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**COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD,  
CONSUMER PRODUCTS AND THE ENVIRONMENT**

**COC Review of Testicular Cancer**

**Trends and Risk Factors: an Overview**

At the 2005 horizon scanning discussion, the committee decided to review the possible chemical aetiology of testicular cancer. As a first step, the Department of Health Toxicology Unit at Imperial College has prepared the attached overview of background information and risk factors in testicular cancer.

The review notes that well-established indicators of risk for testicular cancer are cryptorchidism and carcinoma *in situ* and that there is currently no agreement about the involvement of other factors in the aetiology of testicular cancer. Credible hypotheses that have been proposed involve *in utero* risk factors, maternal hormonal patterns and dietary practices.

Several reports have suggested that men engaged in some occupations may be at higher risk for testicular cancer. These include men working in white collar occupations, aircraft workers, leather workers, paper and printing workers, firefighters and men working in agriculture. However, there are conflicting views in the literature.

Members are asked whether there are any areas relating to chemical aetiology which it would be useful to review in more detail.

Secretariat  
February 2006

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# **Testicular Cancer**

## **Trends and Risk Factors: an Overview**

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**February 2006**

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**5.0 Summary**

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## **Introduction**

This review was requested by the Committee on Carcinogenicity of chemicals in food, consumer products and the environment (COC) as a general overview of testicular cancer. The COC is interested in the role of exposure to chemicals as possible risk factors for testicular cancer. Established risk factors for testicular cancer are cryptorchidism and carcinoma in situ. Apart from this, the aetiology of the disease is unclear; likely hypotheses that have been proposed involve hormonal patterns and dietary factors. Cancer statistics indicate that testicular cancer incidence is increasing, both in the UK and worldwide. This report discusses current patterns and trends in testicular cancer and considers possible causal factors for this disease.

## **Testicular Cancer Trends**

Data for the UK in this section are based primarily on recent publications by the UK Office for National Statistics (ONS) (UK data for these publications were based on ONS statistics covering the period 1950-1999). Data from the US is based primarily on data from US Surveillance, Epidemiology and End Results (SEER, 2005). The most recent data from ONS can be found on the website (<http://www.statistics.gov.uk/>). The most recent data from Cancer Research UK (CRUK) (2001 incidence data/2003 mortality data) are attached in Figure 1-7 and/or can be found on the CRUK website (<http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/>).

## **Prevalence**

Testicular cancer is the commonest cancer in men under 45 years old, accounting for 17% of all cancers occurring men below that age; slightly more than 90% of testicular cancer occur in men aged less than 45 (IARC, 2003). Ninety per cent of men diagnosed with testicular cancer in the three-year period 1990-92 were alive at the beginning of 1993, as were 88% of men diagnosed in the 10 years 1983-92 (Quinn et al., 2001). The prevalence of testicular cancer in Italy in 1992 was 103 per 100,000 (Micheli et al., 1999). The 5 year prevalence (number of living people with a diagnosis of testicular cancer made 5 or less years before the index date) was 18 per 100,000 (Micheli et al., 1999). Early age of diagnosis and the good prognosis that characterises cancer of the testis were the reason the authors state why the 5 year prevalence is low. The SEER database (2005) in the US reported that on January 1, 2002, in the United States there were approximately 164,009 men alive who had a history of cancer of the testis. This includes any person alive on January 1, 2002 who had been diagnosed with cancer of the testis at any point prior to January 1, 2002 and includes persons with active disease and those who are cured of their disease.

## **Incidence**

Testicular cancer is a relatively rare cancer worldwide, accounting for approximately 1-2% of all male cancers diagnosed (IARC, 2003). The international incidence of testis cancer varies considerably. Rates are highest in Scandinavian populations, and rates are also elevated among other populations in Europe or of European Ancestry. By contrast, Asian and African populations, including US blacks, experience very low rates (IARC, 2003). In Europe, the annual incidence rates (world age standardised) range between 7.3 (west) and 4.6 (south) per 100,000. (IARC). In New Zealand, USA,

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and Canada, the incidence is slightly lower than in Europe (ranging from 4.2 in Canada to 5.9 in New Zealand) (IARC and SEER). In the US, the age-adjusted incidence rate was 5.3 per 100,000 men per year. In Africa, the annual incidence rates are very low (less than 1 per 100,000), while in Asia and Japan the rates are less than 2 per 100,000. The incidence of testicular cancer has been increasing rapidly in Great Britain since 1975 (Figure 1, 2 and Table 1 from Cancer Research UK cancer stats) with an incidence rate of 6.5 in the UK for 2001-2003 (Cancer incidence and mortality in the United Kingdom 2001-03, ONS). There are approximately 2,000 new cases registered every year in the United Kingdom and testicular cancer incidence rates in Great Britain have more than doubled since the mid 1970s (Cancer Research UK statistics).

### **Survival**

Survival of testicular cancer is the highest of any cancer in men in the UK (Figures 3, 4, 5 and 6). The most recent figures for patients diagnosed in England and Wales during 1996-99 indicate one-year relative survival of 98 per cent and five-year survival of 95 per cent (ONS). Survival from testicular cancer in England and Wales in the early 1970s was 82% one year after diagnosis and 69% five years after (Power et al., 2001). As a result of the major advances in treatment, one- and five-year survival rose to 94% and 88%, respectively, in the early 1980s; there were only small further improvements in the late 1980s; however, for men diagnosed in 1991-93 one-year survival increased to almost 98% and five-year survival to almost 95%.

Five-year relative survival falls sharply with age: for men diagnosed under the age of 50 in 1991-93 it was 95%, but fell to around 60% for men aged 70-79 and further to under 30% in elderly men (80-99 years) in whom the cancer is rare. For cases diagnosed in 1986-90, survival was significantly better for men in the most affluent group: the gaps between them and men in the most deprived groups was over 3% points at one year after diagnosis and over 6% five years after. These are substantial differences, given the high overall survival rates. There was little variation in survival among the regions of the UK.

Testicular cancer is one of only a very small number of cancers for which survival in the UK was similar to – or better than – most other countries which participated in the EUROCORE studies. Survival is sharply dependent on stage at diagnosis: five-year survival is over 95% for stages I and II, about 85% for stage III, and only 70% for stage IV.

### **Mortality**

The mortality rate for testicular cancer in the UK for 2001-2003 was 0.3 per 100,000 men (ONS data and Cancer Research UK, figure 7 and table 2). The age-adjusted mortality rate from the SEER database (2005) was 0.3 per 100,000 men per year in the US. These rates are based on patients who died in 1998-2002 in the US. Death rates by race were: 0.3 per 100,000 men for whites, 0.2 per 100,000 men for blacks. From 1998-2002, the median age at death for cancer of the testis was 39.5 years of age. Approximately 2.1% died under age 20; 33.5% between 20 and 34; 28.8% between 35 and 44; 15.7% between 45 and 54; 7.5% between 55 and 64; 5.8% between 65 and 74; 4.6% between 75 and 84; and 1.9% 85+ years of age.

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### **Histology of Testicular cancer**

Testicular cancer can be divided into Germ Cell Tumors (GCTs) and non-Germ Cell Tumours (Figure 8). Germ Cell Tumour arise from the sex cells (germ cells) and 95% of all testicular tumours are germ cell tumours. Germ cell tumours in men are classified as either seminomas or nonseminomas. Seminoma is the most common testicular germ cell tumour, accounting for 40-50% of all such tumours. Seminomas are slow-growing, immature germ cells. Seminomas, when found, tend to be localized (i.e., only in the testicles), and they spread relatively slowly. The 2 main subtypes of seminomas are classical (or typical) seminomas and spermatocytic seminomas. Over 95% of seminomas are classical and usually occur in men between their late 30s and early 50s. The average age of men diagnosed with spermatocytic seminoma is about 55, which is 10 to 15 years older than the average age of men with typical seminomas. Nonseminomas, on the other hand, are more-mature germ cells and spread more quickly. Nonseminomas tend to develop earlier in life than seminomas, usually occurring in men between their late teens and early 40s. Nonseminomas are classified as one of three or four subtypes (embryonal carcinoma, teratoma, choriocarcinoma, and yolk sac tumour); their rate of spread varies somewhat, but they are treated similarly. The majority of nonseminomas have more than one cell type and are known as mixed germ cell tumours. When seminomas and nonseminomas are both present, the cancer is classified as nonseminoma. The distinction between seminoma and nonseminoma is the main factor in directing treatment. Pure seminomas are extremely radiosensitive, while nonseminomas have to be treated with platinum-based chemotherapy or surgery. Tumours can also arise in the supportive and hormone-producing tissues, or stroma, of the testicles. Such tumours are known as gonadal stromal tumours. They account for less than 5% of adult testicle tumours. The two main types are Leydig cell tumours and Sertoli cell tumours. Lymphoma is the most common secondary testicular cancer. Among men older than 50, testicular lymphoma is more common than primary testicular tumours.

### **Risk Factors For Testicular Cancer**

#### **Congenital Abnormalities**

##### **4.1 Cryptorchidism**

Cryptorchidism refers to the absence from the scrotum of one or both testes. This usually represents failure of the testis to move, to "descend," during fetal development from an abdominal position, through the inguinal canal, into the ipsilateral scrotum. It is the best established risk factor for testicular cancer and this abnormality is found in approximately 10 % of patients with TC and the overall relative risk reported in most case-control studies was between 5 and 10 (Pottern et al., 1985; Forman et al., 1990; Swerdlow et al., 1997) and in cohort studies the relative risk was between 5 and 7 (Prenner et al., 1996; Giwercman et al., 1987 and Pinczowski et al., 1991). In the UK Testicular Cancer Group study (1994a), a large interview based case-control study, undescended testis was a significant risk factors for testicular cancer. The overall odds ratio for a history of undescended testis was 3.82 (95% confidence interval 2.24 to 6.52). Age at correction in men with unilateral undescended testis also had a strong effect on the risk of cancer. Men who were successfully operated on before the age of 10 years did not have an increased risk (0.60 (0.22 to 1.65)) whereas those corrected at or after the age of 10 years or who had an uncorrected testis had a significantly

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increased risk (7.67 (2.30 to 25.53) for correction at 10-14 years; (infinity) (1.22 to (infinity)) for correction at ages older than 14 years, and 3.00 (0.97 to 9.30) if uncorrected). The odds ratio for men who had an undescended testis corrected at or after the age of 10 was significantly increased in comparison with men who had an undescended testis corrected before 10 years (6.75 (1.55 to 29.48)). A stronger association between a history of undescended testis and pure seminomas than non-seminomas has been reported in a number of studies (OR of 5.30 for seminomas and 3.0 for non-seminomas (Coupland et al., 1999); OR of 15.6 for seminomas and 5.3 for non-seminomas (Morrison, 1976); OR of 7.3 for seminomas and 3.6 for non-seminomas (Prener et al., 1996 and Stone et al., 1991). However, there have been a number of reports indicating similar risks associated with undescended testis in the two histological groups (Henderson et al., 1979; Moss et al., 1986; Swerdlow et al., 1987; Haughey et al., 1989; Gallagher et al., 1995 and Moller et al., 1996).

### **4.2 Inguinal Hernia**

Inguinal Hernia has been implicated as a risk factor for testicular cancer, although the findings are mixed. Inguinal hernias are intestinal bulges that have pushed through a weak spot in the inguinal canal, a triangle-shaped opening between the layers of abdominal muscle near the groin (Garner et al., 2005). Inguinal hernia is often associated with undescended testis. A number of studies have indicated an association between inguinal hernia and testicular cancer risk (Coupland et al., 1999; UK Testicular Cancer Group, 1994a; Haughey et al., 1989; Moller et al., 1996). The UK Testicular Cancer Study (1994) reported that inguinal hernia in the absence of undescended testis was significantly associated with testicular cancer (1.91 (1.12 to 3.23)), but the risk was confined to men who had a hernia diagnosed before the age of 15 years (2.64 (1.32 to 5.28)). Coupland et al. (1999) reported similar odds ratios for inguinal hernia for pure seminomas (OR = 1.6, 95% CI 0.88-2.93) and other tumours (OR = 2.39, 95% CI 1.28-4.46), however, when subdivided by age at diagnosis of hernia the risk associated with hernias diagnosed after the age of 15 was higher for non seminoma tumours than for pure seminomas (OR = 2.28 for non seminomas and 0.56 for seminomas). In the study by Swerdlow et al., (1987) an increased odds ratio for seminomas (OR = 3.8) was associated with childhood herniorrhaphy before the age of 15, whereas no association was found for non-seminomas. Similarly, Prener et al. (1996) reported an OR for hernias diagnosed before 15 years of age of 2.3 for pure seminomas compared with 1.2 for other tumors. Other studies found no association (Morrison, 1976; Moss et al., 1986; Schottenfield et al., 1980; Pinczowski et al., 1991 and Gallagher et al., 1995).

### **4.3 Carcinoma in situ**

Carcinoma in situ (CIS) of the testis is a distinct histologic pattern preceding the development of seminomatous and non seminomatous germ cell tumours of the testis and was first described by Shakkebaek in 1972. Sigg et al. (1984) described CIS as large cells with distinct nucleoli which in a typical pattern are located in a single row at the usually thickened basement membrane of seminiferous tubules. The link of CIS to testicular cancer was supported by the frequent observation of CIS in testicular parenchyma surrounding invasive cancer, as well as the development of invasive testicular germ cell cancer in patients whom CIS had previously been diagnosed (Hoei-Hansen et al., 2005). It is generally agreed that nearly all testicular cancer occurrences are preceded by the presence of CIS cells, with the exception of two rare

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tumour types: infantile germ cell tumors and spermatocytic seminoma, which occur in older men (Rorth et al., 2000). Muller et al. (1984) found that prepubertal testes may occasionally harbour CIS cells in low numbers and their morphology resemble normal adult CIS cells and normal infantile gonocytes, making prepubertal CIS difficult to diagnose. CIS cells stay quiescent during infancy followed by proliferation in puberty, due to hormonal stimulation, with subsequent progression into overt tumours. 50% of patients diagnosed with CIS of the testis develop invasive testicular cancer within 5 years, with 70 % of patients developing testicular cancer within 7 years (Giwerzman et al., 1988; von der Masse et al., 1986). It is assumed that all patients who harbour CIS cells at puberty will eventually develop testicular cancer (Rorth et al., 2000). Also the type of testicular cancer (seminoma or nonseminoma) is hypothesised to be linked with CIS. There is a higher probability of developing nonseminomatous testicular cancer if the transition from CIS to invasive cancer occurs at a young age. In contrast, seminomatous lesions are more likely to result from the progression of CIS at older ages (Rorth et al., 2000).

### **Maternal Risk Factors**

#### **4.4 Age**

There is conflicting evidence on whether maternal age is a risk factor for testicular cancer. Some studies have found older women to be associated with a 2-fold increase in testicular cancer risk (Wanderas et al., 1998 and Moller and Skakkebaek, 1997) but other studies have found no association (Swerdlow et al., 1982 and Weir et al., 2000). In a recent case-control study, Coupland et al. (2004) found a doubling in risk in men whose mothers were aged 15-19 years at conception compared to older mothers.

#### **4.5 Newborn Characteristics**

A number of studies have attempted to correlate newborn measurements such as birth weight and length of newborn and testicular cancer risk associated with maternal in utero environment. The length of a child at birth was found to be a non-significant risk factor for testicular cancer in two studies (Sabroe and Olsen, 1998 and Moller and Skakkebaek, 1997). However, another study examining testicular cancer risk factors in twins found no difference in the length of the affected twin compared with the non-affected twin (Swerdlow et al., 1999). There have been a number of studies examining the effect of birth weight and the risk of testicular cancer. An increased risk of approximately 1.5-2.0 fold among low birth weight children has been reported (Moller and Skakkebaek, 1997; Depue et al., 1983 and Coupland et al., 2004). However, no such association has been found in other reports (Weir et al., 2000; Sabroe and Olsen, 1998; Wanderas et al., 1998 and Rasmussen et al., 2003). In one study a significant trend was found with timing of delivery (Coupland et al., 2004). A 50 % increase in risk was observed in males born at least 2 weeks early, whereas those born late were seen to have a reduced risk. A similar observation was made by Weir et al. (2000).

#### **4.6 Maternal Oestrogen levels**

In 1979, Henderson *et al.* observed that factors such as high maternal weight and excessive vomiting during pregnancy are associated with high levels of endogenous maternal oestrogens such as estradiol. In a study by Giwerzman et al. (1988) nausea in

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pregnancy was associated with a four-fold increase in risk of testicular cancer. Most studies examining vomiting in pregnancy found no excess risk of testicular cancer (Weir et al., 2000; Petridou et al., 1997; Moss et al., 1986 and Henderson et al., 1979) or a protective effect (Moller and Skakkebaek, 1997 and Coupland et al., 2004).

### 4.7 Birth Order

Bernstein et al. (1986) reported higher levels of the hormone oestrogen in mothers during their first pregnancy. If the risk for testicular cancer was associated with maternal oestrogen levels during pregnancy, testicular cancer would be more common among first born than among later born children. Prener et al. (1992) tested this hypothesis in a case-control cohort of Danish boys. Compared with controls, cases were more often first-born and less often later born, with the gradient of risk significant for all testicular cancers ( $P=0.02$ ). A decreasing trend in relative risk with increasing birth order was observed for both testicular cancer seminomas and non-seminomas, but it did not reach statistical significance in either group. Similar results were obtained by a number of authors (Depue et al., 1983; Swerdlow et al., 1987 and Moller and Skakkebaek, 1996).

### 4.8 Family size and parity

Several studies have indicated that children of mothers with high parity have a decreased risk of testicular cancer when compared to children of formerly nulliparous mothers (Prener et al., 1986; Weir et al., 2000; Wanderas et al., 1998; Westergaard et al., 1996). Weir et al. (2000) also found an elevated risk associated with first compared to subsequent births but only among sons born to mothers under 25 years of age at conception. A trend of decreasing risk of testicular cancer with increasing number of previous pregnancies was also observed (Weir et al., 2000). Prener et al. (1992) found a trend of decreased risk with increasing pregnancy number for seminomas but not for the non-seminoma cancer group. Prener et al. (1986) also found an association between sibship size and risk for testicular cancer. Of cases, 13 % were in families of more than three children, while 20 % of controls had three or more siblings. However, a number of studies have found no clear trend with sibship size (Moller and Skakkebaek, 1997 and Coupland et al., 2004).

### 4.9 Twinship

It has been suggested that cancer of the testis may be associated with exposure to oestrogens and other hormones *in utero*. During twin pregnancies, the mean maternal levels of certain pregnancy associated hormones such as oestrogens, human chorionic gonadotropin and human placenta lactogen are higher than in singleton pregnancies (Braun et al., 1995). In addition, zygosity may influence in utero hormone levels. Compared with monozygotic twin pregnancies, dizygotic twin pregnancies can have higher levels of pregnancy hormones (Kappel et al., 1985), because each dizygotic twin has its own placenta, whereas monozygotic twin pairs have only one placenta. Braun et al. (1995) reported that, in contrast with the general Swedish population, dizygotic twins in the Swedish Twin registry had a significantly higher risk of testicular cancer. They found testicular cancer excess among the dizygotic twins (observed/expected [O/E] ratio = 1.6, 95 % confidence interval [CI] = 1.0-2.6) that was greater for men younger than 35 years (O/E ratio = 2.3, CI = 1.1-2.4) compared with older men (O/E ratio = 1.2, CI = 0.5-2.4). In a study that only included twins, Swerdlow et al. (1997) also found that dizygotic twins were at increased risk

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compared with monozygotic twins (odds ratio 1.5, [95 % CI 1.1-2.2]). When Swerdlow et al. (1997) analysed the data by histology, the raised risk in dizygotic twins was entirely consequent on an association with seminomas (odds ratio of 3.2, CI 1.6-6.5, p value = 0.001).

### **4.10 Familial Predisposition**

Tollerad et al. (1985), using data derived from a study of 225 men with testicular cancer, calculated that having a first degree relative with testicular cancer was associated with a 6 fold increase risk in comparison with the general population. Forman et al. (1992) reported that the relative risk for developing testicular cancer if a brother had previously been affected was 8.0 (95% CI 1.1-355.0) and a relative risk of 4.0 (95% CI 0.4-197.0) if a father has been previously affected. Using actuarial analysis, the estimated cumulative risk for brothers of cases developing testicular cancer was 2.2% (CI 0.6-3.8%) by the age of 50 years old, which results in a relative risk of 9.8 (CI 2.8-16.7) in comparison to the general population. Using a population based registry data on family relations, Westergaard et al. (1996) studied the risk of testicular cancer among brothers and fathers of patients with the neoplasm. Fathers of cases with testicular cancer experienced almost a two fold increase in developing testicular cancer themselves (RR =1.96; CI 95 % 1.01-3.43). Similarly, brothers of cases showed an increase risk of developing testicular cancer (RR = 12.3; 95 % CI 3.3-31.5).

### **4.11 Breastfeeding**

Coupland et al., (2004) found a borderline reduction in risk in men who had been breastfed for 6 months or more (odds ratio 0.65, 95% confidence interval 0.41–1.04). They suggested a duration-response relationship between breast-feeding and a lower risk of testicular cancer (P for trend = .05), but recall bias was possible because mothers provided information about method of infant feeding after the men were diagnosed at 15-49 years of age (Coupland et al., 2004). In a case-control study, Henderson et al. (1979) reported a RR value of 0.89 in boys that were breast fed (78 cases, p value = 0.43). A small case-control study (n = 37), by Mori et al., (1999) suggested that breast-feeding was associated with an increased risk of testicular cancer: the odds ratio per month of breast-feeding was 1.05 (95% CI = 0.99 to 1.11; p value = 0.1). A meta-analysis of data from two studies (Coupland et al., 2004 and Henderson et al., 1979) with 524 cases of testicular cancer in total provided only weak evidence of a lower risk of testicular cancer in breast-fed men (pooled RR = 0.82, 95% CI = 0.62 to 1.10; I<sup>2</sup> = 0%; P = .18) (Martin et al., 2005).

### **Personal Risk Factors**

#### **4.12 Age**

The age distribution of testicular cancer is distinct. Peak incidence occurs between the ages of 25-35 (Liu et al., 1999). A second, much smaller peak occurs after the age of 80 years of age (Wanderas et al., 1995). The age distribution is different of that for most cancers, which normally peak much later in life (Garner et al., 2005).

#### **4.13 Race**

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Testicular cancer incidence varies with race. Blacks and nonwhites have low rates of testicular cancer in comparison to Caucasian populations. Using the US Surveillance, Epidemiology, and End Results (SEER) database for the years 1998 to 2002, the incidence of TC is lower among Asian Americans and African Americans than among whites, with an incidence rate of 2.0 per 100,000 for Asians, 1.5 per 100,000 for Africans and 6.3 per 100,000 for whites (SEER, 2005). Although the incidence of TC is lower in black men than white, the incidence has increased by 70.4 % during the entire time period of 1973 -2001 (Mc Glynn et al., 2005). However, Asian-American and African-American males presented with higher stage disease at diagnosis.

### **4.14 Body Size**

Studies on the association of Body Mass Index (BMI) and testicular cancer report both negative associations (Akre et al., 2000; Davies et al., 1990; Petridou et al., 1997) and null associations (Garner et al., 2003; Swerdlow et al., 1989; UK Testicular Cancer Study Group 1994a; Gallagher et al., 1995). A population case-control based study of Danish men (Davies et al., 1990), using logistic regression analysis for all testicular cancers, did not find statistically significant differences in height, weight or body mass index (BMI) between cases (all testicular cancer) and controls were observed. The authors observed that there was a slight trend towards future victims of testicular cancer being lighter, smaller and thinner than unaffected controls rather than being obese. Akre et al. (2000) found that testicular cancer was inversely associated with testicular cancer and positively associated with height. The latter association was independent of BMI. Although Garner et al. (2003) found no overall association between BMI and testicular cancer risk, they did find within the non-seminomas subgroup an increased significant risk with BMI, with an OR of 3.66 (95 % CI 1.87-7.15) in subjects with BMI > 31.0. Gallagher et al. (1995) reported no correlation between weight or body mass and testicular cancer risk but did demonstrate a significant association with adult height and testicular cancer, with taller subjects being at a higher risk. Subjects taller than 180 cm had a significantly increased risk compared with those 174 cm or less (OR =1.5; CI 1.1-2.1). In Davies et al. (1996) dietary fat intake has been suggested to be a risk factor for testicular cancer and that this risk factor owes its association to cancer promotion in later life. During adolescence when the testes are in rapid growth, this may be a likely period when such a promotion could take place. Davies et al. (1996) proposed that men who develop testicular cancer in later life have a higher fat or calorie intake in adolescence and are thus bigger or more obese than unaffected men.

### **4.15 Hormonal Changes and puberty**

The United Kingdom Testicular Cancer Study Group (1994a) looked at three variables associated with age at puberty (age at starting shaving, age at voice breaking and age at first having nocturnal emissions). They found all significantly related inversely to testicular cancer risk. Moss et al. (1986) reported a twofold increase in testicular cancer risk in men who underwent puberty at ages less than 14 years. In a study by Swerdlow et al. (1989) no relationship was found between age of puberty and its timing in relation to other classmates and the risk of testicular cancer. Similarly, Depue et al. (1983) reported no significant association between the risk of testicular cancer and starting shaving and voice breakage.

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## **Lifestyle Risk Factors**

### **4.16 Dietary factors**

A nutritional etiology of testicular cancer has not been extensively examined, but a few studies have found associations with dietary fats, milk and dairy products, red meat and fruit and vegetables.

#### **Dairy Products**

Intake of milk and dairy products has been associated with increased testicular cancer risk (Garner et al., 2003; Davies et al., 1996; Ganmaa et al., 2002; Decarli et al., 1986). Cheese and dairy products contain high levels of fat, protein and calcium, all of which may have an effect on testicular cancer risk. Dairy products also contain high levels of the female sex hormones estrogens and progesterone and the major sources of animal-derived estrogens in the human diet are milk and dairy products, which account for 60–80% of the estrogens consumed (Hartmann et al., 1998). It may be hypothesized that estrogens or progesterone in milk and dairy products could be associated with the development of testicular cancer. Davies et al. (1996) tested the hypothesis that milk and dairy products are risk factors for testicular cancer in a case-control study undertaken in East Anglia. All the corresponding subjects completed a dietary questionnaire that included questions on their current and adolescent consumption of milk, dairy products, fruits and vegetables. Those with testicular cancer had consumed significantly more milk during adolescence than had controls. In a large case control study by Garner et al. (2003) based on the Canadian National Enhanced Cancer Surveillance System, the authors also examined the relationship between dietary intake and testicular cancer risk. Data was collected from 601 cases of testicular cancer and 744 population based controls collected in 8 Canadian provinces between 1994-1997. Data was collected through a 69 item food frequency questionnaire and 17 food groups, 15 nutrients and 4 individual foods were examined. Data analyses were performed for the total study group and for the two major histological subtypes: seminomas and non-seminomas. Garner et al. (2003) found that dairy products but not milk consumption were significantly associated with increased testicular cancer risk. Dairy products food group was disaggregated into specific foods and smaller groupings of foods. Cheese intake demonstrated a strong association with testicular cancer risk. The risk associated with the highest quintile of cheese intake was most notable within the total sample (OR = 1.87) and the non-seminoma samples (OR = 1.97), but was moderately attenuated in the seminoma subgroup (OR = 1.43). Ganmaa et al. (2002) performed a correlation analysis between testicular cancer incidence and mortality data for 42 countries, provided by IARC (1988-1992) and with dietary variables, provided by the Food and Agricultural Organisation (1961-1990). They found that cheese was most closely correlated with the incidence of testicular cancer ( $r = 0.804$ ), followed by animal fats ( $r = 0.77$ ) and milk ( $r = 0.741$ ). Concerning the years when milk was consumed, the correlation coefficient was highest for cheese consumption in the 1961-1965 period. Using Stepwise multiple-regression analysis to clarify the food products affecting testicular cancer, Ganmaa et al. (2002) found that milk + cheese made a significant contribution to increasing incidence of testicular cancer around 1990 (standardised regression coefficient [R] = 0.654).

#### **Meat and meat products.**

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A number of studies have investigated the possible correlation between meat consumption and testicular cancer. Ganmaa et al. (2002) found that meat intake, expressed as animal fats ( $r = 0.777$ ), was associated with an increased risk of testicular cancer. Similar results were obtained by Decarli et al. (1986), Sigurdson et al. (1999) and Gallagher et al (1995) where an increased association was found between meat intake and testicular cancer. Garner et al. (2003) also found that luncheon meat intake was associated significantly with testicular cancer risk in the total sample in the highest intake quintile (OR = 1.49; 95% CI = 1.01-2.19) and in the non-seminoma subgroup (OR = 2.11; 95% CI = 1.09-4.08). Results from Garner et al. (2003) did not show an increased risk in relation to meat intake ( $p$ -trend = 0.98) other than for luncheon meats.

### **Fruits and Vegetables**

Mixed results have been found for fruit and vegetable consumption with increased incidence of testicular cancer. In a case-control study by Davies et al. (1996) cases had a tendency to consume fewer apples, oranges and vegetable and fruit salads than population controls but more than cancer controls. However, the differences were not significant and were possible due to social class effect. Gallagher et al. (1995) found that the consumption of green vegetables was inversely related to the incidence of testicular cancer. Garner et al. (2003) found no association between fruit and vegetable consumption and increased testicular cancer risk. A protective effect was not identified for either food group by Garner et al. 2003; Bonner et al. (2002) and Sigurdson et al. (1999).

### **Nutrients**

No nutrients were associated consistently with testicular cancer risk, either in the total sample or within histological sub-groups (Garner et al., 2003). The ORs were consistently elevated for all levels of calcium intake although statistical significance was borderline. Within the non-seminoma subgroup, an increase in risk was observed with increasing intake of calcium ( $p$ -trend = 0.04), with an OR of 1.94 for the highest quintile of intake (Garner et al., 2003). Bonner et al. (2002) carried out a hospital based case-control study of testicular cancer and selected nutrients. Overall, Bonner et al. (2002) did find that vitamin E intake was suggestive of a reduced risk for mixed germ cell testicular cancer (OR=0.36 95% CI = 0.01-1.31). A similar reduction of risk was noted for non-seminomas (OR = 0.51, 95% CI 0.15 -1.76), whereas in seminoma, vitamin E intake was suggestive of an increased risk (OR = 2.94, 95% CI 0.99-8.78). Total energy intake demonstrated a significant increasing trend in risk with increasing intake for all three groups (high intake odds ratio [OR] = 1.55; 95 % CI 1.08-2.21;  $p$ -trend = 0.02). Carbohydrate intake exhibited a marginally significant effect in the non-seminoma group ( $p$ -trend = 0.05). All of the ORs associated with higher carbohydrate intake were below 1.0, reaching 0.5 for the highest quintile of intake. Garner et al., (2003) found no effect on risk associated with fat intake. However, in their hospital based case-control study, Sigurdson et al. (1999) found an association between fat intake and nonseminoma testicular cancer (OR =6.3, 95% CI 1.9-20.5), but not for seminoma (OR = 1.9, 95% CI 0.6 – 5.5). These findings were non consistent with the results of Bonner et al. (2002) where a suggestion of an association between fat intake and seminomas, but not non-seminomas was observed.

### **4.17 Physical activity**

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The UK Testicular Cancer Group (1994b) investigated the effects of physical activity on testicular cancer risk. They grouped sporting activities into broad categories; contact sports (football, rugby, hockey, American football, lacrosse); racquet sports; water sports; cycling and horse riding; athletics/cricket, baseball and rounders and martial arts. The playing of contact sports 1 year prior to diagnosis had an associated OR of 0.73 (95 % CI 0.55-0.97). At age 20, the odds ratio for playing contact sports was 0.80 (95 % CI 0.64-1.00). Water sports at the age of 16 and 20 were also protective (OR = 0.74; 95% CI 0.58-0.96, at age 16 and OR = 0.74; 95 % CI 0.56 – 0.98 at age 20). Athletic activity and martial arts were also protective. Cycling, horse riding, racquet sports and cricket, baseball and rounders were unrelated to testicular cancer risk (UK Testicular Cancer Group, 1994b). Gallagher et al. (1995) also found that moderate to high level of recreational activity was associated inversely with testicular cancer risk (OR = 0.6; 95% CI = 0.5-0.8). In a population-based cohort study of 53,242 men in Norway, Thune and Lund (1994) found no evidence for any association between physical activity and testicular cancer regardless of physical activity at work or recreation. However, Coldman et al. (1982) has suggested that physical activity acts as a persistent trauma to the scrotum and thus increases the risk of testicular cancer. They found an increased association between cycling and horse riding and testicular cancer risk (Coldman et al., 1982). Analysis of 212 cases and 251 controls by Srivastava and Kreiger (2000) revealed that relatively high frequency of participation in moderate and strenuous recreational activity in the midteens may have an adverse effect on risk of testicular cancer (odds ratio = 2.36, 95% confidence interval: 1.20, 4.64 for moderate activity of greater than five times a week compared with three times or less a month and odds ratio = 2.58, 95% confidence interval: 1.14, 5.85 for strenuous activity of greater than five times a week compared with less than once a month).

### **4.18 Environmental Temperature**

The extra abdominal position of the testes makes them vulnerable to the effect of variation of environmental temperature. Clemmesen et al. (1969) suggested that variation in temperature may be involved in temporal and geographic differences in testicular cancer. The results from epidemiological studies linking increased scrotal temperature and testicular cancer are inconclusive. Loughlin et al. (1980) reported that the wearing of jockey-type underpants increase the risk of testicular cancer. However, Brown et al. (1987); Haughey et al. (1989) and Karagas et al. (1989) found no such association.

### **4.19 Socioeconomic Status**

A number of studies have investigated the association of testicular cancer and socioeconomic status (Pearce et al., 1987; Swerdlow et al., 1988; Graham and Gibson, 1972; Ross et al., 1979). In almost all studies an association with high socioeconomic status has been reported.

### **4.20 Marital Status**

A number of studies have examined the association between marital status and the risk of testicular cancer. Most studies have found no association (Henderson et al., 1979; Graham et al., 1977; Morrison et al., 1976; Graham and Gibson, 1972) but Davies et al. (1981) found an increased risk for single men.

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### 4.21 Disease and viral exposure

Mumps orchitis has been studied in relation to testicular cancer in a number of papers (Brown et al., 1987, Mills et al., 1984; Petridou et al., 1997; Stone et al., 1991; Moller and Skakkebaek, 1999; UK Testicular Cancer Group, 1994b). The majority of the papers have failed to demonstrate a significant association with testicular cancer (Moller and Skakkebaek, 1999; UK Testicular Cancer Group, 1994b; Stone et al., 1991 and Petridou et al., 1997). A case-control study of 271 men with testicular cancer and 259 controls conducted in the Washington, DC area found an excess risk associated with mumps orchitis (RR = 5.8, CI = 0.7-129.7) (Brown et al., 1987)

### 4.22 Vasectomy

In the UK Testicular Cancer Group study, Forman et al. (1994) reported that there was no overall association between testicular cancer and having had a vasectomy (1.09 (0.77 to 1.52)). Similar results were reported by Rosenberg et al. (1994). A computerised record linkage study of cohort of men with vasectomy and comparison of cancer rates with those in the whole Danish population by Moller et al. (1994) did not find an increased incidence in testicular cancer (70 cases; standardised morbidity ratio 1.01 (95% confidence interval 0.79 to 1.28)).

## **Chemical Risk Factors**

### 4.23 Cigarette smoking

A number of studies have investigated the possible correlation between cigarette smoking and testicular cancer. Some studies report no association (Garner et al., 2003; Thune and Lund, 1994, Coldman et al., 1982, Moller et al., 1996 and Henderson et al., 1979), while two studies (Gallagher et al., 1995 and Srivastava and Kreiger, 2004) have suggested an adverse association between smoking and testicular cancer. In a case control study with 686 cases of testicular cancer (mean age of cases 35.2 years, controls 38.8 years, range 20-54 years) by Garner et al. (2003), the authors examined the relationship between smoking and testicular cancer. They found no increased risk of testicular cancer associated with any level of smoking. In a case control study of 510 men with testicular cancer aged 15-79 years and 996 randomly selected age matched controls in British Columbia and Alberta, the risk of testicular cancer was elevated somewhat in smokers with an 11 + pack-year history, although the association was not significant (Gallagher et al., 1995). The UK Testicular Cancer Group study of 794 men, aged 15-49 years reported little evidence of a relationship between testicular cancer and smoking. A slight elevated risk was found among ever smokers relative to non-smokers (OR 1.18 (95% CI 0.96-1.46)). There was only weak evidence of an increasing trend in relative risk with smoking intensity but none with age at start of regular smoking (UK Testicular Cancer Group, 1994b). Data collected between 1995 and 1996 and derived from the Enhanced Cancer Surveillance study, a national case-control study of 212 case and 252 control men aged 20-74 years from Ontario, Canada examined the relationship between smoking and testicular cancer (Srivastava and Kreiger, 2004), where a moderate positive association was observed between smoking and testicular cancer. The study found that smoking to any degree was suggestive of an increased risk and statistically significant results were observed among those who smoked between 12-24 pack years [OR 1.96 (95% CI 1.04-3.69)] or more [ $> 24$  pack-years, OR 2.31 (95% CI 1.12-4.77)] and among those who smoked about  $\geq 21$  years [OR 3.18 (95% CI 1.32 – 7.64)] relative to non smokers.

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#### **4.24 Maternal Cigarette smoking**

Studies that have assessed maternal smoking during pregnancy and testicular cancer risk have yielded negative or contradictory results. Four studies have found no association (Chen et al., 2005; Moller and Skakkabaek, 1996; Swerdlow et al., 1987 and Henderson et al., (1979), one found a non significant 30% increase in testicular cancer risk if the mother reported ever *versus* never smoking during pregnancy (Brown, 1986), and the most recent study reported an increased risk for nonseminoma among the offspring if the mother smoked 1–11 cigarettes/day during gestation but a decreased risk for higher consumption (Weir et al., 2000). The same study also reported a negative association between maternal smoking and seminoma in the offspring (Weir et al., 2000). However, a positive association between parental lung cancer and testicular cancer in the offspring has been suggested in five of six studies (Swerdlow et al., 1987; Heimdal et al., 1996; Spermon et al., 2001; Dong et al., 2001; Kroman et al., 1996; Kaijser et al., 2003), and in two of these studies, the association was confined to the mothers (Swerdlow et al., 1987 and Heimdal et al., 1996). Given that smoking is the predominant cause of lung cancer, these reports suggest that smoking during pregnancy may play a role in testicular carcinogenesis.

#### **4.25 Alcohol**

##### **Alcohol consumption**

The COC concluded in 1995 that there was no convincing evidence of an association between drinking alcohol and cancer of the testis (COC, 1995).

##### **Maternal Alcohol Consumption**

Weir et al. (2000) found no statistical significant difference between case mothers and control mothers with respect to number of alcoholic drinks consumed per week and the risk of testicular cancer ( $P = 0.23$ ). Chen et al. (2005) found no evidence that a childhood Germ Cell Tumour (GCT) was related to prenatal exposure to alcohol. However, Brown et al. (1986) found exposure to alcohol during pregnancy was associated with a statistically significant increase in testicular cancer risk.

#### **4.26 Agent Orange (mixture of 2,4-dichlorophenoxyacetic acid and 2,4,5 trichlorophenoxyacetic acid)**

An association between military service in Vietnam and testicular cancer has been reported by Tarone et al., (1991). A case-control study investigated whether there was an association between Agent Orange exposure during service in Vietnam and an increased risk of testicular cancer (Bullman et al., 1994). It has been reported that large scale spraying of the herbicide Agent Orange was conducted by US Air Force in South Vietnam to destroy crops and defoliate areas believed to encompass enemy installations (Bullman et al., 1994). Among the branches of service, only Navy personnel had a statistically increased risk of testicular cancer (OR = 2.6, 95% CI 1.08-6.24). However, the authors suggest that other risk factors such as race and aviation fuel may have been a potential confounder for the positive association. Risk of testicular cancer was not significantly increased for ground troops, those on combat duty or those working close to the spray tracts (Bullman et al., 1994).

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#### **4.27 Plastics and Polyvinyl Chloride**

Occupational exposure to PVC was assessed by Hardell et al. (1997) and Ohlson and Hardell, (2000) in a case-control study using self-administered questionnaires. Of the 163 cases, 148 (91%) answered the questionnaire compared with 314 (87%) of the 363 controls finally enrolled. In total, 44 subjects reported exposure to plastics, mostly styrene. Exposure to PVC was confirmed by contact with employers or production managers. Hardell and Ohlson (2000) reported an increased risk of testicular cancer for plastic workers with an OR = 2.9, 95% CI 1.3 - 6.5. Exposure to PVC resulted in an increased risk for all testicular cancer cases (OR = 6.6, 95% CI 1.4-32.0) and six of the seven exposed cases had seminomas. The risk increased further if cases of self-reported cryptorchidism and orchitis were excluded (OR = 14.0, 95% CI 1.7 –114) for all cases of testicular cancer. For the other plastics (styrene, urethane, acrylate and unspecified plastics), no significant increase was found. Exposure to PVC entails exposure to antioxidants (butylated hydroxytoluenes, thiobisphenols, and phosphates), plasticizers (phthalates), lubricants (fatty acids and streates), fillers (metal oxides), pigments (metal oxides and sulphates) and flame retardants (chloroparaffins) as well as various stabilizers to protect against heat, biodegradation and UV-light (Westberg et al., 2005). In 2004, Hardell et al. performed a follow-on study of 791 case-control matched pairs with the whole Swedish male population in the years 1993-1997 as the study base. In total 981 (592 seminomas; 389 non seminomas) aged 20-75 years old who had reported to the Swedish Cancer Registry during 1993-1997 took part in the study. Overall exposure to PVC plastics gave an OR of 1.35, 95% CI 1.06–1.71. This increased to 1.45 (95% CI 1.06-1.98) with > 10 year latency period. These results did not indicate an association between exposure to PVC and testicular cancer risk. Using the same dataset as Hardell et al. (2004) a more detailed questionnaire to improve the exposure-response analysis was given to the subjects (Westberg et al., 2005). The questionnaires regarding work histories and employment in PVC production, manufacturing and handling of PVC products were completed. According to expert assessments 360 workers were exposed to PVC. 26% of cases compared to 21% of controls had been exposed to PVC. A small but statistically significant overall risk of testicular cancer was observed (OR =1.3 95% CI 1.05 – 1.69). However, the authors did not find an exposure-response relationship and therefore no association between PVC exposure and testicular cancer could be established (Westberg et al., 2005). In a Danish case-control study of 3,745 cases identified in a Danish pension register, no association between exposure to plastics including PVC and testicular cancer risk was observed (ever exposed 16 and 75 years at diagnosis with plastics in general gave an OR =1.0, 95% CI 0.8-1.2; mainly PVC exposure gave an OR =0.7; 95 % CI = 0.5-1.2) (Hansen et al., 1999). In a cohort study of 428 men working in a plastics plant in Norway, Langard et al. (2000) did not find any increase in testicular cancer (1 case identified) in workers exposed to PVC. Similarly, no excess cases of testicular cancer was observed in a cohort study of 2,031 male workers at a polyvinyl chloride (PVC) processing plant who had been employed for at least 3 months during the period 1945-1980 in Sweden (Hagmar et al., 1990).

#### **4.28 Endocrine-disruption chemicals**

The IPCS has produced a detailed review of endocrine disruptors and their effect on male reproductive health and this review is available online at [http://www.who.int/ipcs/publications/new\\_issues/endocrine\\_disruptors/en/](http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/)

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The endocrine system is a complex network of glands and hormones that regulates many of bodily functions, including growth, development and maturation, as well as the way various organs operate. The endocrine glands, including the pituitary, thyroid, adrenal, thymus, pancreas, ovaries, and testes, release carefully-measured amounts of hormones into the bloodstream that act as natural chemical messengers, travelling to different parts of the body in order to control and adjust many functions. An endocrine disruptor is a synthetic chemical that, when absorbed into the body, either mimics or blocks hormones and disrupts the body's normal functions. The major groups of environmental chemicals, reported to have estrogenic effects are organochlorine pesticides, PCBs, dioxins, alkylphenol polyethoxylates, phytoestrogens, and other xenoestrogens. It has been hypothesised that a high level of oestrogen, especially during foetal life, may disturb the endocrinological control of the male foetal urogenital organs and that an increase in human exposure to compounds with estrogenic properties has taken place during the past half-century. The rise in estrogenic exposures has been proposed to originate from different sources such as the introduction of synthetic estrogens in the late 1960s as oral contraceptives (OC), changing diet with a higher content of phytoestrogens as in soy products, increasing dietary products based on cow's milk and a rise in industrial chemicals containing oestrogenic properties (xenoestrogens).

### **Prenatal Diethylstilbestrol (DES)**

There has been some evidence that variations in the concentration of maternal estradiol are associated with an increase risk of testicular cancer. Diethyl stilbestrol (DES) is a synthetic non-steroidal oestrogen and was used for the purpose of improving pregnancy outcomes. An IARC report in 1989 found no conclusive evidence to indicate an increased risk of testicular cancer in men exposed to DES (Vessey, 1989), although the incidence of cryptorchidism is a well-known risk factor for testicular cancer and has been observed more frequently in this group (Stillman, 1982).

There have been a number of case-control studies that evaluated prenatal hormonal risk factors for testicular cancer (Henderson et al., 1979; Depue et al., 1983; Schottenfeld et al., 1980; Brown et al., 1986; Moss et al., 1986 and Gershman et al., 1988, Strohsnitter et a., 2001). Strohsnitter et al. (2001) investigated the association between prenatal DES exposure and cancer risk in men via prospective follow-up of four cohorts of men (3613 men in total) whose DES exposure status was known. The testicular cancer rate among the DES-exposed men was higher than the national average but the elevation did not reach statistical significance (SIR 2.04; 95% CI 0.82-4.20). Similarly, the rate of testicular cancer among the DES exposed men for all the four cohorts was higher than unexposed men in the study (RR = 3.05, 95% CI 0.65 – 22.0) but this increase was not statistically significant. In a study by Henderson et al. (1988), 131 testicular cancer patients, under 40, and their matched controls were analysed. In 6 cases of cancer the mothers had been treated with hormones during pregnancy, whereas only one mother of the control cases had received any hormones. The difference was not statistically significant, but if another factor, nausea, was combined with hormone treatment, they formed a significant risk factor (relative risk 4.33).

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In the case-control study of Depue et al. (1983), 108 testicular cancer patients, under age 30, were studied. Mothers of 9 cancer patients had been treated with hormones (2 with DES, 1 with oestrogen, 1 with progestin, and 5 had pregnancy tests consisting of a single injection of an oestrogen-progestin preparation), whereas 2 controls had either oestrogen treatment or a pregnancy test. The relative risk (8.00) was significantly increased in the men exposed to hormones ( $p=0.02$ ).

In a case-control study of 273 testicular cancer patients from northern California (Moss et al., 1986), no association was found with the mother's hormone exposure or DES exposure. Mothers of 9 cases and 10 controls had been treated with hormones (OR 0.9). Four of the case mothers and 2 control mothers were exposed to DES. The case-control study of Schottenfeld et al. (1980) was based on questionnaires received from 190 testicular cancer patients (The Sloan Kettering Cancer Hospital, New York), 166 hospital controls, and 143 neighbourhood controls. There was no statistically significant association between hormone treatment and cancer: 5.8% ( $n=11$ ) of cases had been exposed to DES or other hormones, whereas 2.1% ( $n=3$ ) of the neighbourhood controls and 2.5% ( $n=4$ ) of the hospital controls had received exogenous hormones.

Furthermore, two other case control studies (Brown et al., 1986 and Gershman et al., 1988) failed to identify any association between prenatal DES exposure and testicular cancer risk. In a study comprising 202 cancer cases and 206 controls, Brown et al. (1986) found no excess risk associated with the use of hormones during pregnancy: mothers of 4 cancer patients and 5 control mothers had received hormone treatment. Two mothers in each group had been treated with DES, 1 control with oestrogen, 1 case with progesterone, 1 in each group had a hormone pregnancy test, and 1 control had an unidentified hormone treatment. However, it should be noted that 19 mothers in this study were medicated for bleeding problems, but only 2 (both case mothers) mentioned a specific hormone used; 13 of the treated were case mothers and 6 were control mothers. Similarly, a case-control study of 79 testicular cancer patients from the Connecticut Tumour Registry failed to show any increased cancer risk in men exposed to DES (Gershman et al., 1988).

### Organochlorines

The most widespread organochlorines in the environment and in human tissue are Polychlorinated Biphenyls (PCBs), Dichlorodiphenyltrichloroethane (DDT) and its degradation product Dichlorodiphenyldichloroethylene (DDE). Reports from animal studies by Kelce et al. (1997) indicated that DDE inhibits androgen binding to the androgen receptor, androgen-induced transcriptional activity, and androgen action in developing, pubertal and adult male rats. The results suggest that abnormalities in male sex development induced by DDE and related environmental chemicals may be mediated at the level of the androgen receptor. In a report by Cocco and Benichou (1998), the authors found no evidence of a positive association between testicular cancer mortality with DDE environmental contamination. Hardell and co-workers (2003 and 2004) investigated serum levels of 38 PCBs, DDE, hexachlorobenzene (HCB), and chlordanes, in 61 cases with testicular cancer and 58 age-matched controls. Case and control mothers were also asked to participate and 44 case mothers and 45 control mothers agreed. No significant differences in organochlorine levels were observed between testicular cancer cases and controls. However organochlorine

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levels were higher in case mothers than controls (the sum of PCBs yielded an odds ratio (OR) of 3.8; 95% confidence interval (CI), 1.4–10, calculated using the median concentration for the control mothers as cut-off value) (Hardell et al., 2004). Further analysis in Hardell et al., (2004) for 37 congeners of PCBs revealed that case mothers had significantly increased concentrations of a number of PCB congeners. Grouping of PCBs congeners according to structure and biological activity yielded for oestrogenic PCBs an OR = 2.4, 95% CI 0.95-6.0, enzyme-inducing PCBs an OR = 2.6 95% CI 1.03-6.5 and toxic equivalents yielded an OR = 3.3, 95% CI 1.3-8.4. The authors suggest that their results from these two studies indicate that in utero exposure to endocrine disruptors such as PCBs may be of aetiological significance for testicular cancer (Hardell et al., 2005).

### **Phytoestrogens**

The fact that dietary factors may be associated with testicular cancer lead to an investigation by Walcott et al. (2002) of phytoestrogen intake and effect on testicular cancer risk. Phytoestrogens have oestrogenic properties that are known to modulate hormone levels in the body (Aldercreutz, 1995 and Rose, 1993). Using a hospital-based case-control study of 159 testicular cancer cases diagnosed between 1990 and 1996 and 136 adult friend-matched controls Walcott et al. (2002) did not find any association between dietary phytoestrogens consumption and increase or decrease testicular cancer risk in young men. However, Joffe (2005) commented that epidemiological evidence on the effect of phytoestrogens on testicular cancer may come from populations with a high soy intake, notably the Chinese and Japanese, where testicular cancer is rare (IARC, 2003).

### **Bisphenol-A and the phthalate esters**

The agents most extensively tested for oestrogenic properties are phthalates, bisphenol A and nonylphenols. Phthalates are extensively used in polyvinyl chloride (PVC) as plasticizers and are widely spread in the environment. The phthalates reported to have the strongest oestrogenic potencies are butyl benzyl phthalate (BBP) and di-n-butyl phthalate (DBP), being  $10^6 \pm 10^8$  times less potent than the natural hormone 17- $\beta$ -oestradiol (Jobling et al., 1995; Harris et al., 1997). The most commonly used phthalate, di-(2-ethylhexyl)phthalate (DEHP), has an even weaker, if any, oestrogenic effect compared to the effect of 17- $\beta$ -oestradiol. Bisphenol A is used as an antioxidant and co-stabilizer in PVC-products. It has an oestrogenic potency estimated to be a few orders of magnitude stronger than that of phthalates but still  $10^3 \pm 10^4$  times weaker than that of 17- $\beta$ -oestradiol (Steinmetz et al., 1997; Colerangle and Roy, 1997). Occupational exposure to PVC has been associated with an increased risk of testicular cancer (Hardell et al., 1997 and Ohlson and Hardell, 2000). The authors have added an interpretation that phthalates used in PVC as plasticizers have estrogenic properties that could promote the growth of endocrine sensitive tumour cells (Ohlson and Hardell, 2000) and thus be the causative agent.

### **Occupational Risk Factors**

A large number of reports have suggested that men engaged in some occupations may be at higher risk of testicular cancer.

#### **4.29 White Collar or professional Occupations**

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White collar workers and professional occupations have been associated with a moderately elevated risk of testicular cancer in a number of reports (Van Den Eeden., 1991; Mustacchi and Millmore, 1976; Pearce et al., 1987; Davies., 1981, Hayes et al., 1990). Hayes et al. (1990) found a significant elevation in risk for seminomas among a broad occupational category of professional (age adjusted OR = 2.8 (95% CI 1.4-5.4). Two and three-fold increases in risk were seen for all subcategories of professionals, with the risk of teachers and administrators being significantly elevated. In a case-control study, Van Den Eeden et al. (1991) found in men reporting ever having been an administrator or manager (age adjusted RR =1.5 95% CI 1.1-2.2), salesmen or buyers (age adjusted RR =1.5 95% CI 1.0-2.2), physicians and other health-diagnosing occupations (age adjusted RR = 5.5, 95% CI 1.1-26.3) and other health treatment workers such as physical and respiratory therapists (age adjusted RR =15.7, 95% CI 1.7 - 145.7), to all have elevated relative risks. In a perspective study of white and nonwhite men in San Francisco, Mustacchi and Millmore (1976) found that 10% of testicular cancer cases and only 4 % of controls were managers. Findings from a case-control study in New Zealand involving 427 male patients with testicular cancer registered during the period 1979-1983, in a broad category of administrative/managerial occupations, Pearce et al. (1987) found no excess risk of testicular cancer (1.09, 95 % CI 0.6-1.7). Swerdlow and Skeet (1988) also found administrators and managers to be at elevated risk of testicular cancer, in a case-control study using data from the files of the South Thames Cancer Registry in the UK. Analysis from an interview based case-control study by Swerdlow et al. (1991) found that administrators and managers (age adjusted OR 1.33, 95% CI 0.74-2.42), professional and related workers (age adjusted OR 1.29, 95% CI 0.90-1.84) and clerical workers (age adjusted OR = 1.25, 95% 0.80 -1.96). Pearce et al. (1987) found that sales and service managers (RR= 4.8, CI 95% 1.5-15.4) and production supervisors (RR =2.8, CI 95 % 1.0-8.1) to have a higher risk of testicular cancer. Similar results were obtained by Hayes et al. (1990) and Van Den Eeden et al. (1991) for sales managers and service workers. However, in a study conducted at a referral oncology hospital, Mills et al. (1984) reported no association between the occupation of salesman and testicular cancer.

### 4.30 Blue Collar Occupations

Hayes et al. (1990) found no excess risk of seminomas associated with employment in the broad occupational group of blue collar workers. However, the risk for non-seminomas is marginally elevated among those who ever held blue collar jobs (age adjusted OR = 1.4 95% CI 0.8-2.3) and is significantly elevated among production workers (Hayes et al., 1990). The risk of non-seminomas was consistently elevated for all subcategories of production workers: metal and plastics (age adjusted OR = 1.6, 95% CI 0.8 - 3.1), wood (age adjusted OR = 3.0, 95 % CI 0.7 – 28.4), printing (OR = 2.4, 95% CI 0.5 – 12.9), textile (age adjusted OR = 1.8, 95% CI 0.3 - 10.4). Among blue collar workers, Van Den Eeden et al. (1991) found a greater than two fold increase in risk for electricians (age adjusted RR = 2.8, 95% CI 1.2 – 6.4) and an elevated risk for sailors, deckhands, pilots and fishermen (age adjusted RR = 3.1, 95% CI 1.2 - 7.9) and labourers and handlers (RR =1.5, 95% CI 1.0 - 2.2). These results are in contrast to the results of McDowall and Balarajan, (1986) and Pearce et al. (1987). McDowall and Balarajan, (1986) did not find an association between mortality from testicular cancer and working as an electrician (age adjusted RR = 0.9, 95% CI 0.6 – 1.3) or working as a merchant seaman. Pearce et al. (1987) did not find

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an association for labourers, production or transport workers (age adjusted RR =1.05, 95%CI 0.83 -1.33).

### **4.31 Leather workers and dimethylformamide**

Between 1982 and 1984 in Fulton County, New York, a cluster of testicular cancer was observed in three leather tannery workers who performed essentially the same job in the same plant for the same period of time. The first case occurred in 1982, when embryonal cell carcinoma was diagnosed in a 31-year-old worker who had begun work in the leather tanning 13 years earlier. The second case of combined seminoma and embryonal carcinoma was diagnosed in 1984 in a 36-year-old worker who had begun work in this industry 19 years earlier. The third case of embryonal cell carcinoma was also diagnosed in 1984 in a 25 year-old worker who had worked in tanning for 8 years (Levin et al., 1987 and CDC, 1989). The three workers were exposed to a wide range of dyes and solvents and Dimethylformamide (DMF) was suspected to have been responsible for the cluster of testicular cancer. Walrath et al. (1989) undertook a case control study to determine whether the risk of developing testicular cancer was related to the exposure to DMF. Case and control subjects were obtained from four DuPont plants. Analysis for all plants combined did not show any statistical significant differences between ever having been exposed to DMF and subsequent development of testicular cancer (Walrath et al., 1989). Similarly a cohort mortality and cancer morbidity study of 3856 male employees exposed to DMF between 1950 and 1970 did not find an association between DMF exposure and testicular cancer (Chen et al., 1988a, 1988b), one case of testicular cancer was found compared with the 1.7 cases expected on the basis of the DuPont rates. However, a case-control study in Ontario found an elevated but non-significant risk of testicular cancer was observed among workers in the leather products industry (OR = 4.6, 0.75 – 28.28) (Knight et al., 1996).

### **4.32 Aircraft workers**

Foley et al., (1995) reviewed the incidence of testicular cancer in the Royal Air Force (RAF) personnel, both as a whole and by specific occupation within the RAF. They found that age adjusted incidence rates were significantly higher in the RAF than the general population with a relative risk of testicular cancer of 3.27 95% CI 2.43-4.31. Amongst the personnel, men working closely with aircraft, engineers and electronic engineers had a higher incidence of testicular cancer. Ducatman et al. (1986) reported a cluster of testicular cancer tumours among aircraft repairmen, engaged in repair of exterior surfaces and electrical components of the airframes of F4 Phantom Jet aircraft. In a case control study of men in the Royal Navy, a statistically significant increase in relative risk was associated with those working on aircrafts (OR for Fleet Air Arm = 1.90, 95% CI 1.04 - 3.48) (Ryder et al., 1997). This association was linked to air engineers (OR = 2.32, 95% CI 1.20 -48.0) but not air crew (OR = 1.07, 95% CI 0.19 - 5.94 relative to the royal marines). Further analysis of the air engineers showed a statistically significant association in aircraft handlers only (OR = 7.31 95% CI 1.81 -29.53)(Ryder et al., 1997). Authors suggested that it was exposure to glycol ethers in aviation fuel that may be the causative factor. A retrospective cohort mortality study of 77,965 workers employed for at least 1 year at a large aircraft manufacturing facility did not observe any increase risk of testicular cancer or any other disease (Boice et al., 1999). However, among factory workers exposed to mixed solvents on a routine basis, a significant increase in testicular cancer was found, but this was based

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on 6 deaths. Yamane and Johnson (2003) demonstrated an association between testicular cancer and flying exposure in the US Air force during a 10-year period. The association was significant when the exposure was one or more total flight hours, with an age adjusted OR of 1.74 (95% CI 1.04-2.92). The findings of Yamane and Johnson (2003) are consistent with three other studies investigating cancer incidence in military populations. Grayson and Lyons (1996) found an increased SIR (1.84, 95% CI 1.19-2.86) for testicular cancer in US Air Force officer aircrew (Grayson and Lyons, 1996). In a study of Bulgaria's Air Force, Milanov et al. (1999) found that an SIR of 3.48 (95% CI 0.91- 7.72) in civil aviation aircrew and an SIR of 1.61 (95% CI 0.15- 4.62) in military aircrew, but the results were not significant. Hoiberg and Blood (1983) found a statistically significant increased rate of hospitalisations for testicular cancer in US Navy Pilots compared to staff and line officers.

### **4.33 Paper and Printing workers**

Andersson et al. (2003) found an increase risk of testicular cancer (SIR 7.4, 95 % CI 1.5 - 22), especially for seminomas (SIR 10.1, 95% CI 2.1-29.0) among maintenance workers employed both in 1960 and 1970 in paper mills in Sweden. In a large cohort of 14,362 Danish paper mill workers, Rix et al., (1998) found the risk of testicular cancer doubled among paper machine workers with an SIR of 1.9. In an American cohort studies by Matanoski et al. (1998), testicular cancer was also elevated in workers involved in paper making (SMR 2.89, 95% CI 0.58-8.45). Swerdlow et al., (1991) indicated an excess risk of testicular cancer among paper producing and printing workers from an interview case-control study in England (10 cases, OR 2.1, 95% CI 0.84-5.02). No associated increase in testicular cancer was found in other studies (Van Der Eeden et al., 1991; Hardell et al., 1998, Langseth and Andersen, 2000 and Band et al., 2001).

### **4.34 Firefighters**

A cancer based registry case-control study of occupational associations with testicular cancer during a time period of 1958-1979 found no evidence of an increased risk for firefighters in New Zealand (Pearce et al., 1987). However, a detailed investigation into a cluster of testicular cancer cases in firefighters in New Zealand confirmed an increased risk of testicular cancer between 1980-1991 (RR = 8.2, 95% CI 2.2-21.0) based on four cases (Bates and Lane, 1995). In a further retrospective cohort study by Bates et al. (2001), a three fold elevated rate of testicular cancer was found (SIR 3.0 95% CI 1.3-5.9), even when the original cluster was excluded from the analysis. Prompted by the results of Bates et al., Stang et al. (2003) carried out a population case-control study in Germany. Although based on small numbers, results consistent with Bates et al. (2001) were observed where subjects who ever worked as firefighters showed an increased odds of testicular cancer (OR = 4.3, 95% CI 0.7 – 30.5).

### **4.35 Farmers and farm-related workers**

In a hospital based case-control study, Mills et al. (1984) reviewed medical records of 347 patients with histologically confirmed germ-cell testicular cancer and 347 randomly selected controls with other disorders. Occupations in farming, forestry and fishing had an odds ratio of 2.45. Subgroup analysis of these occupations showed that most of the increased risk was due to farming occupations (OR = 6.27, 95% CI 1.83-21.5). Van Den Eeden et al. (1991) found men working as a farmer or a farm

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manager to have an 90 % excess in risk relative to all other men (RR = 1.9, 95 % CI 0.6-5.4). In contrast, subjects reporting to have been a farm worker or gardener were found to have a decreased risk (RR = 0.6, 95% CI 0.3-1.3). The relative risk for men reporting to have worked in agriculture, forestry or fishery industries was 1.0 (95% CI 0.6-1.6). McDowall and Balarajan (1986), in a case control study using death certificate data from England and Wales, reported the relative risk for farmers /farm managers to be 1.8 (95% CI 1.1-3.1), while for farm workers it was 0.9 (95% CI 0.2-3.2). Hardell et al., (1998) also found that farming (including having grown up on a farm) was associated with an increased risk for non-seminomas (OR= 3.1 95% CI 1.03-9.1) but not for seminomas (OR= 0.9, 95% CI 0.5-1.6). Findings from a case-control based study by Pearce et al., (1987) using the New Zealand Cancer registry involving 427 male patients with testicular cancer reported the relative risk for farmers/farm managers and agricultural workers to be 1.1 (95% CI 0.7-1.8) and 0.5 (95% CI 0.2-1.2), respectively. Analysis of cancer incidence of licensed pesticide applicators in Florida, compared with that of Florida's general population, found an increased SIR of testicular cancer (SIR = 2.48; 95% CI, 1.57-3.72) in pesticide applicators (Fleming et al., 1991). Moller (1997) did not find an association between an occupation in agriculture and increased risk of testicular cancer in a population based case-control study in Denmark (OR = 0.76, 95% CI 0.57-1.02). Similarly, analysis by Jensen et al. (1984) of all incident cases of testicular cancer in a well defined Danish population provided no indication of an increased risk associated with farming or related activities (age related odds ratio of germ cell tumour development among farmers compared with other occupations was 0.97, 95% CI 1.56-1.68). A population-based study using the New Mexico Tumour Registry did not reveal a significant association between employment in agriculture and testicular cancer risk (OR 1.37, 95%CI 0.002-5.88) (Sewell et al., 1986). Brown and Pottern (1984) and Swerdlow et al., (1991) did not find any increase in testicular cancer risk with farming. In a study by Hayes et al. (1990) the risk of testicular cancer was significantly decreased in agricultural, forestry and fishery workers.

### **4.36 Workers in the Oil and Natural Gas Extraction Industry**

In a hospital based study, Mills et al. (1984) found an association between workers in the oil and natural gas industry and testicular cancer (OR = 2.29, 95% CI 1.03 – 5.11). The study was based on a total of 347 cases, 20 of whom worked in the oil industry.

## **5.0 Summary**

- 1- Testicular cancer is a relatively rare cancer worldwide, accounting for approximately 1-2% of all male cancers diagnosed. The incidence of testicular cancer varies widely around the world. Gradual increases in incidence have occurred in many countries since the 1960s, with little explanation available for the increase. Survival rates have improved in recent decades, possibly as a result of earlier diagnosis and survival of testicular cancer is the highest of any cancer in men in the UK.

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- 2- Well-established indicators of risk for testicular cancer are cryptorchidism and carcinoma in situ. Incidence also varies widely depending on ethnicity.
- 3- There is currently no agreement about the involvement of other factors in the aetiology of testicular cancer. Credible hypotheses that have been proposed involve *in utero* risk factors, maternal hormonal patterns and dietary practices.
- 4- Several reports have suggested that men engaged in some occupations may be at higher risk for testicular cancer. These include men working in white collar occupations, aircraft workers, leather workers, paper and printing workers, firefighters and men working in agriculture. However, there are conflicting views in the literature. Further and more refined occupational studies are possibly required.

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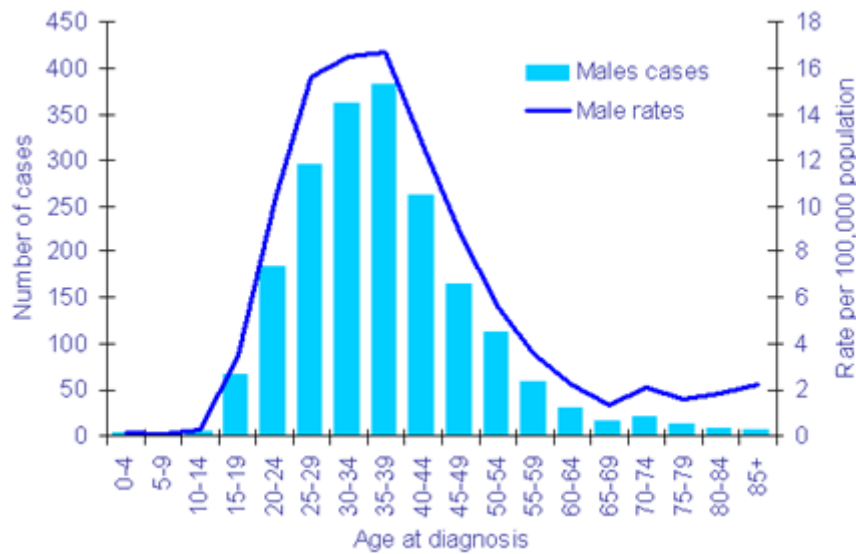
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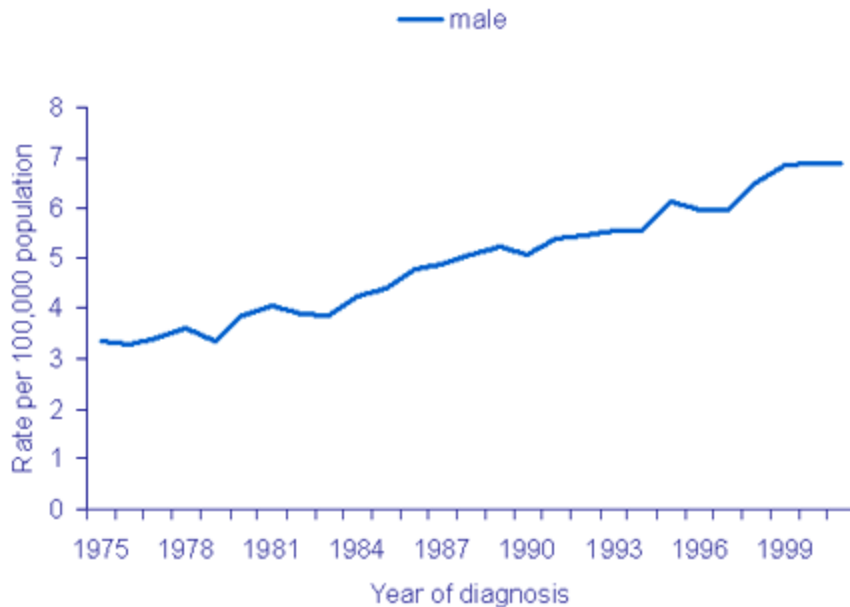
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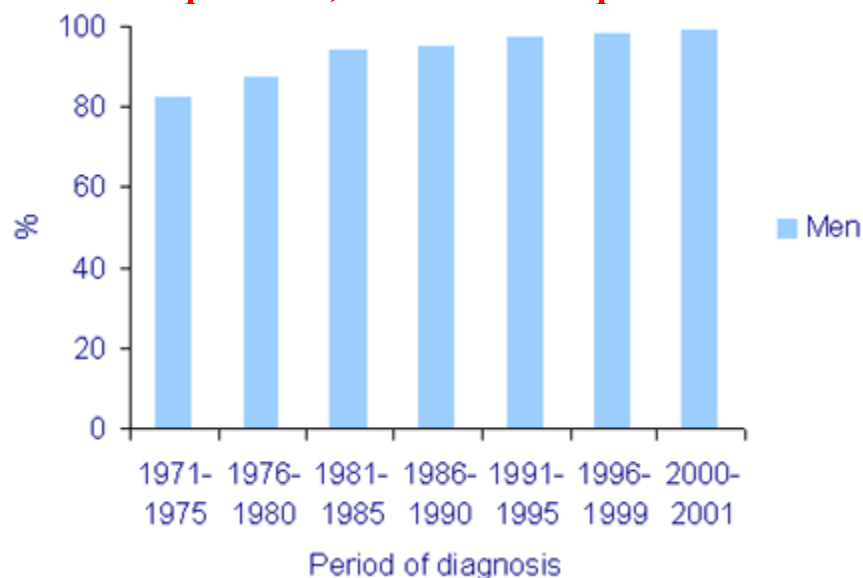


**Figure 1: Testicular cancer incidence statistics for the UK .Number of new cases and age specific incidence rate per 100,000 population, testicular cancer, UK, 2001**

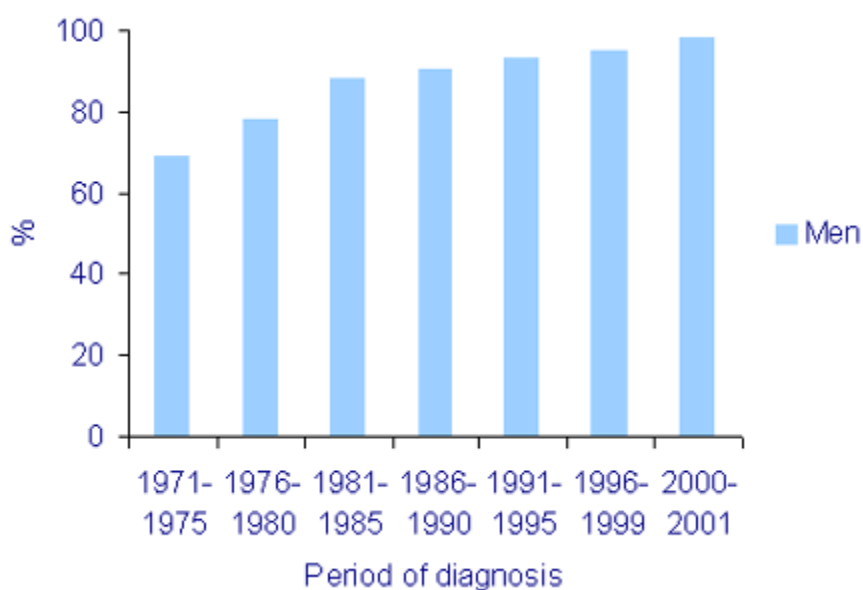


**Figure 2: Trends in age standardised\* incidence rates per 100,000 population for testicular cancer, 1975-2001, Great Britain**

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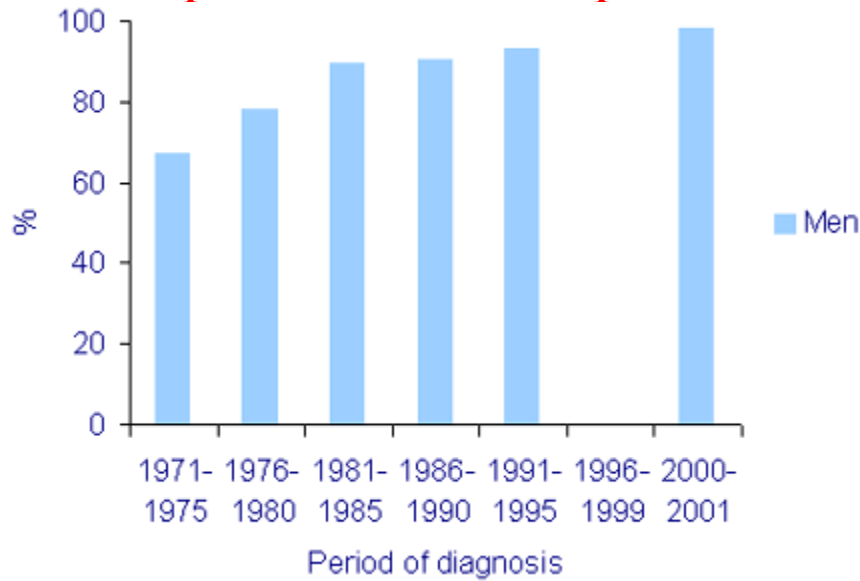


**Figure 3: One-year age standardised\* relative survival for testicular cancer for patients diagnosed in England and Wales during 1971-1999**

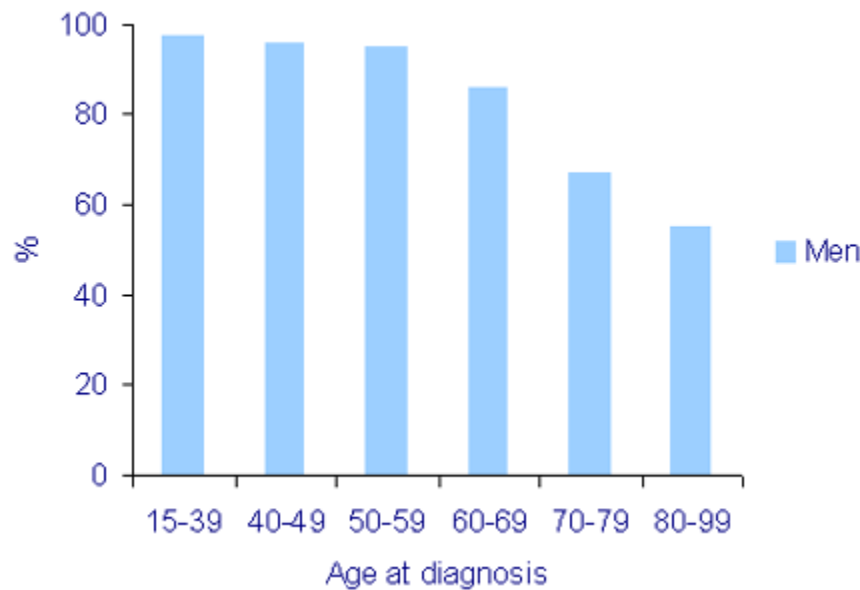


**Figure 4: Five-year age standardised\* relative survival for testicular cancer for patients diagnosed in England and Wales during 1971-1999**

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**Figure 5: Ten-year age standardised\* relative survival for testicular cancer for patients diagnosed in England and Wales during 1971-1999**



**Figure 6: Five-year age standardised\* relative survival for testicular cancer by age for patients diagnosed in England and Wales during 1996-1999**

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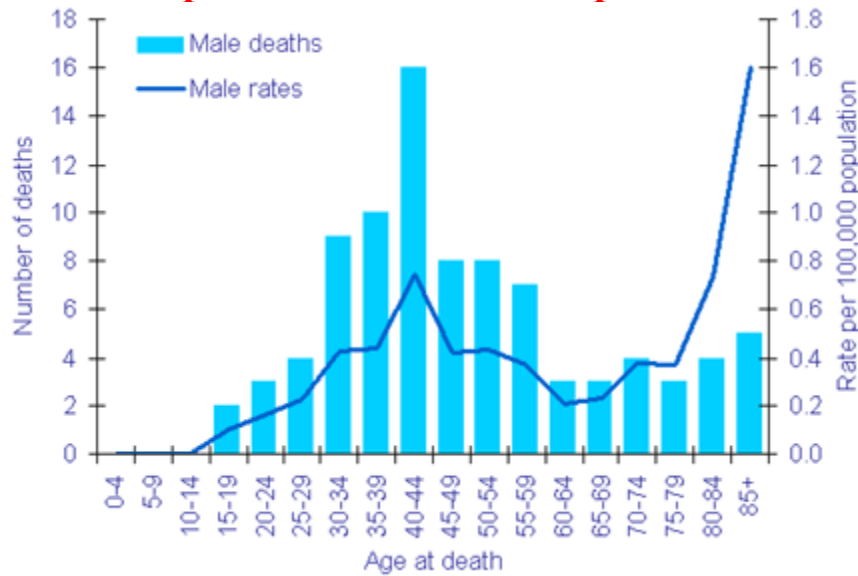


Figure 7: Number of deaths and age specific mortality rate per 100,000 population, testicular cancer, UK, 2003

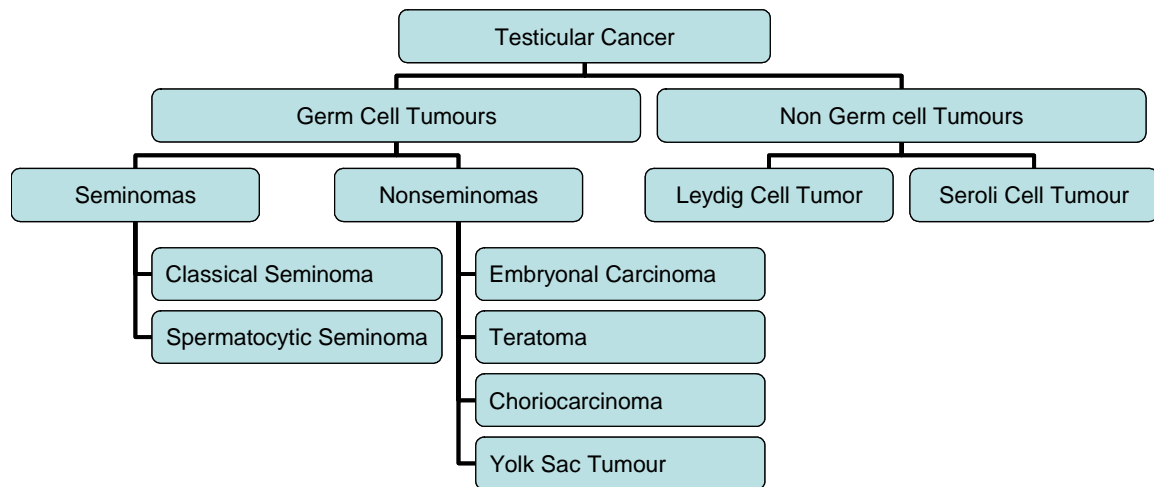


Figure 8. Histology of Testicular cancer

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	England	Wales	Scotland	N.Ireland	UK
Cases					
Males	1,653	81	212	50	1,996
Crude rate per 100,000 population					
Males	6.9	5.8	8.7	6.1	7.0
Age-standardised rate (European) per 100,000 population					
Males	6.8	6.1	8.5	6.0	6.8
CI 95%	6.4 7.1	4.7 7.4	7.4 9.6	4.3 7.6	6.5 7.1

**Table 1: Number of new cases, crude and age standardised\* incidence rates per 100,000 population, testicular cancer, countries of the UK, 2001**

	England	Wales	Scotland	N.Ireland	UK
Deaths					
Males	70	4	13	2	89
Crude rate per 100,000 population					
Males	0.3	0.3	0.5	0.2	0.3
Age-standardised rate (European) per 100,000 population					
Males	0.3	0.3	0.5	0.2	0.3
CI 95%	0.2 0.3	0.0 0.6	0.2 0.8	-0.1 0.6	0.2 0.4

**Table 2: Number of deaths, crude and age standardised\* mortality rates per 100,000 population, testicular cancer, countries of the UK, 2003**