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INCIDENCE OF TESTICULAR GERM-CELL MALIGNANCIES IN ENGLAND AND WALES: TRENDS IN CHILDREN COMPARED WITH ADULTS

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The incidence of testicular cancer has been increasing markedly in most industrialised countries. This rise is known to have affected young adults, but it is less clear whether it has affected other age groups, particularly children. We used data from the National Cancer Registry file at the Office of National Statistics (ONS) and the National Registry of Childhood Tumours to examine trends in testicular germ-cell malignancies overall in England and Wales from 1962 to 1990 and in children from 1962 to 1995. The incidence of testicular cancer at all ages rose by 3.4% (95% CI 3.3–3.6%) per annum from 1962 to 1990. A similar rise in the incidence of germ-cell malignancies occurred during the years for which histological information was available in the ONS files, 1971–1989 (3.4%; 3.1–3.6%), to which both seminomas and non-seminomas contributed equally. The incidence of non-seminomas in adults rose in men under age 55 years and declined in older men, whereas there were increases in the incidence of seminomas in both young and older men. Cohort analysis at young ages showed a marked rise in the risk of germ-cell malignancies up to the cohort born in 1955–1959 but no further rise for those born subsequently. The rise in the incidence of these tumours in young adults was paralleled by a similar trend, although less marked, in children aged under 15 years (1.3% per annum; 0.2–2.5%). The increase in risk for children in this very large data set alongside the rise in young adults is compatible with the hypothesis that childhood and adult testicular germ-cell malignancies may have some common risk factors, presumably pre-natal. *Int. J. Cancer* 83:630–634, 1999.

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The incidence of testicular cancer has been increasing during this century in most industrialised countries, and it is now the most common malignancy in young men (Swerdlow *et al.*, 1998). Most testicular cancers are of germ-cell origin (Pike *et al.*, 1987), which comprises 2 distinct groups: seminomas and non-seminomas. This latter group comprises several different cell types named differently according to various classification systems (Teppo, 1973); it is mainly equivalent to teratomas in the British system. In the England and Wales National Cancer Registry files, which cover a large population of about 50×10^6 , testicular tumours are coded according to both site and histology, but the histological data appear not to have been analysed previously. We used data from these files to examine recent trends in these tumours and, in particular, to assess whether the rises in incidence of testicular cancer at young adult ages have affected similarly its 2 major histological groups.

The rise in the incidence of germ-cell malignancies is known to have affected young adults, but it is less clear whether it has occurred in other age groups, particularly in children. Although the large majority of testicular cancers in children are of germ-cell origin, the main histological types are different from those in adults, with a predominance of yolk-sac tumours. The few studies that have examined trends in children tended to have been based on relatively small numbers of tumours (Schottenfeld *et al.*, 1980; Swerdlow *et al.*, 1982; Møller *et al.*, 1995), and most were not able to examine separately the trend for tumours of germ-cell origin (Schottenfeld *et al.*, 1980; Møller *et al.*, 1995). We have extracted data on malignant testicular germ-cell tumours in children in England and Wales from the National Registry of Childhood Tumours, to assess whether the recent increases in testicular

germ-cell incidence in young adults may have also affected children.

MATERIAL AND METHODS

ONS data

Data on cancers of the testis (ICD7, 178; ICD8-9, 186) (WHO, 1957, 1967, 1977) incident 1962 to 1989 were extracted from the national cancer registry files at the Office for National Statistics (ONS). Tumour histology in these files was coded according to the *Manual of Tumour Nomenclature and Coding* (MOTNAC) (American Cancer Society, 1951) for 1971 to 1978 data and the *International Classification of Diseases for Oncology* (ICD-O) (WHO, 1976) for data from 1979 onward. The histological code used before 1971, a 2-digit OPCS code, was very elementary. Data for the year 1990 were extracted from a published source (ONS, 1997), which does not contain information on histology. Therefore, we examined overall testicular cancer incidence for the years 1962 to 1990 but conducted analyses by histology only for 1971 to 1989. Mid-year population estimates of England and Wales for 1962 to 1995 were also extracted from the ONS files.

Analyses were carried out for testicular germ-cell cancers overall and separately for their 2 major histological categories: 1) seminomas and 2) non-seminomas, including both embryonal and extra-embryonal cell types (*i.e.*, embryonal cell carcinoma, endodermal sinus tumour and choriocarcinoma). Mixed tumours with seminomatous elements were allocated to non-seminomas. Since data on histological type were incomplete in the ONS files, the observed numbers of testicular cancers with germ-cell histology in these files constitute an under-estimation of the true numbers of incident cases, and the extent of this under-estimation will have varied by time and age. The true numbers were therefore estimated by multiplying, in each year of registration and 5-year age group, the observed number of registrations by the inverse of the corresponding proportion of testicular cancers with histological confirmation. The analyses presented here are for tumours of known histology, unless otherwise stated; but we also repeated them, adjusting for tumours of unknown histology. However, the proportion of testicular tumours with known histology was very high (about 94% nationally, see "Results"); therefore, these adjustments made little difference to the findings.

CCRG data

We also extracted data from the National Registry of Childhood Tumours at the Childhood Cancer Research Group (CCRG). This registry collects data on all incident cancers diagnosed in children resident in the country and aged under 15 years. Tumours are ascertained from the regional cancer registries, local population-based childhood cancer registries and the register of patients treated

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by members of the UK Children's Cancer Study Group (UKCCSG). The registry also receives death certificates of all deaths occurring in Britain under the age of 20 and with a neoplasm coded as the underlying cause. As a result, the Group's register is particularly complete. We extracted from its files data on all testicular germ-cell malignancies incident in England and Wales during 1962–1995.

Analysis of time trends

Direct age-standardised incidence rates by single year of age were calculated using the 1971 mid-year male population of England and Wales as the standard. To assess secular trends, a Poisson regression model was fitted (Breslow and Day, 1987). For the ONS data adjusted for incompleteness of histological information, the estimated numbers of incident cases were truncated to whole numbers before the model was fitted.

To examine risks according to birth cohort, standardised cohort incidence ratios (SCIRs) were calculated by the indirect method, using the average age-specific rates for the entire period to derive the expected values for each cohort. These analyses were carried out by 5-year periods of birth. Since the cancer registry files contained information on the exact year of birth of the cancer cases, we also conducted more detailed analyses by single year of birth to examine possible sudden cohort changes in risk due to short-term changes in exposure levels (*e.g.*, changes in maternal diet during World War II).

RESULTS

A total of 23,393 testicular cancers were included in the ONS cancer registry files for 1962–1990. For the years for which histological information was available (1971–1989), there were 17,215 testicular tumours after exclusion of 49 lymphoma and Hodgkin's disease registrations that were erroneously coded as testicular cancers (WHO, 1977). Germ-cell tumours represented 97% ($n = 15,763$) of all testicular cancers of known histology; 55.2% ($n = 8,703$) of these germ-cell tumours were seminomas and 44.8% ($n = 7,060$) non-seminomas.

Ninety-four percent of testicular cancers in the ONS data set were of known histology. However, this percentage varied by age: it was 95% at ages under 65 years but only 76% at ages 65 and over. There was little change in the overall percentage of histologically confirmed testicular cancers over time.

Age distributions by single year for the 2 major types of germ-cell tumour in adults are shown in Figure 1. Non-seminomas started to rise at age 13 and peaked around age 27, whereas seminomas began to increase and peaked some years later (at ages 16 and 34, respectively). As a result, non-seminoma was the most common histology at ages under 30 and seminoma at older ages.

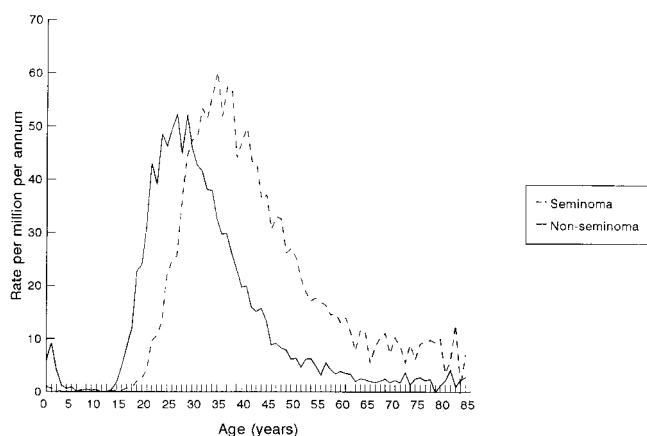


FIGURE 1 – Age-specific incidence rates of testicular germ-cell malignancies by single year of age, England and Wales, 1971–1989.

A total of 298 testicular malignant germ-cell tumours in England and Wales were incident in children under age 15 during 1962–1995. The large majority of these were non-seminomas, with 76% ($n = 225$) being of yolk-sac origin and 21% ($n = 62$) teratomas. There were only 9 seminomas at these ages and 2 cases of unspecified germ-cell origin. Analysis by single year of age showed a peak at ages under 3, which differed for yolk-sac tumours and teratomas. For yolk-sac tumours, rates peaked in the second year of life and decreased thereafter, whereas for teratomas the maximum occurred in the first year of life with rates falling thereafter until they started to rise again at age 13 (the very beginning of the steep rise through adolescence and young adulthood).

There was a statistically significant increase in the risk of testicular cancer overall from 1962 to 1990 [mean annual percent change in rates = 3.4%, 95% confidence interval (CI) 3.3–3.6%; $p < 0.001$; Fig. 2]. This increase was much more marked at ages under 55 years (3.7%, 3.5–3.9%; $p < 0.001$) than at ages 55 years and above (1.2%, 0.7–1.7%; $p < 0.001$). Analyses of testicular cancer trends by histology were possible only for 1971–1989 (see “Material and Methods”). For these years, there was an increase in the overall incidence of germ-cell tumours, to which both seminomas and non-seminomas contributed equally (Table I). Similar results were obtained after adjusting for tumours of unknown histology. However, analyses by age showed diverging time trends in the incidence of non-seminomas for young and older men (Table I): at ages 0–54 there was a significant increase in the incidence of these tumours, whereas at older ages there was a decline. In contrast, the incidence of seminomas increased in both age groups, though more markedly at young than at older ages (Table I). Overall, the incidence of germ-cell tumours increased in young, but not in older, men (Table I). These analyses were unadjusted for cases of unknown histology, but adjusting for this gave similar results.

Further breakdown by 5-year age group showed mean annual percent increases in the incidence of non-seminomas in all age groups from 15 to 54 years but annual declines at older ages. For seminomas, the increase affected all age groups from 15 to 74 years; there was little change in risk at ages 75 and older, but this was based on a smaller number of cases. The mean annual percent increases in the incidence of germ-cell tumours at ages 15–19, 20–24 and 25–34 years were 2.1% (0.6–3.7%), 2.8% (2.0–3.7%) and 2.9% (2.4–3.4%), respectively. There were no statistically significant changes in risk at ages under 15 years, but the 95% CIs were wide because of small numbers. At age 0–4, when the large majority of childhood germ-cell tumours occurred, there was a near significant increase (2.6%, -0.29 –5.6%; $p = 0.08$).

Cohort analyses showed that the risk of testicular cancer at ages under 55 years remained relatively constant for men born from

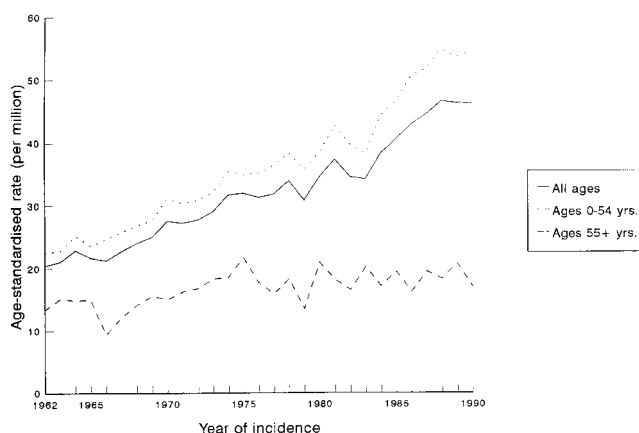


FIGURE 2 – Secular trends in the incidence of testicular cancer of all histological types combined by age, England and Wales, 1962–1990.

TABLE I – TRENDS IN INCIDENCE OF GERM-CELL MALIGNANCY OF THE TESTIS BY AGE AND HISTOLOGY: ENGLAND AND WALES, 1971–1989

Age (years)	Histological type	Rate		Mean annual percent change in rate (95% CI), 1971–1989	p value
		1971–1975 ¹	1986–1989 ¹		
0–54	Seminomas	16.0	25.1	3.7 (3.3–4.1)	<0.001
	Non-seminomas	14.6	22.2	3.6 (3.1–3.9)	<0.001
	All germ cell tumours	30.6	47.2	3.7 (3.5–3.9)	<0.001
55+	Seminomas	10.3	12.0	1.6 (0.5–2.7)	<0.001
	Non-seminomas	3.6	2.1	–2.9 (–5.0 to –0.9)	0.006
	All germ cell tumours	13.9	14.1	0.6 (–0.3–1.6)	0.18
All ages	Seminomas	14.8	22.2	3.4 (3.0–3.8)	<0.001
	Non-seminomas	12.1	17.7	3.4 (2.9–3.8)	<0.001
	All germ cell tumours	26.9	39.9	3.4 (3.1–3.6)	<0.001

¹Rates (per 10⁶) age-standardised by single year to the 1971 England and Wales population.

1911 to 1935, increased for those born from 1935 to 1957 but stabilized again for those born subsequently [the SCIRs for all germ-cell malignancies combined for cohorts born in 1955–1959 and 1965–1969 were 114 (95% CI 109–118) and 106 (97–106), respectively] (Fig. 3). The rise was relative steady, with no obvious dips or peaks (apart from small random fluctuations) (Fig. 3a). In particular, there was no decrease in risk for men born during World War II. At older ages (not shown), the risk remained relatively constant for successive generations except for a slight increase for the last generations in these analyses (born 1920–1930). The cohort increase at young ages was similar for non-seminomas and seminomas (Fig. 3b). At ages 55 and over (not shown), there was a marked decline in the risk of developing a non-seminoma for successive generations of men born since the turn of the century but no clear trend for seminoma except for an increase in risk for the 2 most recent generations in these analyses. Similar results were obtained with the data adjusted for cases of unknown histology.

Analyses of secular trends in children under 15 years of age revealed an overall increase in the incidence of malignant germ-cell tumours during the years 1962–1995, entirely due to a rise in yolk-sac tumours (Table II). The 5-year age-specific trends were more difficult to interpret because of the small number of cases, particularly at ages 5–9. At ages 0–4, there was a rise in risk, but it was not statistically significant; however, the trends diverged by cell type, with a statistically significant rise in yolk-sac tumours and a significant decline in teratomas (Table II). At ages 10–14, the data were consistent with a rise in incidence but the 95% CIs were wide (Table II).

DISCUSSION

Our results show that the incidence of testicular cancer overall has increased markedly since 1962. The trends were different for the 2 main adult age groups, however, resulting from differences by age for non-seminoma: a rise in incidence in young men and a decline in older men. Analysis by birth cohort also implied an increasing risk of non-seminomas for successive generations of men at ages under 55 and a decline at older ages. In contrast, there were increases in the incidence of seminomas in young and older men. Similar increases in testicular cancer incidence at young ages with cohort effects underlying them have been shown in other studies (*e.g.*, Schottenfeld *et al.*, 1980; Brown *et al.*, 1986; Østerlind, 1986; Bergström *et al.*, 1996; Zheng *et al.*, 1996; Weir *et al.*, 1999). In those studies that presented analyses by cell type (*e.g.*, Brown *et al.*, 1986; Østerlind, 1986; Zheng *et al.*, 1996; Weir *et al.*, 1999), as in the present study, the rise in incidence at young ages affected seminomas and non-seminomas to the same degree, suggesting that they may be of similar aetiology. The cohort data presented here appear to indicate that risks have stabilised in the most recent cohorts, a trend seen also in Scotland (Swerdlow *et al.*, 1998). In contrast, the rise in the incidence of testicular cancer at old ages observed in the present study, which was entirely due to

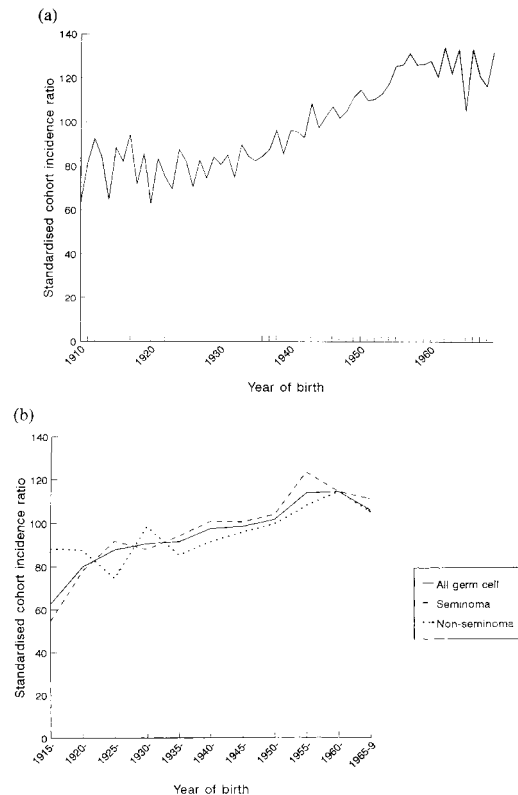


FIGURE 3 – Trends in incidence of testicular cancer by birth cohort. (a) Analyses by single year of birth for all histological types combined among men aged 0–54 years, England and Wales, 1962–1990. (b) Five-year cohort analyses by histological type among men aged 0–54 years, England and Wales, 1971–1989.

seminomas, has not been shown in other studies (*e.g.*, Brown *et al.*, 1986; Østerlind, 1986; Zheng *et al.*, 1996).

The completeness of the England and Wales national cancer registration scheme has probably not altered appreciably since 1971 (Swerdlow *et al.*, 1993). Therefore, although improved completeness could have accounted, at least in part, for the rises of testicular cancer in the 1960s, it is unlikely to do so for more recent years. Potential late registrations, yet to be entered into the national cancer registry files, are likely to have been of negligible effect as the analyses were conducted only to 1990 using data extracted from ONS files several years later. Incompleteness of histological confirmation also is unlikely as an explanation for the findings as the proportion of cancers with unknown histology was small. This was particularly true at younger ages, when most of the tumours

TABLE II – TRENDS IN THE INCIDENCE OF GERM CELL MALIGNANCIES OF THE TESTIS IN BOYS AGED UNDER 15 YEARS BY AGE AND HISTOLOGY, ENGLAND AND WALES, 1962–95

Age (years)	Histological type (n)	Rate		Mean annual percent change in rate (95% CI), 1962–1995	p value
		1962–70 ¹	1986–95 ¹		
0–4	Yolk sac (214)	2.32	3.66	1.7 (0.4–3.1)	0.01
	Teratoma (31)	0.89	0.45	–4.0 (–7.6 to –0.4)	0.03
5–9	All germ cell (247)	3.26	4.16	1.0 (–0.3–2.2)	0.13
	All germ cell ² (13)	0.12	0.12	–1.3 (–6.1–3.6)	0.56
10–14	All germ cell ² (38)	0.31	1.01	4.1 (–1.2–9.6)	0.13
All	Yolk sac (225)	0.81	1.30	1.7 (0.4–3.0)	0.01
	Teratoma (62)	0.04	0.05	–0.3 (–2.8–2.2)	0.80
	All germ cell (298)	1.24	1.77	1.3 (0.2–2.5)	0.02

¹Rates (per 10⁶) age-standardised by single year to the 1971 England and Wales male population. ²Analyses by cell type were not carried out because of the small number of cases in these age groups.

occurred. Moreover, similar results were obtained when the analysis was adjusted for tumours of unknown histology, though the method used assumed a similar degree of incompleteness for the various histological types. Lack of uniform criteria among pathologists and potential changes in diagnostic criteria over time might have affected the histology-specific results. However, the age-distribution curves from the present data were similar to those from another registry-based study in which histology was specially reviewed (Pike *et al.*, 1987). A review of the histology of all testicular tumours registered in the state of Victoria (Australia) during 1950–1978 made no difference to the histology-specific trends (Stone *et al.*, 1992).

In the present study, the increase in the incidence of testicular germ-cell tumours in young adults was paralleled by a trend in the same direction (although of smaller magnitude) in children under 15 years. This included a rise at ages 0–4 years, when the large majority of childhood germ-cell tumours occurred, though this was not statistically significant; the diverging trends by cell type at these ages are likely to be the result of time changes in nomenclature and coding practices. The trend at ages 10–14 was also consistent with a possible rise in risk and corresponds to the initial tail of the young adult peak. Relatively few studies have examined trends in children. No rises in the risk of childhood testicular cancers were observed in Connecticut from 1935 to 1976 (Schottenfeld *et al.*, 1980) or Denmark from 1943 to 1982 (Østerlind, 1986), but both of these studies were based on small numbers of cases. More recently, no statistically significant increases in the incidence of testicular cancer at ages 0–4 and 5–14 were found in the combined data from 3 Nordic countries (Denmark, Norway and Sweden) during 1958–1987 (Møller *et al.*, 1995), but the confidence interval was again very wide and consistent with a possible rise in risk. Moreover, in none of these studies were trends examined separately for testicular cancers of germ-cell origin. In contrast, a rapid increase in testicular cancer mortality in children, presumably reflecting a similar trend in the incidence of these tumours, was observed in Japan during 1947–1970 (Lee *et al.*, 1973).

The fact that the trends in young adults and children were in the same direction suggest that childhood and adult germ-cell tumours may have common risk factors and that these are likely to be of pre-natal origin (Henderson *et al.*, 1982). Undescended testes and other developmental urogenital abnormalities are the only well-established risk factors for testicular cancer in both adults (UK Testicular Cancer Study Group, 1994) and children (Li and Fraumeni, 1972; Swerdlow *et al.*, 1982). Although the apparent incidence of these conditions is rising (John Radcliffe Hospital Cryptorchidism Study Group, 1986), they are too uncommon to account for the entire rise in the risk of testicular cancers. There is evidence that the increase in incidence of disorders of the male reproductive tract in the last decades has been paralleled by a decline in semen quality (Carlsen *et al.*, 1992), though this has been

disputed (Bromwich *et al.*, 1994). Results from a recent population-based case-control study showed that paternity was associated with a decrease in the risk of subsequent testicular cancer, a finding which was regarded by the authors as being consistent with the hypothesis that male subfertility and testicular cancer may have some common risk factors (Møller and Skakkebaek, 1999). It has been proposed that all of these male reproductive abnormalities might be related to exposure to increased levels of endogenous and exogenous oestrogens during the first trimester of pregnancy, when the testis is being formed (Henderson *et al.*, 1982; Depue *et al.*, 1983; Sharpe and Skakkebaek, 1993).

Indirect evidence to support the hypothesis that pre-natal exposures may be important in the aetiology of testicular cancer comes from the fact that men who were born or were young boys during World War II in Denmark, Norway and Sweden had a lower risk of testicular cancer than previous and subsequent generations (Bergström *et al.*, 1996). The decline in risk for men born during the war years may be related to changes in diet and other lifestyle variables that may have affected oestrogen levels in the mother. Paradoxically, there was no similar decline in risk for generations born during World War II in Poland, the former East Germany and Finland, which may have been as affected or more so by the war than the other Nordic countries (Bergström *et al.*, 1996). In the present study, SCIRs were calculated by single year of birth to make it easier to unveil the effect of any short-term changes in exposure levels. Despite this, we did not find any fall in the risk of testicular cancer for generations born in England and Wales during World War II. Similarly, no decline was observed in Scotland (Swerdlow *et al.*, 1998). Although there were marked changes in the British diet during the war years, the levels of caloric intake never dropped as much as in the Nordic countries and the diet of pregnant women on the whole might even have improved. National distribution of free and cheap milk was implemented for expectant mothers in the 1930 and 1940s (MAFF, 1951). In interpreting the observed SCIRs it is important to keep in mind that because the overall (all years) data had to be used to calculate the expected values, the ratio of observed to expected will tend to be conservatively biased, particularly in the earliest and latest cohorts; therefore, real changes might have been under-estimated. Interpretation should also take into account that the experience for the most recent generations was based only on the (young) age groups that they have reached so far.

Post-natal factors may also have contributed to the observed rise in the incidence of testicular germ-cell malignancies at young adult ages and account, at least in part, for the fact that the increase was more marked at these ages than in children. Although the rise in the incidence of testicular cancer has been paralleled by a trend towards an earlier age at puberty, the evidence from analytic studies on the relation to age at puberty has been largely inconsistent. Some studies (Moss *et al.*, 1986; UK Testicular Cancer Study Group, 1994), but not all (Depue *et al.*, 1983; Swerdlow *et al.*,

1989; Gallagher *et al.*, 1995), have found an association with an early age of puberty. Another analysis found reduced risk for late puberty but not raised risk for early puberty (Møller and Skakkebaek, 1996). The increased risk of testicular cancer in tall men found in some studies (Gallagher *et al.*, 1995; Swerdlow *et al.*, 1989) suggests that nutrition and growth before puberty may also be important aetiological factors. Adult height has been increasing through the century (Floud *et al.*, 1990), and this trend could potentially be related to the rise in the incidence of testicular cancer in young adults. The finding of Møller *et al.* (1995) that the secular increase in the incidence of testicular cancer was particularly marked in boys aged 15–19 years would be consistent with a

possible role of peri-pubertal factors on the aetiology of this cancer. No similar finding was observed in our present study.

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