All our research is carried out with the approval of medical research ethics committees. The members of these committees include doctors, health professionals and other ordinary people.

Do I have to take part in the study?
We always try to make sure that you and your parents are happy to take part in the study. If after reading this information sheet, thinking it over for a few days and discussing it with your parents, you decide not to join the study that is OK.

What happens next ?
If you and your parents are happy to take part, one of our research nurses will contact your parents to arrange an interview.

How can I find out more about the study?
For advice or information relating to the study contact:
Professor Jill Birch
Cancer Research UK Research Group,
School of Cancer & Imaging Sciences
The Medical School, Stopford Building, Room 1.900
University of Manchester, Oxford Road
Manchester M13 9PL
TEL: 0161-275-5404
FAX: 0161-275-5348
EMAIL: jillian.birch@manchester.ac.uk

OR

Dr R.G.Feltbower
Centre for Epidemiology & Biostatistics
Paediatric Epidemiology Group, Room 8.49J, Level 8
Worsley Building, University of Leeds
Clarendon Way, Leeds LS2 9JT
TEL/FAX: 0113 343 4841/4877
EMAIL: r.g.feltbower@leeds.ac.uk

OR
Talk to a member of your clinical team at your hospital or clinic

If you have a concern about any aspect of this study, you should ask to speak to researchers who will do their best to answer your questions. If they are unable to resolve your concern, or you wish to make a complaint regarding the study, please contact a University Research Practice and Governance Co-ordinator on 0161 275 7583 or 0161 275 8093 or by email to research-governance@manchester.ac.uk

How can I find out more about bone tumours in children, teenagers and young adults?

The following organizations provide information:

Bone Cancer Research Trust
Suite 1d, Gledhow Mount Mansion
Roxholme Grove, Leeds, LS7 4JJ
Tel: 0113 262 1852
Email: info@bonecancerresearch.org.uk
WEBPAGE:www.bonecancerresearch.org.uk

Children's Cancer & Leukaemia Grp
University of Leicester, 3rd floor,
Hearts of Oak House, 9 Princess Road West
Leicester LE1 6TH
Tel: 0116 249 4460 Email:info@cclg.org.uk
WEBPAGE: www.cclg.org.uk

Teenage Cancer Trust
3rd Floor, 93 Newman Street,
London, W1T 3EZ
Tel: 020 7612 0370
Email: tct@teenagecancertrust.org.
WEBPAGE: www.teenagecancertrust.org

Cancer Research UK
PO Box 123, Lincoln's Inn Fields
London WC2A 3PX
Tel: 020 7242 0200
WEBPAGE: www.cancerresearchuk.org

CTYAB/PIS 16+
Version 2 Aug 09

Pilot Study of Childhood, Teenage & Young Adult Bone Tumours

Information Leaflet for Patients over 16 years

What is the study about ?
A new large-scale multi-centre study of the causes of bone tumours in children, teenagers and young adults is being planned. We shall be studying such things as nutrition, growth and development throughout childhood and adolescence, sport and exercise, viruses and other environmental exposures. Information collected from different centres will be combined and this will allow for powerful analyses of possible causes of these tumours. Prior to this large study, our smaller **pilot study** is being undertaken to collect essential information, for example about your health, to help with the design of the larger project.

What is the aim of the pilot study?
In the pilot study we shall be trying out a questionnaire to look at the range of answers given and whether there are any questions which people find difficult to answer. We would also like to look at whether medical records that would be useful in the study are still available. In addition, it's important to know what proportion of families agree to take part. All of these things will help us design a successful full-scale study.

Who is doing the research?
The pilot study is being carried out by teams of scientists, nurses and hospital doctors from Manchester and Leeds.

Why have you contacted me?
We have contacted you because we are inviting you to take part in this study. The reason for choosing you is that you recently developed a type of bone tumour which we are studying.

What does the study involve ?
If you agree to take part, we shall arrange to carry out an interview which generally takes about 1 hour. The research nurse who will carry out the interview will arrange a time and place which is convenient for you. In addition, with your permission, we should also like to interview your parents.

If I agree what sort of questions will I be asked?
At the interview you will be asked about your health including: illnesses and injuries, your occupations and where you have lived and any sports or other activities you have taken part in. We shall also ask about your early life and your development during adolescence. We should like to ask your parents similar questions and also ask your mother about the time before you were born when she was expecting you. You can choose not to answer any of the questions.

Do you need any other information ?
With your permission, we should like to extract details from your oncology records about the particular type of bone tumour which you developed. We should also like access to your general health records so that we can extract information about your growth and development during your childhood, including height and weight at different ages and your developmental milestones. In addition, we shall be asking your mother if we can extract information from her medical records about her pregnancy, your birth and health soon after birth, including results of scans and other tests before you were born, your birth weight, size and your general health shortly after you were born.

Does the study involve anything else ?
If you agree, we would like a small blood sample or a sample of saliva (spit) from you. The blood samples will be taken by your doctor at the same time as a routine sample is taken.

Why do you need a blood or saliva sample from me?
You can take part in the study without giving a blood or saliva sample but if you agree, the research nurse or hospital clinic staff will take the samples. Between 5-20ml (1-4 teaspoons) of blood will be taken for the research. Alternatively, you could give a saliva sample by spitting into a small pot. The blood and saliva samples will be used to extract genetic material to look for variations in genes which may affect the likelihood of developing bone tumours.

What will happen to the samples ?
The material will be stored at the University of Manchester and will be used for future analysis. The blood/saliva samples will be considered as being gifted to the University and you will have no rights over any commercial developments arising from their use in research.

Will I find out the results on my blood or saliva sample?
No. Results on samples donated for research will not be given to participants and their families and will not be passed on to their doctors or anybody else. The tests that will be carried out are not medical tests and the results will only be used for research. So, taking part in the study should not have any adverse effects on you (including employment status or ability to get insurance).

Who will have access to the data information ?
Only a very restricted number of staff directly working on the project will have access to information collected in the study. NHS and/or University staff responsible for auditing research conduct and data security will also have limited access for this purpose. All staff are trained in confidentiality procedures.

Can I have access to the information ?
Yes. You have a right to see all the information collected at interview and extracted from medical records which concerns you and held by us.

What will happen if I do not want to take part in the research?
Nothing. This research is entirely voluntary and this will NOT affect your medical care in any way.

How do I know if your work is ethical ?
All our research is carried out with the approval of medical research ethics committees. The members of these committees include doctors, health professionals and lay people.

What should I do now?
Please return the reply slip in the envelope provided. If you are willing, one of our research nurses will contact you to arrange an interview.

How can I find out more about the study?
For advice or information relating to the study contact:
Professor Jill Birch
Cancer Research UK Research Group
School of Cancer & Imaging Sciences
The Medical School, Stopford Building, Room 1.900
University of Manchester, Oxford Road, Manchester M13 9PL
TEL: 0161-275-5404
FAX: 0161-275-5348
EMAIL: jillian.birch@manchester.ac.uk
OR
Dr Richard Feltbower
Centre for Epidemiology & Biostatistics
Paediatric Epidemiology Group, Room 8.49J, Level 8
Worsley Building, University of Leeds
Clarendon Way, Leeds LS2 9JT
TEL/FAX: 0113 343 4841/4877
EMAIL: r.g.feltbower@leeds.ac.uk
OR
Talk to a member of your clinical team at your hospital or clinic

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If they are unable to resolve your concern, or you wish to make a complaint regarding the study, please contact a University Research Practice and Governance Co-ordinator on 0161 275 7583 or 0161 275 8093 or by email to research-governance@manchester.ac.uk

How can I find out more about bone tumours in children, teenagers and young adults?

The following organizations provide information

Bone Cancer Research Trust
Suite 1d, Gledhow Mount Mansion
Roxholme Grove, Leeds, LS7 4JJ
Tel: 0113 262 1852
Email: info@bonecancerresearch.org.uk
WEBPAGE:www.bonecancerresearch.org.uk

Children's Cancer & Leukaemia Group
University of Leicester, 3rd floor, Hearts of Oak House, 9 Princess Road West,
Leicester LE1 6TH
Tel: 0116 249 4460
Email:info@cclg.org.uk
WEBPAGE: www.cclg.org.uk

Teenage Cancer Trust
3rd Floor, 93 Newman Street,
London, W1T 3EZ
Tel: 020 7612 0370
Email: tct@teenagecancertrust.org.
WEBPAGE: www.teenagecancertrust.org

Cancer Research UK
PO Box 123, Lincoln's Inn Fields
London WC2A 3PX
Tel: 020 7242 0200
WEBPAGE: www.cancerresearchuk.org

CTYAB/PIS Parents
Version 2 Aug 09

Pilot Study of Childhood, Teenage & Young Adult Bone Tumours

Information Leaflet for Parents & Guardians

What is this study about ?
A new large multi-centre study of causes of bone tumours in children, teenagers and young adults is being planned. We shall be studying such things as nutrition, growth and development during childhood and adolescence, sport and exercise, viruses and other environmental exposures. Information collected from different centres will be combined and this will allow for powerful analyses of possible causes of these tumours. Prior to this large study, our smaller **pilot study** is being undertaken to collect essential information, for example about your child's health, to help with the design of the larger project.

What is the aim of the pilot study?
In the pilot study, we shall be trying out a questionnaire to look at the range of answers given and whether there are any questions which people find difficult to answer. We would also like to look at whether medical records that would be useful in the study are still available. In addition, it's important to know what proportion of families agree to take part. All of these things will help us design a successful full-scale study.

Who is doing the research?
The pilot study is being carried out by teams of scientists, nurses and hospital doctors from Manchester and Leeds.

Why have you contacted me?
We have contacted you because we are inviting you to take part in this study. The reason for choosing you is that you have a son or daughter who developed a type of bone tumour which we are studying.

What does the study involve?
If you agree to take part, we shall arrange to carry out an interview which generally takes about 1 hour. The research nurse who will carry out the interview will arrange a time and place which is convenient for you.

If I agree what sort of questions will I be asked?
At the interview you will be asked about your son's/daughter's and your family's health including: illnesses and injuries, your occupations and where you have lived and any sports or other activities your son/daughter has taken part in. We shall also ask about your son's/daughter's growth and development including adolescence. For mothers, we shall ask about the pregnancy with your child who developed the bone tumour and other pregnancies (if any). You can choose not to answer any of the questions.

Do you need any other information ?
With your permission we should like to have access to certain medical records. These include your child's oncology records so that we can extract details about the particular type of bone tumour which they developed. We should also like access to your child's general health records so that we can extract information about their growth and development, including height and weight at different ages and their developmental milestones. For mother's, we should like to extract information from their obstetric records including results of scans of the baby before birth, results of mother's blood tests and details of any problems during pregnancy e.g. high blood pressure. We should also like to record the baby's birth weight, size, general condition and any problems shortly after birth.

Does the study involve anything else ?
If you agree, we would like a small blood sample or saliva (spit) sample from you and your son/daughter. The blood sample from your son/daughter will be taken by their doctor at the same time as a routine sample is taken.

Why do you need a blood or saliva sample from me and my son/daughter ?
You can take part in the study without giving blood or a saliva sample but if you agree, the research nurse or hospital clinic staff will take the samples. Between 5 and 20ml (1-4 teaspoons) of blood will be taken for the research. Alternatively, you and/or your son/daughter could give a saliva sample by spitting into a small pot. For young children, saliva samples are collected by placing tiny sponges in the child's mouth between the gums and the inner cheek. The sponges are gently moved around for about half a minute to soak up as much saliva as possible. The blood and saliva samples will be used to extract genetic material to look for variations in genes which may affect the likelihood of developing bone tumours.

What will happen to the samples ?
The material will be stored at the University of Manchester and will be used for future analysis. The blood/saliva samples will be considered as being gifted to the University and you will have no rights over any commercial developments arising from their use in research.

Will I find out the results on my or my son's/daughter's blood or saliva sample?
No. Results on samples donated for research will not be given to participants nor to their families and will not be passed on to their doctors or anybody else. The tests that will be carried out are not medical tests and the results will only be used for research. So, taking part in the study should not have any adverse effects on you or your son/daughter (including employment status or ability to get insurance).

Who will have access to the information ?
Only a very restricted number of staff directly working on the project will have access to information collected in the study. NHS and/or University staff responsible for auditing research conduct and data security, will also have limited access for this purpose. All staff are trained in confidentiality procedures.

Can I have access to the information ?
Yes. You have a right to see all the information collected at interview and extracted from medical records which concerns you and held by us.

What will happen if I do not want to take part in the research?
Nothing. This research is entirely voluntary and this will NOT affect your or your son's/daughter's medical care in any way.

How do we know if your work is ethical?
All our research is carried out with the approval of medical research ethics committees. The members of these committees include doctors, health professionals and lay people.

What should I do now?
Please return the reply slip in the envelope provided. If you are willing, one of our research nurses will contact you to arrange an interview.

How can I find out more about the study?
For advice or information relating to the study contact:
Professor Jillian M. Birch
Cancer Research UK Research Group,
School of Cancer & Imaging Sciences
The Medical School, Stopford Building, Room 1.900
University of Manchester, Oxford Road
Manchester M13 9PL
TEL: 0161-275-5404
FAX: 0161-275-5348
EMAIL: jillian.birch@manchester.ac.uk
OR
Dr R.G.Feltbower
Centre for Epidemiology & Biostatistics
Paediatric Epidemiology Group, Room 8.49J, Level 8
Worsley Building, University of Leeds
Clarendon Way, Leeds LS2 9JT

TEL/FAX: 0113 343 4841/4877
EMAIL: r.g.feltbower@leeds.ac.uk

OR: Talk to a member of your clinical team at your hospital or clinic.

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If they are unable to resolve your concern, or you wish to make a complaint regarding the study, please contact a University Research Practice and Governance Co-ordinator on 0161 275 7583 or 0161 275 8093 or by email to research-governance@manchester.ac.uk

How can I find out more about bone tumours in children, teenagers and young adults?

The following organizations provide information

Bone Cancer Research Trust
Suite 1d, Gledhow Mount Mansion
Roxholme Grove, Leeds, LS7 4JJ
TEL: 0113 262 1852
EMAIL: info@bonecancerresearch.org.uk
WEBPAGE: www.bonecancerresearch.org.uk

Children's Cancer & Leukaemia Group
University of Leicester, 3rd floor, Hearts of Oak House, 9 Princess Road West,
Leicester LE1 6TH
Tel: 0116 249 4460.Email:info@cclg.org.uk
WEBPAGE: www.cclg.org.uk

Teenage Cancer Trust
3rd Floor, 93 Newman Street,
London, W1T 3EZ
TEL: 020 7612 0370
EMAIL: tct@teenagecancertrust.org.
WEBPAGE: www.teenagecancertrust.org

Cancer Research UK
PO Box 123, Lincoln's Inn Fields
London WC2A 3PX
TEL: 020 7242 0200
WEBPAGE: www.cancerresearchuk.org

CTYAB/CFPts 12-15

Version 2 Aug 09

Pilot Study of Childhood, Teenage & Young Adult Bone Tumours

Consent Form for Patients aged 12-15 years

Researchers: Professor Jillian Birch and Dr Richard Feltbower
This form should be completed by patients aged 12 years to 15 years.
You will be given a copy of the information leaflet and a copy of this form to keep.

Name of Patient …… **Date of Birth of Patient** ……

Hospital/Clinic ……..

Please read and complete the following:	**Initials**
I have read and understood the information contained in the information leaflet	☐
I have had the opportunity to ask questions and have received satisfactory answers to my questions.	☐
I understand that participation is voluntary and I am free to withdraw my agreement at any time without having to give a reason and without affecting my treatment.	☐
I agree to my mother/father/guardian(s)* being interviewed for the above study and understand that the information they give will be for confidential use in the study and future studies of childhood teenage and young adult bone tumours.	☐
I agree to my medical notes, including; GP/oncology/child health/neonatal* being viewed by a member of the research team and to information being extracted from them.	☐
I understand that the information from my medical notes containing clinical and personal information (including NHS number, addresses and post codes) will be held securely and confidentially by the research team for use in the study and future studies of childhood, teenage and young adult bone tumours.	☐
I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from The University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
I agree to give a blood/saliva sample* for use in the study and future studies into childhood, teenage and young adult bone tumours.	☐
I understand that I will not be given the results from the blood samples or saliva samples.	☐

Patient signature aged 12-15 years

Signature……..

Full name (block capitals) ……. Date …….

Doctor/researcher taking consent

Signature …….. Full name (block capitals) …….

Position ……. Date …….
Please return this form to: Professor J M Birch, Cancer Research UK Research Group,
School of Cancer & Imaging Sciences, The Medical School, Stopford Building, Room 1.900
University of Manchester, Oxford Road, Manchester M13 9PL
* Delete as necessary

CTYAB/CF par 16+
Version 2 Aug 09

Pilot Study of Childhood, Teenage & Young Adult Bone Tumours

Consent Form for Parents/Guardians of Patients over 16 years of age.

Researchers: Professor Jillian Birch and Dr Richard Feltbower
This form should be completed by the parent/guardian of patients who are over 16 years of age. You will be given a copy of the information leaflet and a copy of this form to keep.

Name of Patient …… **Date of Birth of Patient** ……

Hospital/Clinic/GP ……..

Please read and complete the following:	**Initials**
I have read and understood the information contained in the information leaflet	☐
I have had the opportunity to ask questions and have received satisfactory answers to my questions.	☐
I understand that participation is voluntary and I am free to withdraw my agreement at any time without having to give a reason and without affecting my child's treatment.	☐
I agree to be interviewed for the above study and understand that the information I give will be for confidential use in the study and in future studies of childhood, adolescent and young adult bone tumours.	☐
I agree to my medical notes, including; GP/obstetric* being viewed by a member of the research team and to information being extracted from them.	☐
I understand that the information from my medical notes containing clinical and personal information (including NHS number, addresses and post codes) will be held securely and confidentially by the research team for use in the study and future studies of childhood, adolescent and young adult bone tumours.	☐
I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from The University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
I agree to give a blood/saliva sample* for use in the study and future studies into childhood, teenage and young adult bone tumours.	☐
I understand that I will not be given the results from the blood samples or saliva samples.	☐

Parent/Guardian signature of child over 16 years

Signature……..

Full name (block capitals) ……. Date …….

Doctor/researcher taking consent

Signature …….. Full name (block capitals) …….

Position ……. Date …….
Please return this form to: Professor J M Birch, Cancer Research UK Research Group,
School of Cancer & Imaging Sciences, The Medical School, Stopford Building, Room 1.900,
University of Manchester, Oxford Road, Manchester M13 9PL

* Delete as necessary

CTYAB/CF par under 16
Version 2 Aug 09

Pilot Study of Childhood, Teenage & Young Adult Bone Tumours

Consent Form for Parents/Guardians of Patients under 16 years of age.

Researchers: Professor Jillian Birch and Dr Richard Feltbower
This form should be completed by the parent/guardian of patients who are under 16 years of age. You will be given a copy of the information leaflet and a copy of this form to keep.

Name of Patient …… **Date of Birth of Patient** ……

Hospital/Clinic……..

Please read and complete the following:	**Initials**
I have read and understood the information contained in the information leaflet	☐
I have had the opportunity to ask questions and have received satisfactory answers to my questions.	☐
I understand that participation is voluntary and I am free to withdraw my agreement at any time without having to give a reason and without affecting my child's treatment.	☐
I agree to be interviewed for the above study and understand that the information I give will be for confidential use in the study and future studies of childhood, teenage and young adult bone tumours.	☐
I agree to my medical notes, including; GP/obstetric* being viewed by a member of the research team and to information being extracted from them.	☐
I agree to my child's medical notes, including; GP/oncology/child health/neonatal* being viewed by a member of the research team and to information being extracted from them.	☐
I understand that the information from my and my child's medical notes containing clinical and personal information (including NHS number, addresses and post codes) will be held securely and confidentially by the research team for use in the study and future studies of childhood, teenage and young adult bone tumours.	☐
I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from The University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
I agree that a blood/saliva sample* may be taken from my child for use in this study and for future studies into child, teenage and young adult bone tumours.	☐
I agree to give a blood/saliva sample* for use in the study and future studies into child, teenage and young adult bone tumours.	☐

I understand that I will not be given the results from any of the blood samples or saliva samples. ☐

Parent/guardian signature of child under 16 years

Signature……..

Full name (block capitals) ……. Date …….

Doctor/researcher taking consent

Signature …….. Full name (block capitals) …….

Position ……. Date …….
Please return this form to: Professor J M Birch, Cancer Research UK Research Group,
School of Cancer & Imaging Sciences, The Medical School, Stopford Building, Room 1.900,
University of Manchester, Oxford Road, Manchester M13 9PL
* Delete as necessary

ID No: | | | | | | | |
Study ID | Family ID

Index Case (16 to 24 Years) Questionnaire

ID No: [ ][ ] Study ID [ ][ ][ ][ ] Family ID

Personal Details

Thank you for agreeing to help us with this study. Most of the questions I am going to ask you are about your childhood and adolescence.

[ ][ ] [ ][ ] [ ][ ][ ][ ]
day month year

[ ][ ] [ ][ ]
Time Started Hr Min
(24 hr clock)

Can I stress again that all your answers will be treated in the strictest confidence and the information will not be passed to anyone outside the study.

Index Case Sheet no. [ ][ ]

First Name_____ Last Name_____ Total Sheets [ ][ ]

Address
at interview_____Date of Diagnosis [ ][ ] [ ][ ] [ ][ ][ ][ ]
day month year

_____

_____ Sex: 1=male 2=female [ ]

Postcode [ ][ ] [ ][ ] [ ][ ] [ ][ ]

Date of Birth [ ][ ] [ ][ ] [ ][ ][ ][ ]
day month year

NHS No. [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

Mother (or Surrogate) Parent I.D. [ ]

First Name_____ Last Name_____Title_____
Current
Address_____ All previous names_____

_____

_____ Name when _____was born:

Postcode [ ][ ] [ ][ ] [ ][ ] [ ][ ]

_____

NHS No. [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

Father (or Surrogate) Parent I.D. [ ]

First Name_____ Last Name_____Title_____
Current
Address _____

_____

_____

Postcode: [ ][ ] [ ][ ] [ ][ ] [ ][ ]

NHS No. [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

ID No: | | | | | | |
Study ID Family ID

GP Details

May I have (or confirm) the name and address of the GP you are **currently** registered with.

Name _____

Address_____

_____

_____

Postcode: | | | | | | |

| |

ID No: Study ID | Family ID

Section I **General background**

May I ask you some general questions about yourself?

01. Would you currently describe yourself as **circle** 1=married/ 2=cohabiting/ 3=widowed 4=separated/ 5=divorced/ 6=single?

02. How would you describe yourself ?

circle 1=White/ 2=Black-Carribean / 3=Black-African/ 4=Black-'Other'/ 5=Indian/ 6=Pakistani/ 7=Bangladeshi/ 8=Chinese/ 9=any 'other' ethnic group.

If other:

How would you describe yourself ?_____

03. Are you still at school? 1=yes/ 2=no

04. (*If appropriate)* How old were you when you left school? years

05. (*If appropriate)* Do you have any educational qualifications such as

CSEs /'O' Levels / 'O' Grades / GCSEs / or their equivalents ? 1=yes 2=no 9=NK

Highers / 'A' levels or their equivalents ? 1=yes 2=no 9=NK

Any higher or professional qualifications ? 1=yes 2=no 9=NK

If yes:
What are these qualifications ?_____ _

_____ _

06. Do you own or rent your current home or do you live with your parents/siblings ?
1=owner/ 2=tenant/ 3=parents/siblings/ 4=other/ 9=NK

If other : specify_____

_____

If tenant, who do you rent it from? 1=council/ 2=housing association/ 3=private/ 4=other/ 9=NK

If other : specify_____

_____

ID No: [ ][ ] Study ID [ ][ ][ ][ ] Family ID

Section II **Growth**

1. At what age did you enter infant school (Year 1)? [ ][ ] Years [ ][ ] Mths

   OR

   When did you enter infant school (Year 1)? [ ][ ] month [ ][ ] year

2. When you entered infant school (Year 1), compared to other children in the same class, were you *1=Taller/ 2=Shorter/ 3=Average Height* [ ]

3. At what age did you enter junior school (Year 4)? [ ][ ] Years [ ][ ] Mths

   OR

   When did you enter junior school (Year 4)? [ ][ ] month [ ][ ] year

4. When you entered junior school (Year 4), compared to other children in the same class, were you *1=Taller/ 2=Shorter/ 3=Average Height* [ ]

5. At what age did you enter secondary school (Year 7)? [ ][ ] Years [ ][ ] Mths

   OR

   When did you enter secondary school (Year 7)? [ ][ ] month [ ][ ] year

6. When you entered secondary school (Year 7), compared to other children in the same class, were you *1=Taller/ 2=Shorter/ 3=Average Height* [ ]

7. At what age did you leave school? [ ][ ] Years [ ][ ] Mths

   OR

   When did you leave school? [ ][ ] month [ ][ ] year

8. When you left school, compared to other children in the same class, were you *1=Taller/ 2=Shorter/ 3=Average Height* [ ]

9. What was height at diagnosis
   If not known ask Q10
   [ ] ft [ ][ ] in OR [ ][ ][ ] cm

10. Around the time when you were diagnosed with a bone tumour, compared to other children of same age, were you *1=Taller/ 2=Shorter/ 3=Average Height* [ ]

ID No: | | | Study ID | | | | | Family ID

Section III **Puberty**

If Index case is FEMALE

1. At what age did you notice any change in your breasts?

   Years | | Mths | |

2. At what age did you shoot up in height?

   Years | | Mths | |

   OR

   At what age did you suddenly outgrow your clothes?

   Years | | Mths | |

   OR

   At what age did you suddenly increase your shoe size?

   Years | | Mths | |

3. At what age did you start your periods?

   Years | | Mths | |

If the Index Case is MALE

1. At what age did you shoot up in height?

   Years | | Mths | |

   OR

   At what age did you suddenly outgrow your clothes?

   Years | | Mths | |

   OR

   At what age did you suddenly increase your shoe size?

   Years | | Mths | |

2. At what age did you start shaving regularly $\geq$ twice/week?

   Years | | Mths | |

3. At what age did your voice change?

   Years | | Mths | |

ID No: [ ][ ] Study ID [ ][ ][ ][ ] Family ID

Section IV **Sports/Exercise**

Which of the following sports or physical activities did you participate at any time prior to diagnosis?

1. Swimming	*1=Yes / 2=No*	☐
2. Cycling	*1=Yes / 2=No*	☐
3. Horse Riding	*1=Yes / 2=No*	☐
4. Walking/Hiking > 2 miles	*1=Yes / 2=No*	☐
5. Running/Jogging/Cross-Country	*1=Yes / 2=No*	☐
6. Skiing/Snowboarding	*1=Yes / 2=No*	☐
7. Athletics	*1=Yes / 2=No*	☐
8. Aerobics/Dance Exercise	*1=Yes / 2=No*	☐
9. Gymnastics	*1=Yes / 2=No*	☐
10. Martial Arts (Judo, Karate, etc.)	*1=Yes / 2=No*	☐
11. Street Sports (skate boarding, rollerblading, etc.)	*1=Yes / 2=No*	☐
12. Weight lifting or weight training	*1=Yes / 2=No*	☐
13. Football	*1=Yes / 2=No*	☐
14. Rugby	*1=Yes / 2=No*	☐
15. Cricket	*1=Yes / 2=No*	☐
16. Basketball	*1=Yes / 2=No*	☐
17. Netball	*1=Yes / 2=No*	☐
18. Hockey	*1=Yes / 2=No*	☐
19. Tennis	*1=Yes / 2=No*	☐
20. Badminton	*1=Yes / 2=No*	☐
21. Squash	*1=Yes / 2=No*	☐
22. Others _____	*1=Yes / 2=No*	☐
23. Others _____	*1=Yes / 2=No*	☐
24. Others _____	*1=Yes / 2=No*	☐

ID No: [ ][ ] [ ][ ][ ][ ]
Study ID Family ID

Section IV **Sports/Exercise**

Please complete one for each sport recorded YES on previous page (*attach extra sheets if necessary*)

1. Sport/Physical Activity ________________________________
2. At what age did you first start doing the sport/physical activity [ ][ ] Years [ ][ ] Mths
3. At what age did you stop doing the sport/physical activity (if applicable) [ ][ ] Years [ ][ ] Mths
4. How many times did you participate in the sport/physical activity in a typical 4 week period [ ][ ][ ]
5. To what level did you participate in the sport
   1=Informal/ 2=School or Local/ 3=County or Regional/ 4=National/ 5=International [ ]

---

1. Sport/Physical Activity ________________________________
2. At what age did you first start doing the sport/physical activity [ ][ ] Years [ ][ ] Mths
3. At what age did you stop doing the sport/physical activity (if applicable) [ ][ ] Years [ ][ ] Mths
4. How many times did you participate in the sport/physical activity in a typical 4 week period [ ][ ][ ]
5. To what level did you participate in the sport
   1=Informal/ 2=School or Local/ 3=County or Regional/ 4=National/ 5=International [ ]

---

1. Sport/Physical Activity ________________________________
2. At what age did you first start doing the sport/physical activity [ ][ ] Years [ ][ ] Mths
3. At what age did you stop doing the sport/physical activity (if applicable) [ ][ ] Years [ ][ ] Mths
4. How many times did you participate in the sport/physical activity in a typical 4 week period [ ][ ][ ]
5. To what level did you participate in the sport
   1=Informal/ 2=School or Local/ 3=County or Regional/ 4=National/ 5=International [ ]

ID No: ☐☐ ☐☐☐☐
Study ID Family ID

Section IV **Sports/Exercise**

Please complete one for each sport recorded YES on previous page (*attach extra sheets if necessary*)

1. Sport/Physical Activity ____________________________________
2. At what age did you first start doing the sport/physical activity ☐☐ ☐☐ Years Mths
3. At what age did you stop doing the sport/physical activity (if applicable) ☐☐ ☐☐ Years Mths
4. How many times did you participate in the sport/physical activity in a typical 4 week period ☐☐☐
5. To what level did you participate in the sport

   1=Informal/ 2=School or Local/ 3=County or Regional/ 4=National/ 5=International ☐

---

1. Sport/Physical Activity ____________________________________
2. At what age did you first start doing the sport/physical activity ☐☐ ☐☐ Years Mths
3. At what age did you stop doing the sport/physical activity (if applicable) ☐☐ ☐☐ Years Mths
4. How many times did you participate in the sport/physical activity in a typical 4 week period ☐☐☐
5. To what level did you participate in the sport

   1=Informal/ 2=School or Local/ 3=County or Regional/ 4=National/ 5=International ☐

---

1. Sport/Physical Activity ____________________________________
2. At what age did you first start doing the sport/physical activity ☐☐ ☐☐ Years Mths
3. At what age did you stop doing the sport/physical activity (if applicable) ☐☐ ☐☐ Years Mths
4. How many times did you participate in the sport/physical activity in a typical 4 week period ☐☐☐
5. To what level did you participate in the sport

   1=Informal/ 2=School or Local/ 3=County or Regional/ 4=National/ 5=International ☐

ID No: [ ][ ] [ ][ ][ ][ ]
Study ID Family ID

Section V **Social Habits**

I now have some questions about smoking

01. Have you ever done any of the following

1=yes
2=no
9=NK

Smoked at least 100 cigarettes in your life [ ]

Smoked at least one cigar per week for 6 months or longer [ ]

Smoked at least one pipe of tobacco per week for 6 months or longer [ ]

If yes, ask questions below; if no, go to next section

		Cigarettes	**Cigars**	**Pipe**
		Yrs	*Yrs*	*Yrs*
02. How old were you when you started to smoke regularly?	Age	[ ][ ]	[ ][ ]	[ ][ ]
03. Do you still smoke now?	1=yes/2=no/ 9=NK	[ ]	[ ]	[ ]
04. If no,		*Yrs*	*Yrs*	*Yrs*
How old were you when you stopped smoking?	Age	[ ][ ]	[ ][ ]	[ ][ ]

06. What about smoking prior to diagnosis? (*Check all that apply until age of diagnosis)*

	no.	*no.*	*no.*
On average how many did you smoke per day in the year before diagnosis	[ ][ ]	[ ][ ]	[ ][ ]
On average how many did you smoke per day 2 years before diagnosis	[ ][ ]	[ ][ ]	[ ][ ]
On average how many did you smoke per day 3 years before diagnosis	[ ][ ]	[ ][ ]	[ ][ ]
On average how many did you smoke per day 4 years before diagnosis	[ ][ ]	[ ][ ]	[ ][ ]
On average how many did you smoke per day 5 years before diagnosis	[ ][ ]	[ ][ ]	[ ][ ]
On average how many did you smoke per day more than 5 years before diagnosis	[ ][ ]	[ ][ ]	[ ][ ]

ID No: | | | Study ID | | | | Family ID

Section VI **Illness history**

01. Did you ever have any of the following infections (prior to diagnosis), and if so, can you remember when?

Date of diagnosis of tumour: | | | | | | | | |

	1=yes 2=no 9=NK	If 'yes', when						Consult GP 1=yes 2=no 9=NK	If 'yes', when						Consult GP 1=yes 2=no 9=NK
		Month		Year					Month		Year				
Measles															
Mumps															
German Measles															
Chicken Pox															
Shingles															
Whooping Cough															
Pneumonia															
Glandular Fever															
Meningitis															
Cold sores / Herpes															

ID No: [ ][ ] Study ID [ ][ ][ ][ ] Family ID

Section VI **Illness history**

Do you have, or have you ever had any of the following ?

	1=yes 2=no 9=NK
Diabetes **01**	[ ]
Asthma **02**	[ ]
Eczema or other chronic skin conditions e.g. psoriasis **03**	[ ]
Congenital abnormalities/syndromes **04**	[ ]
Other neoplasms (inc.benign) before or since diagnosis **05**	[ ]
Hernias **06**	[ ]
Fractures **07**	[ ]
Any Bony conditions (including metallic/prosthetic implants) **08**	[ ]
Other Conditions requiring regular visits to clinics or hospital **09**	[ ]

Total illness records following [ ][ ]

ID No: [ ][ ] Study ID [ ][ ][ ][ ] Family ID

Section VI **Illness history**

Please complete one for each illness recorded on Page 180 (attach extra sheets as necessary)
May I have more details of these illnesses ?

illness no. [ ][ ] ICD-10 [ ][ ][ ][ ]

01..Condition_____

02. When was it first diagnosed ? date Month [ ][ ] Year [ ][ ][ ][ ] or age Years [ ][ ] Months [ ][ ]

03. How was it treated ? _____ [ ][ ]

04. Was ..... treated as a hospital inpatient, an outpatient or by the GP ?
(Please record as appropriate). If 'other', please specify: _____

1=inpatient
2=outpatient
3=GP
4=other
9=NK

[ ]

[ ]

GP_____ Address_____

_____

Consultant_____ Hospital_____

Hospital code [ ][ ][ ][ ][ ]

illness no. [ ][ ] ICD-10 [ ][ ][ ][ ]

01. Condition_____

02. When was it first diagnosed ? date Month [ ][ ] Year [ ][ ][ ][ ] or age Years [ ][ ] Months [ ][ ]

03. How was it treated ? _____ [ ][ ]

04. Was ..... treated as a hospital inpatient, an outpatient or by the GP ?
(Please record as appropriate). If 'other', please specify: _____

1=inpatient
2=outpatient
3=GP
4=other
9=NK

[ ]

[ ]

GP_____ Address_____

_____

Consultant_____ Hospital_____

Hospital code [ ][ ][ ][ ][ ]

ID No: Study ID | Family ID

Section VI **Illness history**

Please complete one for each illness recorded on Page 180 (attach extra sheets as necessary)
May I have more details of these illnesses ?

---

illness no. ICD-10

01..Condition_____

02. When was it first diagnosed ? date Month Year or age Years Months

03. How was it treated ? _____

04. Was ..... treated as a hospital inpatient, an outpatient or by the GP ?
(Please record as appropriate). If 'other', please specify: _____

1=inpatient
2=outpatient
3=GP
4=other
9=NK

GP_____ Address_____

_____

Consultant_____ Hospital_____

Hospital code:

---

illness no. ICD-10

01. Condition_____

02. When was it first diagnosed ? date Month Year or age Years Months

03. How was it treated ? _____

04. Was ..... treated as a hospital inpatient, an outpatient or by the GP ?
(Please record as appropriate). If 'other', please specify: _____

1=inpatient
2=outpatient
3=GP
4=other
9=NK

GP_____ Address_____

_____

Consultant_____ Hospital_____

Hospital code

ID No: [ ][ ] [ ][ ][ ][ ]
Study ID Family ID

Section VII **Further information**

Is there anything else you would like to tell me about

_____

_____

_____

Do you have any comments on this interview? (This may help in the design of studies in the future)

_____

_____

_____

May we have permission to contact you if we need further information or to resolve any queries? 1 = yes 2 = no 9 = NK [ ]

Home telephone or mobile number: [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

Thank you for your help and co-operation in this interview. *Time completed:* hours [ ][ ] mins [ ][ ]

Interview conducted by: _____ [ ][ ][ ]

Place of Interview [ ] **Home** [ ] **Clinic** [ ] **Other** _____

Mode of Interview [ ] **Face to Face** [ ] **Phone** [ ] **Other** _____

Samples Taken [ ] **Blood** **Date** _____

[ ] **Saliva** **Date** _____

ID No: | | | | | | | | | |
Study ID | Family ID | Person ID

Parent's Questionnaire

ID No: | | | | | | | | | | |

Study ID | Family ID | Person ID

Personal Details

Thank you for agreeing to help us with this study. Most of the questions I am going to ask you are about your life, work and health, and about …….'s childhood and adolescence.

day month year

Time Started (24 hr clock) Hr Min

Can I stress again that all your answers will be treated in the strictest confidence and the information will not be passed to anyone outside the study.

Index Case Sheet no. | |

First Name_____ Last Name_____ Total Sheets | |

Address
at interview_____Date of Diagnosis | | | | | | | | |

day month year

_____

_____ Sex: 1=male 2=female |

Postcode | | | | | | |

Date of Birth | | | | | | | | |

day month year

NHS No. | | | | | | | | | | |

Mother (or Surrogate) Parent I.D. |

First Name_____ Last Name_____Title_____

Current
Address_____ All previous names_____

_____

_____ Name when _____was born:

Postcode | | | | | | |

_____

NHS No. | | | | | | | | | | |

Father (or Surrogate) Parent I.D. |

First Name_____ Last Name_____Title_____

Current
Address _____

_____

_____

Postcode: | | | | | | |

NHS No. | | | | | | | | | | |

ID No: | | | | | | | | | |

Study ID | Family ID | Person ID

GP Details

May I have (or confirm) the name and address of the GP you are **currently** registered with.

Name _____

Address_____

_____

_____

Postcode: | | | | | | | |

is ……registered with the same GP? 1 = Yes 2 = No | |

If NO:

Name _____

Address _____

_____

_____

Postcode: | | | | | | | |

ID No: ☐☐ Study ID ☐☐☐☐ Family ID ☐☐☐ Person ID

Section I **General background**

1a) So that I can make this interview as short as possible and collect the right information may I ask if you are the natural mother/father of ……...?

1=yes
2=no
9=NK ☐

1b)If no: then ask When did ……first live with you ?

Date ☐☐☐☐☐☐ month year

Or

Child's age ☐☐☐☐ years months

If mother/father is **not** the biological parent limited questions to be asked: see separate instructions (Appendix A)

2a) Has ……. ever lived away from you for longer than six months?

1=yes
2=no
9=NK ☐

If Yes :

2b) Why was this_____ ☐☐☐

Please could you tell me when this was? from date ☐☐☐☐ month year or age ☐☐ years ☐☐ months

to date ☐☐☐☐ month year or age ☐☐ years ☐☐ months ☐☐

2b) Why was this_____ ☐☐☐

Please could you tell me when this was? from date ☐☐☐☐ month year or age ☐☐ years ☐☐ months

to date ☐☐☐☐ month year or age ☐☐ years ☐☐ months

Total number of times away ☐☐

ID No: Study ID | Family ID | Person ID

Section I **General background**

May I ask you some general questions about yourself?

03. What is your date of birth ?

day month year

04. Would you currently describe yourself as

circle 1=married/ 2=cohabiting/ 3=widowed 4=separated/ 5=divorced/ 6=single?

05. How would you describe yourself ?

circle 1=White/ 2=Black-Carribean / 3=Black-African/ 4=Black-'Other'/ 5=Indian/ 6=Pakistani/ 7=Bangladeshi/ 8=Chinese/ 9=any 'other' ethnic group.

If other:

How would you describe yourself ?_____

06. How old were you when you left school?

years

07. Do you have any educational qualifications such as

CSEs /'O' Levels / 'O' Grades / GCSEs / or their equivalents ? 1=yes 2=no 9=NK

Highers / 'A' levels or their equivalents ? 1=yes 2=no 9=NK

Any higher or professional qualifications ? 1=yes 2=no 9=NK

If yes:
What are these qualifications ?_____ _

_____ _

08. Do you own or rent your current home ? 1=owner/ 2=tenant/ 3=other/ 9=NK

If other : specify_____

_____

If tenant, who do you rent it from? 1=council/ 2=housing association/ 3=private/ 4=other/ 9=NK

If other : specify_____

_____

Section II **Employment History**

Please go through the employment section of the pre-interview questionnaire (Appendix B), confirm jobs and dates recorded, and correct where necessary. Show card listing exposures as below.

Then ask the following about each job in turn.

I would like to ask you some more details about each of your jobs

Did your job as _____ ever involve you in handling or being exposed to:

Show prompt card and code answers on the pre-interview questionnaire

None	0
Solvents, degreasers or cleaning agents such as benzene, toluene or carbon tetrachloride?	1
Paints, lacquers, paint removers, turpentine products or thinners?	2
Dyes or pigments?	3
Petrol, petroleum products or paraffin?	4
Lead or compounds containing lead?	5
Fertilizers?	6
Pesticides, fungicides or herbicides?	7
Radioactive materials, X Rays or any other kind of ionizing radiation?	8
Wood dust/Sawdust (including MDF)?	9
Farm Animals/ Poultry?	10
Unknown?	11

Fill in after interview

Section II **Employment History** Mother/father Detail Number of sheets | |

ID No: Study ID | Family ID | Person ID

Section II **Employment History** **Exposure Record** *Page:*

To be completed for any job where an exposure is reported.
Complete record for each exposure.

Fill in after interview
Total number of job exposures

01. Do you remember the names of the materials involved? (*specify*) _____ Job No.

_____ Exp. No.

02. Did you yourself work with _____ (*as above*)? 1=Yes 2=No 9=NK

03. Please can you describe in detail your contact with _____ (*as above*)?

_____
_____
_____
_____

04. Over what period was this? *Date from* (month year) *to* (month year)

Or Age (years months) *to* (years months)

If exposure was to ionizing radiation:

05. During this time were you monitored for exposure to radiation? 1=Yes 2=No 9=NK

If ye:, how *Circle* 1=film badge/ 2= blood tests/ 3=film badge & blood tests/ 4=other/ 9=NK

If other: specify _____

---

01. Do you remember the names of the materials involved? (*specify*) _____ Job No.

_____ Exp. No.

02. Did you yourself work with _____ (*as above*)? 1=Yes 2=No 9=NK

03. Please can you describe in detail your contact with _____ (*as above*)?

_____
_____
_____
_____

04. Over what period was this? *Date from* (month year) *to* (month year)

Or Age (years months) *to* (years months)

If exposure was to ionizing radiation:

05. During this time were you monitored for exposure to radiation? 1=Yes 2=No 9=NK

If ye:, how *Circle* 1=film badge/ 2= blood tests/ 3=film badge & blood tests/ 4=other/ 9=NK

If other: specify _____

ID No: [ ][ ] [ ][ ][ ][ ] [ ][ ][ ]
Study ID Family ID Person ID

Section III **General health**

1. What is your height? [ ] ft [ ][ ] in OR [ ][ ][ ] cm

If Respondent is Mother

2. At what age did you start your periods? [ ][ ][ ][ ] Years Mths

If Respondent is Father

3. At what age did you start shaving regularly ≥ twice/week? [ ][ ][ ][ ] Years Mths

4. At what age did your voice change? [ ][ ][ ][ ] Years Mths

ID No: | | | | | | | | | |
Study ID | Family ID | Person ID

Section III **General health** **Illnesses**

Do you or have you ever suffered from any of the following illnesses?:

		1=yes 2=no 9=NK
Diabetes	**1**	
Thyroid disease	**2**	
Rheumatoid arthritis	**3**	
Asthma	**4**	
Epilepsy	**5**	
Leukaemia or Lymphoma	**6**	
Other cancer or malignant tumour	**7**	
Benign tumour	**8**	
Hereditary disease	**9**	
Congenital abnormality	**10**	
Chronic illness	**11**	

If 'yes' to any of above, please complete a record for each condition
And enter the total number of illnesses below.

Total number of illness records to follow: | |

ID No: | | | | | | | | | | |
Study ID | Family ID | Person ID

Section III **General health** **Illnesses**

Please complete for each illness listed on the previous page (attach extra sheets if necessary).

Illness no. *ICD-10*

01. Condition?_____ | | | | | | . | |

02. What treatment did you have ?_____ _ | |

03. Can you remember the date this condition began ? date | | | | | | | |
month year

or: or

How old were you ? age | | | | |
years months

04. Were you treated : | |
1=as a hospital in patient/ 2=as an outpatient/ 3=by your GP/ 4=other/ 9=NK

if other: Specify_____ | |

05. Which hospital did you attend when the treatment began (*if appropriate*) ?

Name_____

Address_____

_____

Who was the consultant (*if appropriate) ?*_____ Hospital code | | | | | |

Illness no. *ICD-10*

01. Condition?_____ | | | | | | . | |

02. What treatment did you have ?_____ _ | |

03. Can you remember the date this condition began ? date | | | | | | | |
month year

or: or

How old were you ? age | | | | |
years months

04. Were you treated : | |
1=as a hospital in patient/ 2=as an outpatient/ 3=by your GP/ 4=other/ 9=NK

if other: Specify_____ | |

05. Which hospital did you attend when the treatment began (*if appropriate*) ?

Name_____

Address_____

_____

Who was the consultant (*if appropriate) ?*_____ Hospital code | | | | | |

ID No: | | | | | | | | | | | | | | | |

Study ID | Family ID | Person ID

Section III **General health** **Illnesses**

Please complete for each illness listed on the previous page (attach extra sheets if necessary).

Illness no. *ICD-10*

01. Condition?_____ | | | | | | . | |

02. What treatment did you have ?_____ _ | |

03. Can you remember the date this condition began ? date | | | | | | | |

month year

or: or

How old were you ? age | | | | |

years months

04. Were you treated : | |

1=as a hospital in patient/ 2=as an outpatient/ 3=by your GP/ 4=other/ 9=NK

if other: Specify_____ | |

05. Which hospital did you attend when the treatment began (*if appropriate*) ?

Name_____

Address_____

_____

Who was the consultant (*if appropriate) ?*_____ Hospital code | | | | | |

Illness no. *ICD-10*

01. Condition?_____ | | | | | | . | |

02. What treatment did you have ?_____ _ | |

03. Can you remember the date this condition began ? date | | | | | | | |

month year

or: or

How old were you ? age | | | | |

years months

04. Were you treated : | |

1=as a hospital in patient/ 2=as an outpatient/ 3=by your GP/ 4=other/ 9=NK

if other: Specify_____ | |

05. Which hospital did you attend when the treatment began (*if appropriate*) ?

Name_____

Address_____

_____

Who was the consultant (*if appropriate) ?*_____ Hospital code | | | | | |

ID No: ☐☐ ☐☐☐☐ ☐☐☐

Study ID | Family ID | Person ID

Section IV **Social Habits**

I now have some questions about smoking

1=yes
2=no
9=NK

01. Have you ever done any of the following

Smoked at least 100 cigarettes in your life ☐

Smoked at least one cigar per week for 6 months or longer ☐

Smoked at least one pipe of tobacco per week for 6 months or longer ☐

If yes, ask questions below; if no, go to next section

		Cigarettes	**Cigars**	**Pipe**
		Yrs	*Yrs*	*Yrs*
02. How old were you when you started to smoke regularly?	Age	☐☐	☐☐	☐☐
03. Do you still smoke now?	1=yes/2=no/ 9=NK	☐	☐	☐
04. If no,		*Yrs*	*Yrs*	*Yrs*
How old were you when you stopped smoking?	Age	☐☐	☐☐	☐☐

05. What about during the one year before _____ was born?

	no.	*no.*	*no.*
On average how many did you smoke per day?	☐☐	☐☐	☐☐

06. What about during the pregnancy - On average how many did you smoke per day?

	no.	*no.*	*no.*
Before you knew you were pregnant	☐☐	☐☐	☐☐
During 1st trimester (after mother knew she was pregnant)	☐☐	☐☐	☐☐
During 2nd trimester	☐☐	☐☐	☐☐
During 3rd trimester	☐☐	☐☐	☐☐

07. What about after _____ was born? (*Check all that apply until_____ age of diagnosis)*

	no.	*no.*	*no.*
On average how many did you smoke per day when _____ <12 mths of age	☐☐	☐☐	☐☐
On average how many did you smoke per day when _____ 1 -4 years of age	☐☐	☐☐	☐☐
On average how many did you smoke per day when _____ 5-9 years of age	☐☐	☐☐	☐☐
On average how many did you smoke per day when _____ 10-14 years of age	☐☐	☐☐	☐☐
On average how many did you smoke per day when _____ 15-19 years of age	☐☐	☐☐	☐☐
On average how many did you smoke per day when _____ 20-24 years of age	☐☐	☐☐	☐☐

ID No: Study ID | Family ID | Person ID

Section V **Reproductive History (mother only)**

Now, I would like to ask a few questions about all your pregnancies, including any ectopics, miscarriages, stillbirths and terminations, starting with the first.

01. Initials			
02. ID of Pregnancy	P	P	P
03. When did the pregnancy end?	month year	month year	month year
04. How many weeks did the pregnancy last?	Weeks	Weeks	Weeks
05. Was this a: (Miscarriage = <20 wks stillbirth = 20+ wks)	1=live birth 2=miscarriage 3=still birth 4=termination/abortion 5=ectopic 6=hydatid mole	1=live birth 2=miscarriage 3=still birth 4=termination/abortion 5=ectopic 6= hydatid mole	1=live birth 2=miscarriage 3=still birth 4=termination/abortion 5=ectopic 6=hydatid mole
06. How was the baby delivered? (if appropriate)	1=normal 2=assisted 3=caesarean 9=not known	1=normal 2=assisted 3=caesarean 9=not known	1=normal 2=assisted 3=caesarean 9=not known
07. What sex was the baby?	1=male 2=female 9=NK	1=male 2=female 9=NK	1=male 2=female 9=NK
08. What was the baby's birthweight?	lbs oz Gms	lbs oz Gms	lbs oz Gms
09. Did this baby have the same father as ……?	1=yes 2=no 9=NK	1=yes 2=no 9=NK	1=yes 2=no 9=NK
10. Was there anything wrong with the baby noted during pregnancy? ***If 'yes' please detail p 15***	1=yes 2=no 9=NK	1=yes 2=no 9=NK	1=yes 2=no 9=NK
11. Was there anything wrong with the baby noted shortly after birth? ***If 'yes' please detail p 15***	1=yes 2=no 9=NK	1=yes 2=no 9=NK	1=yes 2=no 9=NK
12. Is he/she alive and well?(Do not ask for index child)	1=yes 2=no 9=NK	1=yes 2=no 9=NK	1=yes 2=no 9=NK
13 ***If 'no':*** date of death	day month year	day month year	day month year
14. Cause of death			
15. Place of death (town)			

ID No: Study ID | Family ID | Person ID

Section V **Reproductive History (mother only)**

Continued from page 196. (attach extra sheets if necessary)

01. Initials			
02. ID of Pregnancy	P	P	P
03. When did the pregnancy end?	month year	month year	month year
04. How many weeks did the pregnancy last?	Weeks	Weeks	Weeks
05. Was this a: (Miscarriage = <20 wks stillbirth = 20+ wks)	1=live birth 2=miscarriage 3=still birth 4=termination/abortion 5=ectopic 6=hydatid mole	1=live birth 2=miscarriage 3=still birth 4=termination/abortion 5=ectopic 6=hydatid mole	1=live birth 2=miscarriage 3=still birth 4=termination/abortion 5=ectopic 6=hydatid mole
06. How was the baby delivered? (if appropriate)	1=normal 2=assisted 3=caesarean 9=not known	1=normal 2=assisted 3=caesarean 9=not known	1=normal 2=assisted 3=caesarean 9=not known
07. What sex was the baby?	1=male 2=female 9=NK	1=male 2=female 9=NK	1=male 2=female 9=NK
08. What was the baby's birthweight?	lbs oz Gms	lbs oz Gms	lbs oz Gms
09. Did this baby have the same father as ……?	1=yes 2=no 9=NK	1=yes 2=no 9=NK	1=yes 2=no 9=NK
10. Was there anything wrong with the baby noted during pregnancy? ***If 'yes' please detail p 15***	1=yes 2=no 9=NK	1=yes 2=no 9=NK	1=yes 2=no 9=NK
11. Was there anything wrong with the baby noted shortly after birth? ***If 'yes' please detail p 15***	1=yes 2=no 9=NK	1=yes 2=no 9=NK	1=yes 2=no 9=NK
12. Is he/she alive and well?(Do not ask for index child)	1=yes 2=no 9=NK	1=yes 2=no 9=NK	1=yes 2=no 9=NK
13. ***If 'no':*** date of death	day month year	day month year	day month year
14. Cause of death			
15. Place of death (town)			

ID No: | | | Study ID | | | | Family ID | | | Person ID

Section V **Reproductive History (mother only)**

FURTHER DETAILS: ***(attach extra sheets if necessary)***

Please identify if additional details refer to Q10(during pregnancy) or Q11(shortly after birth) on Pages 196/197.

Pregnancy Number P | | |

Q10/11	Details	ICD

Pregnancy Number P | | |

Q10/11	Details	ICD

Section V **Reproductive History (mother only)**

FURTHER DETAILS: ***(attach extra sheets if necessary)***

Please identify if additional details refer to Q10(during pregnancy) or Q11(shortly after birth) on Pages 196/197.

Pregnancy Number P | | |

Q10/11	Details	ICD

Pregnancy Number P | | |

Q10/11	Details	ICD

Section VI **Index Pregnancy (mother only) Illnesses**

I would like to ask you now in more detail about your pregnancy with……..…..

01. What type of antenatal care did you have ? 1=hospital/ 2=shared/ 3=G.P./ 4=none/ 5=other/ 9=NK

if other: specify _____

02. Which GP and consultant looked after you during your pregnancy?

GP _____ Consultant_____

Address_____ Hospital_____

_____ _____

Hospital code

03. At any time during the pregnancy were you admitted to hospital for **any** reason including an emergency admission 24 hours **before** delivery ?

1=yes
2=no
9=NK

If no: go to Page 18
If yes: complete for each admission

---

i)Why was this ?_____

ii) When was this (weeks since LMP) ? from week to week

iii) Which hospital ? _____

iv) Who was the consultant ? _____ Hospital code

---

i) Why was this ?_____

ii) When was this (weeks since LMP) ? from week to week

iii) Which hospital ? _____

iv) Who was the consultant ? _____ Hospital code

Total number of admissions

ID No: Study ID | Family ID | Person ID

Section VI **Index Pregnancy (mother only) Illnesses**

01. We are interested in illnesses which you may have had during your pregnancy with……. Did you have any of the following?

	1=yes 2=no 9=NK	Weeks of pregnancy since last LMP				Treatment
		From week	To week	From week	To week	
German measles						
Measles						
Shingles						
Chickenpox						
Glandular fever						
Mumps						
Pneumonia						
Influenza						
Cystitis or Kidney infections						
Any other infection (Please specify)						

02. During your pregnancy did you have any other illnesses or conditions requiring visits to your doctor? 1=yes 2=no 9=NK

If yes:

What was wrong?_____

When was this (weeks since LMP)?_____ from week

to week

What treatment did you have? _____

What was wrong?_____

When was this (weeks since LMP)?_____ from week

to week

What treatment did you have? _____

ID No: | | | | | | | | | |

Study ID | Family ID | Person ID

Section VII **Index Case Neo-natal history**

I would like to ask you about ……..'s. Birth and early childhood.

01. Where was ……..… born 1=hospital / 2 = GP unit / 3=Home/ 4= other

If other : specify_____

Name (Hospital/ GP Unit) _____

Address(Hospital/ GP Unit) _____

_____ Hospital code

02. In total, how many days was ……in the hospital ? days

03. Was the baby admitted to special care baby unit (SCBU) after birth? 1=yes/2=no/ 9=NK

If yes :

Why was this? _____

How was he/she treated? _____

How many days was …… kept in the special care baby unit ? days

04. Did the baby have any illness or abnormality noted at birth, or shortly after birth 1=yes/2=no/ 9=NK
(In addition to question 11 on page 10)

If yes :

Please describe this? _____

How was he/she treated? _____

How many days old was …… at the time? days

05. Was the baby kept in hospital for any reason, or given a follow-up appointment? 1=yes/2=no/ 9=NK

If yes :

Why was this? _____

How was he/she treated? _____

ID No: | | | | | | | | | | | | | | | | | | | |

Study ID | Family ID | Person ID

Section VII **Index Case** **Early life and Development**

01. Was …… breast fed at all? 1=yes/2=no/ 9=NK

IF NO; go to Q 4

IF YES:

02. For how long (until CHILD was what age) were you giving …… ONLY breastmilk?? Days | | or Weeks | | or Months | |

03. How old was ……. When you gave your last breastfeed Days | | Weeks | | Months | |

04. Did you ever use formula milk? 1=yes/2=no/ 9=NK

IF No: go to Q6

IF YES

05a) How old was …….when he/she had his /her first formula feed ? Days | | Weeks | |

05b) Was this soya based ? 1=yes/2=no/ 9=NK

06. At what age did you introduce cow's milk ? Years | | Months | |

07. How old was …….. when you first introduced solid food ? Months | | or Weeks | |

08. At what age did……..…begin sitting without support ? Years | | Months | |

09. At what age did……..……..……begin crawling or moving about ?

10. At what age did……..……..…….begin walking ?

11. Did ……..attend the recommended developmental checks? 1=yes/2=no/ 9=NK

12. At the development checks were there any problems e.g. with growth or weight gain; or hearing or speech problems ?

1=yes
2=no
9=NK

IF YES; please specify_____

_____ | | | |

_____

_____

_____

ID No: | | | | | | | | | | |

Study ID | Family ID | Person ID

Section VII **Index Case Vaccinations**

Ask questions 2 - 4

Please check all the immunisations on record card and transfer details to vaccinations record on Page 205.

01. Record card seen (fill in by interviewer) 1=yes 2=no 9=NK

02. Did ……...have all the recommended immunisations during the first years of life? 1=yes 2=no 9=NK

IF NO:

03. Which ones were missed or not given and why was this?

Name_____

Reason_____

Name_____

Reason_____

Name_____

Reason_____

04. Did ……..….ever have any other vaccinations, for example for a foreign holiday? 1=yes 2=no 9=NK

IF YES:

Which ones were they?

(i)Name_____ Years Months

(ii) How old was he/she at the time?

(i) Name_____ Years Months

(ii) How old was he/she at the time?

(ii) Name_____ Years Months

(ii) How old was he/she at the time?

ID No: Study ID | Family ID | Person ID

Section VII **Index Case Vaccinations**

Details on this form were taken from:
1 - Mother's record / 2 - GP record card/ 3 - clinic record card/ 4 - other/ 9 - NK _____

If other : please specify_____

Details recorded at interview 1=yes/2=no/ 9=NK

	"Triple Vaccine" Diphtheria/ Tetanus/ Whooping cough	HIB	Diphtheria/ Tetanus	Polio drops
	Day Month Year	Day Month Year	Day Month Year	Day Month Year
Dose 1				
Dose 2				
Dose 3				
Booster				

Other vaccinations

Immunization	Day Month Year	Immunization	Day Month Year
Smallpox		Mantoux testing for BCG	
BCG		Tetanus (booster)	
Measles		Polio (booster)	
Measles/Mumps/Rubella		HIB (single dose)	
Rubella (alone)		Other_____ dose 1	
		Other_____ dose 2	
		Other_____ dose 3	

ID No: [ ][ ] [ ][ ][ ][ ] [ ][ ][ ]
Study ID Family ID Person ID

Section VII **Index Case Growth**

1. What was _____ length at birth? [ ][ ] in OR [ ][ ] cm

2. At what age did _____enter infant school (Year 1)? [ ][ ][ ][ ] Years Mths

   OR

   When did _____ enter infant school (Year 1)? [ ][ ][ ][ ] month year

3. When _____ entered infant school (Year 1), compared to other children in the same class, was he/she *1=Taller/ 2=Shorter/ 3=Average Height* [ ]

4. At what age did _____enter junior school (Year 4)? [ ][ ][ ][ ] Years Mths

   OR

   When did _____ enter junior school (Year 4)? [ ][ ][ ][ ] month year

5. When _____ entered junior school (Year 4), compared to other children in the same class, was he/she *1=Taller/ 2=Shorter/ 3=Average Height* [ ]

6. At what age did _____enter secondary school (Year 7)? [ ][ ][ ][ ] Years Mths

   OR

   When did _____ enter secondary school (Year 7)? [ ][ ][ ][ ] month year

7. When _____ entered secondary school (Year 7), compared to other children in the same class, was he/she *1=Taller/ 2=Shorter/ 3=Average Height* [ ]

8. At what age did _____ leave school? [ ][ ][ ][ ] Years Mths

   OR

   When did _____ leave school? [ ][ ][ ][ ] month year

9. When _____ left school, compared to other children in the same class, was he/she *1=Taller/ 2=Shorter/ 3=Average Height* [ ]

10. What was _____ height at diagnosis [ ] ft [ ][ ] in OR [ ][ ][ ] cm
    If not known ask Q11

11. Around the time when _____ was diagnosed with a bone tumour, compared to other children of same age, was he/she *1=Taller/ 2=Shorter/ 3=Average Height* [ ]

Section VII **Index Case Puberty**

If Index case is FEMALE

5. At what age did _____ notice any change in her breasts? | | | | | Years Mths

6. At what age did _____ shoot up in height? | | | | | Years Mths

OR

At what age did _____ suddenly outgrow her clothes? | | | | | Years Mths

OR

At what age did _____ suddenly increase her shoe size? | | | | | Years Mths

7. At what age did _____ start her periods? | | | | | Years Mths

If the Index Case is MALE

1. At what age did _____ shoot up in height? | | | | | Years Mths

   OR

   At what age did _____ suddenly outgrow his clothes? | | | | | Years Mths

   OR

   At what age did _____ suddenly increase his shoe size? | | | | | Years Mths

2. At what age did _____ start shaving regularly ≥ twice/week? | | | | | Years Mths

3. At what age did _____ his voice change? | | | | | Years Mths

Section VII **Index Case Sports/Exercise**

Which of the following sports or physical activities did _____ participate at any time prior to diagnosis?

1. Swimming	*1=Yes / 2=No*	☐
2. Cycling	*1=Yes / 2=No*	☐
3. Horse Riding	*1=Yes / 2=No*	☐
4. Walking/Hiking > 2 miles	*1=Yes / 2=No*	☐
5. Running/Jogging/Cross-Country	*1=Yes / 2=No*	☐
6. Skiing/Snowboarding	*1=Yes / 2=No*	☐
7. Athletics	*1=Yes / 2=No*	☐
8. Aerobics/Dance Exercise	*1=Yes / 2=No*	☐
9. Gymnastics	*1=Yes / 2=No*	☐
10. Martial Arts (Judo, Karate, etc.)	*1=Yes / 2=No*	☐
11. Street Sports (skate boarding, rollerblading, etc.)	*1=Yes / 2=No*	☐
12. Weight lifting or weight training	*1=Yes / 2=No*	☐
13. Football	*1=Yes / 2=No*	☐
14. Rugby	*1=Yes / 2=No*	☐
15. Cricket	*1=Yes / 2=No*	☐
16. Basketball	*1=Yes / 2=No*	☐
17. Netball	*1=Yes / 2=No*	☐
18. Hockey	*1=Yes / 2=No*	☐
19. Tennis	*1=Yes / 2=No*	☐
20. Badminton	*1=Yes / 2=No*	☐
21. Squash	*1=Yes / 2=No*	☐
22. Others _____	*1=Yes / 2=No*	☐
23. Others _____	*1=Yes / 2=No*	☐
24. Others _____	*1=Yes / 2=No*	☐

ID No: ☐☐ ☐☐☐☐ ☐☐☐
Study ID Family ID Person ID

Section VII **Index Case** **Sports/Exercise**

Please complete one for each sport recorded YES on previous page (*attach extra sheets if necessary*)

1. Sport/Physical Activity ____________________________________
2. At what age did __________ first start doing the sport/physical activity ☐☐ ☐☐ Years Mths
3. At what age did __________ stop doing the sport/physical activity (if applicable) ☐☐ ☐☐ Years Mths
4. How many times did ___________ participate in the sport/physical activity in a typical 4 week period ☐☐☐
5. To what level did __________ participate in the sport
1=Informal/ 2=School or Local/ 3=County or Regional/ 4=National/ 5=International ☐

---

1. Sport/Physical Activity ____________________________________
2. At what age did __________ first start doing the sport/physical activity ☐☐ ☐☐ Years Mths
3. At what age did __________ stop doing the sport/physical activity (if applicable) ☐☐ ☐☐ Years Mths
4. How many times did ___________ participate in the sport/physical activity in a typical 4 week period ☐☐☐
5. To what level did __________ participate in the sport
1=Informal/ 2=School or Local/ 3=County or Regional/ 4=National/ 5=International ☐

---

1. Sport/Physical Activity ____________________________________
2. At what age did __________ first start doing the sport/physical activity ☐☐ ☐☐ Years Mths
3. At what age did __________ stop doing the sport/physical activity (if applicable) ☐☐ ☐☐ Years Mths
4. How many times did ___________ participate in the sport/physical activity in a typical 4 week period ☐☐☐
5. To what level did __________ participate in the sport
1=Informal/ 2=School or Local/ 3=County or Regional/ 4=National/ 5=International ☐

ID No: ☐☐ ☐☐☐☐ ☐☐☐
Study ID Family ID Person ID

Section VII **Index Case** **Sports/Exercise**

Please complete one for each sport recorded YES on previous page (*attach extra sheets if necessary*)

1. Sport/Physical Activity ____________________________________
2. At what age did __________ first start doing the sport/physical activity ☐☐☐☐ Years Mths
3. At what age did __________ stop doing the sport/physical activity (if applicable) ☐☐☐☐ Years Mths
4. How many times did ___________ participate in the sport/physical activity in a typical 4 week period ☐☐☐
5. To what level did __________ participate in the sport
1=Informal/ 2=School or Local/ 3=County or Regional/ 4=National/ 5=International ☐

---

1. Sport/Physical Activity ____________________________________
2. At what age did __________ first start doing the sport/physical activity ☐☐☐☐ Years Mths
3. At what age did __________ stop doing the sport/physical activity (if applicable) ☐☐☐☐ Years Mths
4. How many times did ___________ participate in the sport/physical activity in a typical 4 week period ☐☐☐
5. To what level did __________ participate in the sport
1=Informal/ 2=School or Local/ 3=County or Regional/ 4=National/ 5=International ☐

---

1. Sport/Physical Activity ____________________________________
2. At what age did __________ first start doing the sport/physical activity ☐☐☐☐ Years Mths
3. At what age did __________ stop doing the sport/physical activity (if applicable) ☐☐☐☐ Years Mths
4. How many times did ___________ participate in the sport/physical activity in a typical 4 week period ☐☐☐
5. To what level did __________ participate in the sport
1=Informal/ 2=School or Local/ 3=County or Regional/ 4=National/ 5=International ☐

ID No: | | | | | | | | | | |

Study ID | Family ID | Person ID

Section VII **Index Case Illness history**

01. Did……..have any of the following infections (prior to diagnosis), and if so, can you remember when?

Date of diagnosis of tumour: | | | | | | | | |

	1=yes 2=no 9=NK	If 'yes', when						Consult GP 1=yes 2=no 9=NK	If 'yes', when					Consult GP 1=yes 2=no 9=NK
		Month		Year					Month		Year			
Measles														
Mumps														
German Measles														
Chicken Pox														
Shingles														
Whooping Cough														
Pneumonia														
Glandular Fever														
Meningitis														
Cold sores / Herpes														

ID No: | | | | | | | | | | |

Study ID | Family ID | Person ID

Section VII **Index Case Illness history**

Does…….have, or has he/she ever had any of the following ?

1=yes
2=no
9=NK

Diabetes **01**	
Asthma **02**	
Eczema or other chronic skin conditions e.g. psoriasis **03**	
Congenital abnormalities/syndromes **04**	
Other neoplasms (inc.benign) before or since diagnosis **05**	
Hernias **06**	
Fractures **07**	
Any Bony conditions (including metallic/prosthetic implants) **08**	
Other Conditions requiring regular visits to clinics or hospital **09**	

Total illness records following | |

ID No: | | | | | | | | | | |
Study ID | Family ID | Person ID

Section VII **Index Case Illness history**

Please complete one for each illness recorded on Page 212 (attach extra sheets as necessary)
May I have more details of these illnesses ?

illness no. | | | ICD-10 | | | | |

01..Condition_____

02. When was it first diagnosed ? date Month | | Year | | | | or age Years | | Months | |

03. How was it treated ? _____ | |

1=inpatient
2=outpatient
3=GP
4=other
9=NK

04. Was ..... treated as a hospital inpatient, an outpatient or by the GP ? | |
(Please record as appropriate). If 'other', please specify: _____ | |

GP_____ Address_____

_____

Consultant_____ Hospital_____

Hospital code | | | | | |

---

illness no. | | | ICD-10 | | | | |

01. Condition_____

02. When was it first diagnosed ? date Month | | Year | | | | or age Years | | Months | |

03. How was it treated ? _____ | |

1=inpatient
2=outpatient
3=GP
4=other
9=NK

04. Was ..... treated as a hospital inpatient, an outpatient or by the GP ? | |
(Please record as appropriate). If 'other', please specify: _____ | |

GP_____ Address_____

_____

Consultant_____ Hospital_____

Hospital code | | | | | |

ID No: | | | Study ID | | | | Family ID | | | Person ID

Section VII **Index Case** **Illness history**

Please complete one for each illness recorded on Page 212 (attach extra sheets as necessary)
May I have more details of these illnesses ?

illness no. | ICD-10

01..Condition_____

02. When was it first diagnosed ? date Month | Year or age Years | Months

03. How was it treated ? _____

04. Was ..... treated as a hospital inpatient, an outpatient or by the GP ?
(Please record as appropriate). If 'other', please specify: _____

1=inpatient
2=outpatient
3=GP
4=other
9=NK

GP_____ Address_____

_____

Consultant_____ Hospital_____

Hospital code:

illness no. | ICD-10

01. Condition_____

02. When was it first diagnosed ? date Month | Year or age Years | Months

03. How was it treated ? _____

04. Was ..... treated as a hospital inpatient, an outpatient or by the GP ?
(Please record as appropriate). If 'other', please specify: _____

1=inpatient
2=outpatient
3=GP
4=other
9=NK

GP_____ Address_____

_____

Consultant_____ Hospital_____

Hospital code

ID No: | | | | | | | | | | |

Study ID | Family ID | Person ID

Section VIII **Family illnesses**

MOTHER ONLY: We are interested in certain illnesses ……'s brothers and sisters may have had, Including half-brothers and sisters. (Refer back to obstetric history Page 196-197 and go through pregnancies)

FATHER ONLY Do you have any children who are not members of this household? 1=yes 2=no 9=NK ☐

If yes: How many? ☐☐

Initials				
Month and Year of Birth				

*(Ask for **all** siblings)* Has.<*sibling*> ever been diagnosed with any of the following ?

Pregnancy number: /F1				
	1=yes,2=no,9=NK	1=yes,2=no,9=NK	1=yes,2=no,9=NK	1=yes,2=no,9=NK
01. Diabetes	☐	☐	☐	☐
02. Leukaemia or Lymphoma	☐	☐	☐	☐
03. Other cancer or tumour	☐	☐	☐	☐
04. Asthma/Eczema	☐	☐	☐	☐
05. Congenital Abnormalities	☐	☐	☐	☐
06. Chronic Illness	☐	☐	☐	☐
07. Any Bony Condition	☐	☐	☐	☐

Total number ☐☐

ID No: | | | | | | | | | | |

Study ID | Family ID | Person ID

Section VIII **Family illnesses**

Please complete for each illness recorded above.
May I have more details of these illnesses ? (only record details not already obtained).

Preg. No. / ID | | | |

illness no. | | icd code | | | | |

Condition_____

Month/Year of birth | | | | | | | (month | year)

Date of death | | | | | | | | | (day | month | year)

Cause of death_____ Place of death_____

Yrs | Mths

How old was.....when it was first diagnosed? | | | |

1=inpatient
2=outpatient
3=GP
4=other
9=NK

Was.....treated as a hospital inpatient, an outpatient, or by the GP? | |
(Please record as appropriate). If 'other', please specify _____

Further details:_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

ID No: | | | | | | | | | | |

Study ID | Family ID | Person ID

Section VIII **Family illnesses**

Please complete for each illness recorded above.
May I have more details of these illnesses ? (only record details not already obtained).

Preg. No. / ID | | |

illness no. | | icd code | | | | |

Condition_____

Month/Year of birth | | | | | | | (month | year)

Date of death | | | | | | | | | (day | month | year)

Cause of death_____ Place of death_____

Yrs | Mths

How old was.....when it was first diagnosed? | | | |

Was.....treated as a hospital inpatient, an outpatient, or by the GP?
(Please record as appropriate). If 'other', please specify _____

1=inpatient
2=outpatient
3=GP
4=other
9=NK
| |

Further details:_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

ID No: [ ][ ] [ ][ ][ ][ ] [ ][ ][ ]

Study ID | Family ID | Person ID

Section VIII **Family illnesses**

Please complete for each illness recorded above.
May I have more details of these illnesses ? (only record details not already obtained).

Preg. No. / ID [ ][ ][ ]

illness no. [ ][ ] icd code [ ][ ][ ][ ]

Condition_____

Month/Year of birth [ ][ ][ ][ ][ ][ ] (month / year)

Date of death [ ][ ] [ ][ ] [ ][ ][ ][ ] (day / month / year)

Cause of death_____ Place of death_____

How old was.....when it was first diagnosed? Yrs [ ][ ] Mths [ ][ ]

Was.....treated as a hospital inpatient, an outpatient, or by the GP? [ ]
(Please record as appropriate). If 'other', please specify _____

1=inpatient
2=outpatient
3=GP
4=other
9=NK

Further details:_____

Section IX **Family History - Instructions For Questionnaire**

I would now like to ask you some questions about your family.

We are interested in both how many close relatives you have and whether they have had some particular illnesses.

Firstly, please may I have some details of your own parents and your brothers and sisters and their children. Also include any children and grandchildren you may have. This gives us an idea of the size of your family.

Now I should like to know whether any of your family members have ever developed tumours, cancer, leukaemia, or any other growths. If so, please would you let me have some details about the type of condition and when it was diagnosed. Is your (sister/brother/etc *as appropriate*) still alive? (*If not obtain date and cause of death*)

ID No: | | | | | | | | | |

Study ID Family ID Person ID

Section IX **Family History Summary**

Line No.	Initials	Relation to respondent	Line No.(s) of Parent(s)	Month & Year of birth	Date and place of death	Specified illness (complete separate sheet for illness details)	Alive-1 Dead-2 NK-9
1		Father					
2		Mother					
3		Brother/Sister					
		Nieces/Nephews					
4		Brother/Sister					
		Nieces/Nephews					

ID No: | | | | | | | | | |

Study ID | Family ID | Person ID

Section IX **Family History Summary**

Line No.	Initials	Relation to respondent	Line No.(s) of Parent(s)	Month & Year of birth	Date and place of death	Specified illness (complete separate sheet for illness details)	Alive-1 Dead-2 NK-9
		Brother/Sister					
		Nieces/Nephews					
		Brother/Sister					
		Nieces/Nephews					
		Brother/Sister					
		Nieces/Nephews					

ID No: | | | | | | | | | (Study ID, Family ID, Person ID)

Study ID Family ID Person ID

Section IX **Family History**

Line No.	Initials	Relation to respondent	Line No.(s) of Parent(s)	Month & Year of birth	Date and place of death	Specified illness (complete separate sheet for illness details)	Alive-1 Dead-2 NK-9

ID No: | | | | | | | | | |

Study ID | Family ID | Person ID

Section IX **Family History Details**

The following 3 questions apply to any **blood** relatives other than your children, parents or siblings or their children i.e. to grandparents, aunts, uncles and first cousins under 55 years of age.

01. Have any developed cancer, leukaemia or lymphoma? 1=yes 2=no 9=NK ☐

02. Are you aware of any congenital illnesses or conditions in such relatives? 1=yes 2=no 9=NK ☐

03. Are you aware of any hereditary illnesses or conditions in your family? 1=yes 2=no 9=NK ☐

If the answer to any of the above is “yes”, please complete brief summary information below

Initials	Sex	Relationship	1=pat 2=mat	Condition	Age

ID No: | | | | | | | | | |
Study ID | Family ID | Person ID

Section X **Further information**

Is there anything else you would like to tell me about

_____

_____

_____

Do you have any comments on this interview? (This may help in the design of studies in the future)

_____

_____

_____

May we have permission to contact you if we need further information or to resolve any queries? 1 = yes 2 = no 9 = NK ☐

Home telephone or mobile number: ☐☐☐☐☐☐☐☐☐☐☐

hours mins

Thank you for your help and co-operation in this interview. *Time completed:* ☐☐☐☐

Interview conducted by: _____ ☐☐☐

Place of Interview ☐ **Home** ☐ **Clinic** ☐ **Other** _____

Mode of Interview ☐ **Face to Face** ☐ **Phone** ☐ **Other** _____

Samples Taken ☐ **Blood** **Date** _____

☐ **Saliva** **Date** _____

Appendix A INSTRUCTIONS FOR INTERVIEWING NON-BIOLOGICAL PARENTS.

Pre interview questionnaires

When sending out pre interview questionnaires to non-biological parents note clearly that we only require information dating from when they and the INDEX child commenced living together.

The questionnaire.

1. General background

Page 4 : Ask when the child first came to live with the family.
Page 5 Ask this page as normal.

II Employment History

Only take details of jobs that parents have had since the index child came to live with the family

III General health

Do not ask these questions of non-biological parents, fill in with 9's (since there is no genetic or germ cell link) as details are unknown for the natural parents.

IV Social Habits

For this question we can only really ask about the index child's exposure to passive smoking after they came to live with the family.

Question 1) ask as normal, "Have you ever smoked any of the following …."

Omit next question, "How old were you when you started smoking regularly?"

Question 3) as normal, "Do you still smoke?"

If NO to Question 3), ask question 4) as normal and then ask "Was that before index child came to live with you?"
If YES to the above question, then leave smoking questions and go to next section

If YES to Question 3), ask question 5), 6) and 7) as normal

V Reproductive History

Make a note that the natural mother is not available and leave this section.

VI Index Pregnancy

Make a note that the natural mother is not available and leave this section.

VII Index Case - Neo-natal history

If child adopted as a baby the respondent may know these answers.

Fill this section with 9's if the respondent does not know

VII Index Case – Early Life and Development

Begin this section with question 6), "At what age did you introduce cow's milk?"

Fill in boxes with 9's prior to question 6) in this section

VII Index Case – Vaccinations, Growth, Puberty, Sports/Exercise, Illness History

Again adapt this section to the situation. It is likely the respondent will have some details about the child's illness history.

This may also apply to the Vaccination record.

VIII Family Illnesses

Unless any other children in the household are actually related to the index child, it is not relevant to take details on this section.

IX Family History

This section should not be asked of non-biological parents. If the respondent knows of any medical conditions known to be in the natural family of the index, please take details .

X Further Information.

As normal.

ID No: | | | | | | | | | |

Study ID | Family ID | Person ID

Appendix – B Occupational History

Please could you fill in as much detail as you can remember about all the jobs you have had since leaving school until……., starting with the first and including time as a student. If possible, please specify your job title and state exactly what you did.

National Insurance Number, if known | | | | | | | | | | |

---

0 1

employer _____ job title _____ start

street _____ duties _____ | | | | | | |

locality _____ _____ month year

town _____ _____ finish

county _____ _____ | | | | | | |

month year

---

0 2

employer _____ job title _____ start

street _____ duties _____ | | | | | | |

locality _____ _____ month year

town _____ _____ finish

county _____ _____ | | | | | | |

month year

---

0 3

employer _____ job title _____ start

street _____ duties _____ | | | | | | |

locality _____ _____ month year

town _____ _____ finish

county _____ _____ | | | | | | |

month year

---

0 4

employer _____ job title _____ start

street _____ duties _____ | | | | | | |

locality _____ _____ month year

town _____ _____ finish

county _____ _____ | | | | | | |

month year

---

0 5

employer _____ job title _____ start

street _____ duties _____ | | | | | | |

locality _____ _____ month year

town _____ _____ finish

county _____ _____ | | | | | | |

month year

Please use continuation form if necessary

ID No: Study ID Family ID Person ID

Appendix – B Occupational History (continued)

employer ______ job title ______ start
street ______ duties ______ month year
locality ______ ______ finish
town ______ ______
county ______ ______ month year

employer ______ job title ______ start
street ______ duties ______ month year
locality ______ ______ finish
town ______ ______
county ______ ______ month year

employer ______ job title ______ start
street ______ duties ______ month year
locality ______ ______ finish
town ______ ______
county ______ ______ month year

employer ______ job title ______ start
street ______ duties ______ month year
locality ______ ______ finish
town ______ ______
county ______ ______ month year

employer ______ job title ______ start
street ______ duties ______ month year
locality ______ ______ finish
town ______ ______
county ______ ______ month year

employer ______ job title ______ start
street ______ duties ______ month year
locality ______ ______ finish
town ______ ______
county ______ ______ month year

Please use continuation form if necessary

ID No: | | | | | | | | | | |

Study ID | Family ID | Person ID

Appendix –C Residential History

Please could you fill in the addresses of all houses where you have lived for longer than one year, starting with where you lived the year before…… was born, and ALL addresses where……has lived up until……..…. If you can remember ANY part of the postcode it would be most helpful.

Address	**Moved in**	**Moved out**
0 1 street _____ locality _____ town _____ county _____ Postcode	month (Birth) year	month year
0 2 street _____ locality _____ town _____ county _____ Postcode	month year	month year
0 3 street _____ locality _____ town _____ county _____ Postcode	month year	month year
0 4 street _____ locality _____ town _____ county _____ Postcode	month year	month year
0 5 street _____ locality _____ town _____ county _____ Postcode	month year	month year

Please use continuation form if necessary

ID No: | | | | | | | | | |

Study ID | Family ID | Person ID

Appendix –C Residential History (continued)

Address **Moved in** **Moved out**

street	month (Birth) year	month	year
locality			
town			
county			
Postcode			

street	month year	month	year
locality			
town			
county			
Postcode			

street	month year	month	year
locality			
town			
county			
Postcode			

street	month year	month	year
locality			
town			
county			
Postcode			

street	month year	month	year
locality			
town			
county			
Postcode			

Please use continuation form if necessary