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Incidence of malignant disease by morphological type, in young persons aged 12–24 years in England, 1979–1997

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Abstract

Cancer incidence data are generally presented in terms of primary site, but this method is inappropriate for cancers in young persons. We have used a morphology-based classification system to produce national incidence rates for cancers in persons aged 12–24 years by detailed diagnostic sub-type. The overall incidence rates for malignant disease in young persons aged 12–14, 15–19 and 20–24 years were 10.1, 14.4 and 22.6 per 100 000 population, respectively. The three most frequent cancer types in 12–14-year-olds were leukaemias, lymphomas and central nervous system (CNS) tumours. In 15–19-year-olds, lymphomas were most frequent and leukaemias second with carcinomas third. In 20–24-year-olds, lymphomas were again most frequent, but carcinomas and germ cell tumours were second and third. There was also variation with age in the ratios of rates in males and females. These changing incidence patterns have aetiological implications and provide clues for future hypothesis-based research.

Keywords: Cancer incidence; Epidemiology; Adolescent cancer; Teenage cancer; Young adult cancer; Leukaemia; Lymphoma; Brain tumours; Solid tumours

1. Introduction

Cancer is most often diagnosed in the late middle-aged and elderly, and over 50% of all cancer registrations in England are for patients aged 70 years and above. In 1999, only 0.5% of all cancer registrations were teenagers and young adults aged up to 24 years [1]. However, cancer is the most common natural cause of death in this age group and is exceeded only by accidents [2]. Little is known about the aetiology of cancers in young persons. It is likely that environmental agents (in the wider sense, including diet) account for most late onset cancers, following chronic exposures over many years [3], but there is no such opportunity for such long-term exposures in teenagers and young adults. The mechanisms operating between exposure to a risk factor and clinical onset of a cancer may therefore differ either fundamentally or proportionally in young people compared with late onset cancers, and genetic susceptibility may play a greater role.

While a national co-ordinated approach to the treatment of cancers in younger children has been established for many years [4], teenagers and young adults with cancer have fared less well [5]. The teenage years and early twenties represent a critical period in terms of educational, social and career development. Disruption to education and vocational or professional training because of a prior diagnosis of cancer can have a profound impact on later life. Furthermore, the potential impact of cytotoxic treatment is of far greater importance in the young, than in the late middle-aged and elderly. Reduction in fertility, the possibility of developing treatment-induced second malignancies and organ failure are very important considerations in this age group. Furthermore, the spectrum of cancers encountered in teenagers and young adults differs

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markedly from both that seen in young children and in older patients [6].

All these considerations argue for the development of specialist services targeted towards teenage and young adult cancer patients. In order to develop those services, detailed and high quality statistics on the incidence and characteristics of cancers in this age group are required. To produce such statistics, a scheme for classifying cases into a manageable number of diagnostic groups is necessary. Such a scheme must be appropriate to the types of cancers that occur in the population group under study.

We have recently published a classification scheme which is specifically tailored to the adolescent and young adult cancer groups [6]. The scheme is largely based on morphology, and diagnostic groups are specified in terms of the International Classification of Diseases for Oncology (ICD-O) morphology and topography codes [7]. We proposed that our classification scheme should be used in future studies of cancers in adolescents and young adults to encourage a standard format for presentation of such data ('a common language') and thereby facilitate international comparisons and encourage research interest into these cancers. The scheme is available on our website at http://www.biomed2.man.ac.uk/crcpfcrg/CRUKPFCRG/PFCRG.htm.

We applied the scheme to national cancer registration data for England for the years 1979–1997 for patients aged 15–24 years. The main cancer types in this age range are lymphomas, leukaemias, bone tumours, central nervous system (CNS) tumours, germ cell tumours, soft tissue sarcomas and carcinomas. However, in contrast to older age groups, in which carcinomas of the lung, breast, large bowel and prostate account for over half of all cases [1], these carcinomas represent only 2% of malignancies in 15–24-year-olds. On the other hand, melanoma and carcinoma of the thyroid represent 8 and 3% of all cancers, respectively, in 15–24-year-olds, whereas across all age groups these cancers make up only 2 and 0.4% of the total [6].

The purpose of this study was to apply the classification scheme to an extended age range, including younger adolescents, and also to present incidence rates by detailed morphological type rather than by the site of origin.

2. Materials and methods

Anonymised individual level national cancer registration data for the years 1979–1992 were obtained on CD-ROM [8]. More recent data up to 1997 were supplied directly by the Office for National Statistics (ONS). From 1979 to 1994, data are coded by the ICD-O first edition [9] and ICD ninth revision [10] and from 1995 onwards by ICD-O second edition [7] and ICD tenth revision [11]. National population estimates by single year of age, gender and calendar year were supplied by the Population Estimates Unit, ONS.

2.1. Statistical analyses

Eligible cases included all malignant tumours, except carcinomas of skin, occurring in England from 1979 to 1997 in individuals aged 12–24 years. *In situ* cancers and neoplasms of uncertain behaviour were excluded. Scrutiny of the data for non-malignant CNS tumours suggested that there were variations in registration practices between regional cancer registries, so only unequivocally malignant CNS tumours were included in the analyses.

Individual cancer registrations were classified by cancer type, age group (12–14, 15–19, 20–24 years) and gender. The cancer groups were defined by specific morphology and topography code combinations according to the scheme described by Birch and colleagues [6]. Algorithms for selecting tumour groups are given at http://www.biomed2.man.ac.uk/crcpfcrg/CRUKPFCRG/PFCRG.htm. The person years at risk for each sub-group were calculated from the population data. Age group-, gender- and diagnostic group-specific annual incidence rates per 100 000 population were calculated. The significance of variability in incidence by gender was assessed by Poisson regression using the statistical package GLIM 4 [12].

3. Results

The study included 28 573 cases of malignant neoplasms, 3673 in the 12–14 year age range, 9307 in 15–19-year-olds and 15 593 in 20–24-year-olds. The study population encompassed a total of 170 263 000 person-years at risk, including 36 479 000 in the 12–14 year age range, 64 753 000 in the 15–19 year age range and 69 031 000 in the 20–24 year age range.

Table 1 shows the incidence of malignant disease among the study population by age group, gender and main diagnostic group. The incidence of all malignancies combined in the 20–24 year age group was more than double that observed in 12–14-year-olds. Among 12–14-year-olds, the highest rates were seen for leukaemias followed by lymphomas, CNS tumours and bone tumours. In this age group, soft-tissue sarcomas, germ cell tumours, melanoma and carcinomas were relatively uncommon. In 15–19-year-olds, the most striking difference compared with the younger adolescents was a doubling of the incidence rates for lymphomas, which were the most common malignancies in this age group. Rates for leukaemias, CNS tumours and bone tumours were similar to those observed in the 12–14 year age

Table 1
Incidence of malignant disease per 100 000 population in adolescents and young adults in England, 1979–1997, by gender

	Age group (years)							
	12–14		15–19		20–24		12–24	
	Male	Female	Male	Female	Male	Female	Male	Female
All malignant disease	10.81	9.28	15.83	12.83	23.71	21.43	17.93	15.58
Leukaemias	2.62	2.03	2.73	1.73	2.07	1.43	2.44	1.67
Lymphomas	2.53	1.40	4.38	3.51	5.96	4.97	4.62	3.65
CNS tumours	2.05	1.76	1.68	1.44	2.03	1.51	1.90	1.54
Bone tumours	1.34	1.43	1.63	1.10	0.97	0.53	1.30	0.94
Soft-tissue sarcomas	0.70	0.63	1.01	0.78	1.11	1.09	0.98	0.87
Germ cell tumours	0.28	0.54	2.06	0.58	6.77	0.52	3.58	0.55
Melanoma	0.25	0.25	0.59	1.05	1.48	3.08	0.87	1.71
Carcinomas	0.65	0.83	1.19	2.02	2.29	7.19	1.52	3.87
Miscellaneous specified neoplasms NEC	0.24	0.21	0.17	0.22	0.18	0.26	0.19	0.23
Unspecified neoplasms NEC	0.16	0.20	0.38	0.41	0.84	0.85	0.52	0.54

CNS, central nervous system; NEC, not elsewhere classified.

Table 2
Incidence per 100 000 population of leukaemia and lymphoma in adolescents and young adults in England, 1979–1997

	Age group (years)							
	1–14		15–19		20–24		12–24	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate
All leukaemias	850	2.33	1455	2.25	1214	1.76	3519	2.07
Acute lymphoid leukaemia	575	1.58	813	1.26	427	0.62	1815	1.07
Acute myeloid leukaemia	205	0.56	457	0.71	542	0.79	1204	0.71
Chronic myeloid leukaemia	31	0.08	80	0.12	147	0.21	258	0.15
Other specified leukaemia	13	0.04	36	0.05	40	0.06	89	0.05
Unspecified leukaemia	26	0.07	69	0.11	58	0.08	153	0.09
All non-Hodgkin's lymphomas (NHL)	295	0.81	755	1.17	989	1.43	2039	1.20
NHL specified sub-type	150	0.41	343	0.53	453	0.66	946	0.56
NHL sub-type not specified	145	0.40	412	0.64	536	0.78	1093	0.64
All Hodgkin's disease (HD)	428	1.17	1806	2.79	2791	4.04	5025	2.95
HD specified sub-type	281	0.77	1221	1.89	1896	2.75	3398	2.00
HD sub-type not specified	147	0.40	585	0.90	895	1.30	1627	0.96

group but the rates of soft-tissue sarcomas (STS), germ cell tumours, melanoma and carcinomas, although still relatively uncommon, were higher than in the 12–14-year-olds. There were distinct differences in the pattern of malignancies seen in the 20–24 year age range compared with the two younger age groups. There was a marked increase in the rates of lymphomas, which were the most common malignancies, and a marked decrease in the rates for leukaemias. However, the most striking differences were the increases in the rates for carcinomas, germ cell tumours and melanomas, which ranked second, third and fourth, respectively, and were thus among the more common cancers diagnosed in these young people. By contrast, bone tumours were much less frequent than in the younger age groups, but the overall incidence of STS was increased. The incidence of CNS tumours was fairly similar across all three age groups.

Table 2 shows incidence rates for sub-types of leukaemia and the proportions of non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD) coded according to specified sub-types. In 12–14-year-olds, acute lymphoid (lymphoblastic) leukaemia (ALL) accounted for more than two-thirds of all cases. Acute myeloid (myeloblastic) (AML) accounted for most of the remaining cases. The pattern of leukaemias among 15–19-year-olds was similar, but there was an increase in the rates for AML and a decrease for ALL compared with the younger age group. However, among 20–24-year-olds, AML was the most common sub-type, accounting for nearly half the cases, whilst ALL accounted for just over one-third. Although infrequent at all these ages, chronic myeloid leukaemia (CML) showed increasing rates with increasing age and the incidence of CML in 20–24-year-olds was nearly 3 times that seen in 12–14-year-olds.

In contrast to ALL, rates for NHL showed steady increases with increasing age. Only about half of all registered cases were coded to a specific sub-type of NHL in the database. The classification of NHL has changed substantially during the period covered by the study [13] and the sub-types specified in the dataset are inconsistent with the current international classification of lymphomas [14]. However, in summary, 78% of all cases with a specified sub-type across the age range 12–24 years were classified as diffuse, 10% as follicular/nodular and 12% as other miscellaneous sub-types. HD showed a very marked increasing trend in incidence with age and the incidence among 20–24-year-olds was more than 3 times that seen in 12–14-year-olds. More than two-thirds of the HD cases were coded to a specified sub-type. The HD sub-classification was consistent across the time period and was based on the Rye Conference scheme [15]. Among those cases with specified sub-types, 72% were nodular sclerosing HD (NSHD) and this proportion did not differ markedly between age groups, although NSHD was somewhat more frequent (75%) among 12–14-year-olds. Mixed cellularity Hodgkin's disease (MCHD) comprised 18% of all specified cases and was more frequent among 15–19-year-olds (18%) and 20–24-year-olds (19%) than in 12–14-year-olds (13%). Lymphocyte-predominant HD formed just 7% of all specified cases and was rather more frequent among 12–14-year-olds (11%) than among 15–19 year olds (8%) and 20–24-year-olds (6%). Lymphocyte-depleted Hodgkin's disease was infrequent in all the age groups.

Table 3 presents data on the rates of malignant CNS tumours. The rates for these tumours overall did not differ greatly across the age groups, but were somewhat higher in the 12–14-year-olds. The most common sub-type of CNS tumour was astrocytoma. Among those with a specified sub-type, low-grade astrocytomas were more common than glioblastoma and anaplastic astrocytoma in 12–14-year-olds and 15–19-year-olds. However, in the 15–19-year-olds, the difference in the rates between low-grade and high-grade astrocytoma was less marked than in the younger age group. In 20–24-year-olds, high-grade astrocytomas were more frequent than low-grade astrocytoma. Rates for ependymoma did not differ markedly between the age groups, but medulloblastoma and other primitive neuroectodermal tumours (PNETs) were twice as common in the younger age group as in patients aged 15–24 years.

Table 4 shows the incidence of bone tumours, STS, germ cell tumours and melanoma. Rates for bone tumours were higher among patients aged 12–19- than among 20–24-year-olds. In all three age groups, osteosarcoma was by far the commonest tumour, but the proportion of osteosarcoma is lower in 20–24-year-olds with a relatively higher proportion of chondrosarcoma (12%) compared with the younger patients (3% in 12–14-year-olds and 6% in 15–19-year-olds). Ewing's tumour is the second most frequent tumour in all three age groups comprising 32% of all bone tumours overall, but is somewhat more frequent in 12–14-year-olds (37%) than in 15–19-year-olds and 20–24-year-olds (30% in both age groups).

STS, although less frequent than bone tumours, are an important group of malignancies in adolescents and young adults and constitute 6% of all malignancies in this age group. The most common type of STS overall, rhabdomyosarcoma (RMS), is also the most common STS in 12–14 year olds (42%) and 15–19-year-olds (35%), but in 20–24-year-olds, only 13% of all STS are RMS. Sub-classification of STS has improved markedly with the development of immunohistochemical techniques [16] and the terms fibrosarcoma and malignant fibrous histiocytoma are now applied much more stringently. It is therefore likely that the incidence of fibromatous neoplasms is actually lower than the rates shown in Table 4, but special histopathological review of all cases nationally registered during the period 1979–1997 would be required to determine the true incidence of the sub-types.

Table 3
Incidence per 100 000 population of malignant CNS tumours in adolescents and young adults in England, 1979–1997

	Age group (years)							
	12–14		15–19		20–24		12–24	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate
All malignant CNS tumours	696	1.91	1013	1.56	1223	1.77	2932	1.72
Specified low grade astrocytoma	101	0.28	117	0.18	70	0.10	288	0.17
Glioblastoma and anaplastic astrocytoma	32	0.09	76	0.12	100	0.14	208	0.12
Astrocytoma, NOS	216	0.59	342	0.53	423	0.61	981	0.58
Other glioma	114	0.31	190	0.29	306	0.44	610	0.36
Ependymoma	55	0.15	65	0.10	80	0.12	200	0.12
Medulloblastoma and other PNET	110	0.30	96	0.15	105	0.15	311	0.18
Other specified CNS tumours	8	0.02	26	0.04	28	0.04	62	0.04
Unspecified CNS tumours	60	0.16	101	0.16	111	0.16	272	0.16

CNS, central nervous system; NOS, not otherwise specified; PNET, primitive neuroectodermal tumour.

Table 4
Incidence per 100 000 population of bone tumours, soft tissue sarcomas, germ cell tumours and melanoma in adolescents and young adults in England, 1979–1997

	Age group (years)							
	12–14		15–19		20–24		12–24	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate
All bone tumours	506	1.39	889	1.37	522	0.76	1917	1.13
Osteosarcoma	275	0.75	496	0.77	225	0.33	996	0.58
Chondrosarcoma	17	0.05	53	0.08	65	0.09	135	0.08
Ewing's tumour	186	0.51	265	0.41	159	0.23	610	0.36
Other specified bone tumours	6	0.02	25	0.04	29	0.04	60	0.04
Other unspecified bone tumours	22	0.06	50	0.08	44	0.07	116	0.07
All soft tissue sarcomas (STS)	244	0.67	581	0.90	758	1.10	1583	0.93
Fibromatous neoplasms	43	0.12	113	0.17	206	0.30	362	0.21
Rhabdomyosarcoma	103	0.28	201	0.31	98	0.14	402	0.24
Other specified STS	62	0.17	186	0.29	345	0.50	593	0.35
Unspecified STS	36	0.10	81	0.13	109	0.16	226	0.13
All germ cell neoplasms	147	0.40	869	1.34	2557	3.70	3573	2.10
Gonadal germ cell neoplasms	80	0.22	764	1.18	2422	3.51	3266	1.92
Intracranial germ cell neoplasms	35	0.10	50	0.08	35	0.05	120	0.07
Other non-gonadal germ cell neoplasms	32	0.09	55	0.08	100	0.14	187	0.11
Malignant melanoma	91	0.25	527	0.81	1563	2.26	2181	1.28

With respect to other specified sub-types of STS, the most common type across the 12–24 year age range was synovial sarcoma (SNS). SNS was more frequent among 20–24-year-olds (10%) than among 12–14-year-olds (8%) and 15–19-year-olds (7%). Blood vessel tumours were also relatively frequent and constitute 2% of STS in 12–14-year-olds, 5% in 15–19-year-olds and 11% in 20–24-year-olds. Among 20–24-year-olds, malignant peripheral nerve sheath tumours (MPNST), leiomyosarcoma (LMS) and liposarcoma (LPS) were also relatively frequent constituting 8, 7 and 6%, respectively, of all STS in this age group. MPNSTs were also relatively frequent in 12–14-year-olds (6%) and 15–19-year-olds (7%), but LPS and LMS were rare among 12–14-year-olds (2 and 3%, respectively) and relatively uncommon among 15–19-year-olds (4 and 5%, respectively).

The most dramatic increase in incidence rates with age among the adolescent and young adult groups occurs in the gonadal germ cell tumours with increases from 0.22 per 100 000 in 12–14-year-olds to 1.18 in 15–19-year-olds and to 3.51 in 20–24-year-olds, representing a 16-fold increase in rates over the age range. This is almost entirely due to an increase in testicular germ cell tumours. Non-gonadal germ cell tumours are much less frequent than gonadal and trends with age are less obvious. There is a small decrease in rates with increasing age for intra-cranial germ cell tumours and a small increase with age for germ cell tumours of other non-gonadal sites.

Table 5 summaries the incidence rates for carcinomas. In 12–14-year-olds and 15–19-year-olds, carcinomas of the head and neck form the most common group making up 46 and 42%, respectively, of all carcinomas among these two age groups, but in 20–24-year-olds, carcinomas of the head and neck region make up only 24% of all carcinomas. The thyroid is by far the most common head and neck primary site for carcinomas and the rates for carcinoma of the thyroid increase steadily across the three age groups. Nasopharyngeal carcinoma, which is extremely rare in the population in Britain in general [1], makes up 12% of all carcinomas in 12–14-year-olds, but represents only 2% among 20–24-year-olds, although the actual incidence is similar to that seen in the younger age group.

The common carcinomas seen in older adults, such as, carcinomas of the bronchus, breast, colon, rectum and bladder, are all very rare in adolescents and young adults, but examples of all of these carcinomas are seen and the rates increase from the 12–14 year age group to the 20–24-year-olds. The proportion of carcinomas of the genito-urinary (GU) tract increases quite markedly across the three age groups and these carcinomas make up 15% of all carcinomas in 12–14-year-olds, but 21 and 43% in the 15–19- and 20–24-year-olds, respectively. All sites within the GU tract show increases with age, but the greatest increases are seen for invasive carcinomas of the cervix and uterus. Among carcinomas of the gastrointestinal tract, the most common sites in all three age groups are the colon and rectum. Adrenocortical

Table 5
Incidence per 100 000 of carcinomas in adolescents and young adults in England, 1979–1997

	Age group (years)							
	12–14		15–19		20–24		12–24	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate
All carcinomas	269	0.74	1032	1.59	3240	4.69	4541	2.67
Thyroid	44	0.12	261	0.40	542	0.79	847	0.50
Nasopharyngeal	33	0.09	93	0.14	60	0.09	186	0.11
Other head and neck	46	0.13	81	0.13	160	0.23	287	0.17
Trachea, bronchus and lung	6	0.02	25	0.04	80	0.12	111	0.07
Breast	2	0.01	38	0.06	355	0.51	395	0.23
Kidney	12	0.03	29	0.04	92	0.13	133	0.08
Bladder	10	0.03	32	0.05	146	0.21	188	0.11
Gonads	12	0.03	107	0.17	381	0.55	500	0.29
Cervix and uterus	3	0.02	25	0.08	715	2.11	743	0.89
Other and ill-defined, GU tract	4	0.01	19	0.03	53	0.08	76	0.04
Colon and rectum	33	0.09	124	0.19	260	0.38	417	0.24
Stomach	4	0.01	20	0.03	71	0.10	95	0.06
Liver	11	0.03	52	0.08	67	0.10	130	0.08
Pancreas	3	0.01	8	0.01	26	0.04	37	0.02
Other and ill-defined, GI tract	2	0.01	8	0.01	33	0.05	43	0.03
Adrenocortical	5	0.01	9	0.01	19	0.03	33	0.02
Other and ill-defined sites	39	0.11	101	0.16	180	0.26	320	0.19

GU, genito-urinary; GI, gastrointestinal.

Table 6
Incidence per 100 000 population of miscellaneous specified neoplasms in adolescents and young adults in England, 1979–1997

	Age group (years)							
	12–14		15–19		20–24		12–24	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate
All miscellaneous neoplasms	82	0.22	126	0.19	153	0.22	361	0.21
Wilms' tumour	14	0.04	13	0.02	13	0.02	40	0.02
Neuroblastoma	25	0.07	33	0.05	23	0.03	81	0.05
Other paediatric and embryonal, NEC	17	0.05	14	0.02	20	0.03	51	0.03
Paraganglioma and glomus	2	0.01	10	0.02	22	0.03	34	0.02
Other specified gonadal	2	0.01	14	0.02	7	0.01	23	0.01
Myeloma, mast cell tumours and miscellaneous lymphoreticular, NEC	19	0.05	19	0.03	35	0.05	73	0.04
Other miscellaneous neoplasms	3	0.01	23	0.04	33	0.05	59	0.03

NEC, not elsewhere classified.

carcinoma is exceedingly rare, but does occur in all three age groups.

Table 6 includes incidence rates for several tumours typically seen in younger children. Wilms' tumour and neuroblastoma have peak incidences in children aged less than 5 years, but cases have been registered in all three age groups of adolescents and young adults. Less than 10 cases each of hepatoblastoma and retinoblastoma and 37 cases of peripheral primitive neuroectodermal tumours are included. Single cases of pancreatoblastoma and pulmonary blastoma were also diagnosed. In addition, it is interesting to note that there are a number of cases of multiple myeloma, which usually occurs in much older patients.

Examination of the rates of malignancies in males compared with females showed a number of statistically significant differences. In ALL overall, the male to female rate ratio was significantly above 1 ($P = 0.0003$), but the ratio also increased with increasing age—the male to female ratios in 12–14-year-olds, 15–19-year-olds and 20–24-year-olds were 1.3, 2.0 and 2.2, respectively ($P < 0.0001$). For AML, there was a small excess rate among males ($P = 0.007$), but this did not vary by age. The pattern for CML was similar to that for AML. In NHL, there was a marked excess rate among males in all age groups ($P < 0.0001$), but the male to female (m:f) ratio fell slightly with increasing age (m:f = 2.7, 2.1 and 1.8 in 12–14-, 15–19- and 20–24-year-olds, respectively)

($P = 0.02$). The pattern of incidence amongst males and females with HD across the three age groups was similar to that seen for NHL, although the male to female ratio was only slightly above 1.

There was a significantly higher incidence of CNS tumours in males than in females ($P < 0.0001$), but this did not differ by age group. There were no significant differences in male to female ratios for the various types of CNS tumours except for medulloblastoma and other PNETs, where the ratio was highest among 12–14 year olds (m:f = 2.9), but lower in 15–19-year-olds (m:f = 1.4) and 20–24-year-olds (m:f = 1.6).

An interesting pattern was observed among the bone tumours. Overall, there was a significant excess incidence among males ($P < 0.0001$), but the rate ratio differed significantly between age groups ($P < 0.0001$). In both osteosarcoma and Ewing's tumour, the ratio of incidence in males to females varied from an excess rate in females aged 12–14 years (m:f = 0.9) to an excess in males aged 20–24 years (m:f = 2.1) with an intermediate ratio in 15–19-year-olds (for osteosarcoma $P < 0.0001$, for Ewing's tumour $P = 0.001$).

The incidence rates of gonadal germ cell tumours between males and females changed strikingly with increasing age. In 12–14-year-olds, the incidence ratio in males to females was 0.4 and in 15–19-year-olds was 3.7, but in 20–24-year-olds, the male to female ratio had increased to 17.2 ($P < 0.0001$). Intracranial germ cell tumours, by contrast, showed a consistent male excess ($P < 0.0001$) across the age groups. There was no significant difference in the rates of other non-gonadal germ cell tumours in males and females overall, but the gender ratio changed with age ($P < 0.0001$), with higher rates in females aged 12–14 years and somewhat higher rates in males than females at older ages. Rates for melanoma and carcinoma of the thyroid were markedly higher in females at all ages (in both groups $P < 0.0001$). There was also a significant overall excess of females with adrenocortical carcinoma ($P = 0.002$) and with carcinoma of the pancreas ($P = 0.03$). There was a significant male excess in the incidence rate of nasopharyngeal carcinoma and carcinoma of the bladder ($P < 0.0001$), which did not differ by age group.

Apart from the gender-specific carcinomas (breast, cervix and uterus), there were no other statistically significant differences in the incidence rates between males and females in other diagnostic groups.

4. Discussion

Worldwide cancer incidence data are generally presented mainly by primary site, grouped according to the ICD [11,17]. While this is acceptable for cancers in older adults—which are mainly carcinomas. ICD cannot distinguish non-epithelial cancers from carcinomas or different types of non-epithelial cancers from each other. Data on cancers in young people are more appropriately presented in terms of histopathological type (morphology). Morphology-based classification systems for analysis and presentation of data on cancers in children aged 0–14 years were developed some time ago [18,19]. Recently, this childhood cancer classification scheme has been applied to cancer incidence data in adolescents aged 15–19 years [20]. However, a number of the major groups of cancers in children, including most embryonal tumours, are irrelevant in teenagers and young adults because they are so uncommon. Conversely, carcinomas are inappropriately sub-divided in childhood classifications [21]. Consequently, it was suggested that a separate nosological system should be used for cancers that occur in adolescents and young adults to take account of the unique features in this age group [5].

We have developed such a system which, in common with its childhood cancer counterparts, is also based primarily on morphology. In this study, we applied this adolescent and young adult cancer classification scheme to national data from England for cancers in young persons aged 12–24 years. A particular emphasis of the study was to compare the incidence and patterns of cancers seen in younger adolescents aged 12–14 years, in older teenagers aged 15–19 years and in young adults aged 20–24 years. From the results, it is apparent that the proposed new adolescent and young adult classification is more suited to the 12–14 year age group than the childhood cancer classifications. Attention was paid to the pattern of diagnostic sub-groups at different ages as well as to trends with age for the main diagnostic groups. Detailed data, as presented in this study, are of importance in assessing service needs and the delivery of appropriate service provision to this neglected and therefore vulnerable age group. Observation of detailed patterns of incidence by age and gender can also provide pointers to aetiology and identify areas of interest for future research.

Epidemiological features of childhood ALL, mainly precursor B-cell ALL, where the majority of cases occur in the first five years of life, suggest that delayed exposure to infections in early childhood, resulting in an unusual pattern of delayed immune stimulation, may be involved in aetiology. It is also likely that an initial mutational event predisposing to subsequent development of leukaemia in early childhood occurs *in utero* [22–26]. An infectious aetiology for childhood leukaemia is also supported by results of studies of space–time clustering patterns [27]. The decline in incidence rates of ALL with age between early childhood and young adulthood suggests a change in aetiological factors and/or mechanisms. The involvement of infections in the aetiology of leukaemia in teenagers and young adults is still a possibility, but in these older age groups, a

directly transforming virus may be more likely rather than the indirect mechanisms suggested for the ALL peak of early childhood [28]. *In utero* exposure to certain chemicals has been associated with MLL-positive infant acute leukaemia [29]. Although these observations apply to a very small sub-group of cases, they do suggest the possibility of a role for environmental chemical exposures in other cases of leukaemia in young people and it may be that the increasing rates of AML with age are, in part, due to postnatal exposures to environmental chemical agents.

An infectious aetiology has also been suggested for both NHL and HD. In NHL, increased risk is associated with systemic HIV1, HTLV1 and Epstein–Barr virus (EBV) infections and for gastric lymphoma, with *Helicobacter pylori* infection of the stomach. However, other viruses and indirect mechanisms involving common infections cannot be ruled out [30]. It has been established that a proportion of cases of HD, particularly MCHD, is aetiologically linked to EBV. The magnitude of the risk and the proportion of cases attributable to EBV varies with age, gender, ethnicity and the level of economic development/material deprivation. However, EBV infection, in the presence of known and unknown modifying factors, is likely to be an important aetiological factor in HD in adolescents and young adults [31,32].

The changing pattern of incidence of PNETs and astrocytomas with age may reflect a change in aetiological mechanisms in these tumours. There has been much speculation about the possible role of polyoma viruses including simian virus 40 (SV40), JC and BK viruses in the pathogenesis of CNS tumours. Viral DNA sequences have been detected in human PNETs, ependymomas, high- and low-grade astrocytomas and meningiomas [33–35]. Furthermore, space–time clustering has been reported in childhood brain tumours, which is particularly evident for astrocytoma and ependymoma in older children [36] and is consistent with an infectious aetiology. Similar temporal trends in incidence have been observed for brain tumours and childhood, adolescents and young adults [6,37]. There may be shared aetiological factors for brain tumours occurring in adolescents and young adults, particularly in older children. Hypotheses relating to viral exposures should therefore be investigated.

Genetic factors are of importance in the aetiology of some CNS tumours in young people, and brain tumours occur as manifestations of certain cancer predisposition syndromes, characterised by germ-line mutations in a variety of genes [38]. Of particular relevance to the adolescent and young adult cases of anaplastic astrocytoma and glioblastoma, is the fact that these tumours may arise in patients with germ-line *TP53* mutations [39,40]. The peak incidence of anaplastic astrocytoma is in the fourth decade of life and glioblastoma is in the fifth decade. Glioblastoma is rare before the age of 30 years [41]. However, in patients with germ-line *TP53* mutations, these tumours tend to arise at much earlier ages [40,42]. In addition, brain tumours, notably medulloblastoma, arising in association with germ-line mutations in the *APC* gene, tend to be diagnosed in older children, adolescents and young adults [43]. This unusually early age of onset of brain tumours in association with familial cancer syndromes may reflect a combination of genetic susceptibility and environmental exposure. In this context, the detection of SV40 viral sequences in tumours from patients with germ-line *TP53* mutations is of particular interest [44].

The increasing ratio of male to female cases across the three age groups suggests that the onset of osteosarcoma and Ewing's tumour may be associated with the adolescent growth spurt, which occurs earlier in females than in males. It also appears that genetic factors may be important in the aetiology of both osteosarcoma and Ewing's tumour. Osteosarcoma is one of the more common tumours to occur in association with germ-line *TP53* mutations and cases are usually diagnosed during adolescence and young adulthood [42,45]. Evidence for genetic susceptibility to Ewing's tumour comes from the striking variation in incidence with ethnic origin. Ewing's tumour is virtually absent among black Africans and also among African-Americans [46]. The possibility of a viral aetiology for osteosarcoma has also been considered and it is of particular interest that SV40-like sequences have been detected in osteosarcoma tissue in a number of studies [47–50]. Furthermore, in a recent study the frequency of SV40-like sequences in peripheral blood cells from osteosarcoma patients was compared with that in normal, healthy controls. The frequency in the osteosarcoma patients was substantially increased [50].

In common with osteosarcoma, soft tissue sarcomas are a principal component of the cancer predisposition syndrome associated with germ-line *TP53* mutations [45]. Space–time clustering has been reported among incident cases of soft tissue sarcoma in children [51]. It would be of considerable interest to determine whether space–time clustering can be detected among STS in teenagers and young adults.

The dramatic temporal increase in testicular germ-cell tumours in young men has been reported and discussed previously. The aetiology of testicular germ-cell tumours is uncertain, but genetic and hormonal factors, including exposure to oestrogen *in utero*, appears to be important [52]. Similarly, the incidence trends for melanoma of skin have also previously been presented and discussed. Melanoma of skin shows associations with socio-economic factors, endogenous factors, e.g. skin and hair colouring, certain heritable syndromes and, notably, patterns of sun exposure [52].

The pattern of carcinomas in teenagers and young adults, as noted above, is very different from that seen in older age groups. Carcinomas of the head and neck, including carcinoma of the thyroid and nasopharyngeal carcinoma (NPC), constitute nearly 30% of the total carcinomas in the 12–24 year age range. We have discussed the temporal increase in carcinoma of the thyroid in young people elsewhere [6]. The highest incidence rates for NPC are found in parts of the Far East, where it is associated with EBV infection. It is likely also that the rare cases of NPC occurring in young people in Western developed countries may also be linked aetiologically to EBV and this is an area worthy of investigation. However, it is probable that other co-factors are involved [53].

Of the common late-onset carcinomas, carcinoma of the cervix and uterus are relatively frequent in adolescent and young adult females and nearly all the cases occur in the 20–24 year age range. Aetiology appears to be closely linked with sexually transmitted infections including herpes simplex virus type 2, and human papilloma virus [52]. Although carcinoma of the breast is extremely rare in the adolescent and young adult age range, it is of particular interest since a recent study has detected pathogenic alterations in breast cancer susceptibility genes in 20% of a large series of women with breast cancer diagnosed under the age of 30 years [54]. It is possible that a similarly high rate of mutations in the susceptibility genes associated with colorectal carcinoma might also be found among very young patients. The frequency of mutations in relevant genes among these very early onset cases of common carcinomas should be determined.

In summary, the data presented above provide a basis for service planning and also provide a stimulus for studies of aetiology in these young cancer patients. It is unlikely that the chronic occupational and social exposures (including cigarette smoking) that are responsible for most late-onset cancers contribute substantially to cancers in young people. In some circumstances, exposure to such environmental agents may be involved in aetiology, but it is likely that other co-factors, e.g. genetic susceptibility and hormonal factors are of greater importance. In a number of the principal groups of cancers occurring in young people, the most promising areas for investigation include the role of specific viruses and other infections, including their effects on the immune system, and inherited predisposition. As regards 'predisposition', high penetrance and low penetrance mutations or polymorphisms in known and yet-to-be discovered cancer-associated genes should all be considered. It is to be hoped that the cancer research community will rise to the challenge and initiate studies in this fascinating, but relatively neglected, group of patients.

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