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DRAFT

ANNEX 1 TO CC/03/35

PROSTATE CANCER – TRENDS AND RISK FACTORS: AN OVERVIEW

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 prostate cancer. The COC is interested in the role of exposure to chemicals as possible risk factors for prostate cancer.

Established risk factors for prostate cancer (PC) are age, family history and ethnicity/country of residence. Apart from this, the aetiology of the disease is unclear; likely hypotheses that have been proposed involve hormonal patterns and dietary factors. There is some indication that PC incidence is increasing, both in the UK and worldwide, although at least part of this increase may be attributed to diagnostic factors. This report discusses current patterns and trends in PC and considers possible causal factors for this disease.

Prostate Cancer Trends

Data in this section are based primarily on recent publications by the UK Office for National Statistics (ONS) (Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part I: international comparison. Part II: individual countries (Quinn and Babb, 2002a; Quinn and Babb, 2002b)). UK data for these publications were based on ONS statistics covering the period 1950-1999. The most recent data from Cancer Research UK (CRUK) (1999 incidence data/2001 mortality data) are attached in Appendices 2 and 3 and can be found on the CRUK website (<http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/>). The most recent data from ONS can be found on the website (<http://www.statistics.gov.uk/>).

Prevalence

Globally, PC is estimated to be the third most common cancer in men. The disease is prevalent in the elderly, with around three-quarters of cases occurring in men aged ≥ 65 years. A combination of shifting age distributions towards the elderly, increasing incidence rates and good survival times means that in some countries PC now comprises a substantial proportion of the total number of prevalent cancer cases (estimated as ~ 15% of all cases in men in developed countries; 4% in developing countries). European figures for PC prevalence in 1992 are shown in Figure 1. The highest levels occurred in Sweden and Switzerland (~ 600 and 400 cases per 100 000 population, respectively), whilst levels in Great Britain were similar to the overall European prevalence (~ 200 cases per 100 000 population). Figures for 1997 (England and Wales) show PC (19 300 cases) as the second most prevalent cancer in men, accounting for approximately 17% of all malignancies (excluding nonmelanoma skin cancer) (Quinn and Babb, 2002a; Quinn and Babb, 2002b).

Incidence

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PC incidence shows a wide variation throughout the world. This can, to some extent, be accounted for by differences in population age structures. However, large differences still remain after age-standardisation. The highest rates occur in the USA, approximately 2-fold those in Sweden and Australia, 3-fold those in the UK and other parts of Europe and 10-fold those in East Asian countries such as Singapore, Japan, India and China (Quinn and Babb, 2002a) (Figure 2a). Age-standardised PC incidence rates have been increasing gradually in many countries since the 1960s. Increases prior to prostate-specific antigen (PSA) testing have been attributed partly to increased use of trans-urethral resection of the prostate (TURP) for benign prostate hyperplasia¹ (BPH). Sharp increases occurred in the USA in the late 1980s and early 1990s (> 100% increase from 1986-1992), followed by a decline. This pattern has been associated with the rise and fall of rates of first PSA tests, and is attributed primarily to diagnostic artefacts following the introduction of PSA testing. PC incidence rates in the UK over the last few decades have shown a similar pattern to those in the USA. Age-adjusted rates increased in all age groups in England and Wales during the 1970s and 1980s. A marked increase occurred after this, rates peaked in 1994 and subsequently decreased in some, but not all, age groups (Quinn and Babb, 2002b) (Figure 3). Similar patterns were observed in Scotland, where the increases in incidence were closely correlated with rates of TURP (up to 1988) and, subsequently, PSA testing (1989-1996) (Brewster et al., 2000). Incidence rates in England, Wales and Scotland showed an inverse correlation with socio-economic deprivation status (Quinn and Babb, 2002b). Rates also showed significant variation between, and within, regions in Great Britain, with considerable variation throughout Scotland. However, a recent study showed no evidence of localised geographical clustering of PC incidence in Great Britain, suggesting that varying environmental factors are not strongly involved in PC aetiology within Great Britain (Jarup et al., 2002). The latest available data from UK ONS (for the year 1997) showed PC as the second most incident cancer in men in England and Wales, after lung cancer (http://www.statistics.gov.uk/downloads/theme_health/cancertrends_5099.pdf). Cancer Research UK reported a 35% increase in PC incidence in Great Britain between 1989 and 1998. Latest figures (for the year 1999) from CRUK showed that PC was the most common cancer in UK males (http://www.cancerresearchuk.org/aboutcancer/statistics/statsmisc/pdfs/cancerstats_incidence.pdf) (Appendix 2).

In one study (Post et al., 1999) reported an increase in PC incidence rates during the period 1971-1989 (prior to the introduction of PSA testing in 1990) in men aged 40-59 years in south-east Netherlands (8.8-12.5 per 10⁵) and East Anglia (UK) (7.0-11.6 per 10⁵). Mortality rates also increased in both regions, with a subsequent decline in the 1990s. In the Netherlands, 5-year relative survival fell (65-48%), and the proportion of patients with poorly differentiated tumours increased (15-25%), although the proportion of patients with localised cancer also increased (47-56%).

Survival

Survival times from PC are considered to be moderately good. (Quinn and Babb, 2002a) cited an average 5-year relative survival rate in Western Europe during the late

¹ A description of the biology, histology and pathology of the prostate gland can be found in (OH et al., 2000)

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1980s of 56% (Figure 4). There was considerable variation between countries. The lowest rates were seen in former Eastern bloc countries and in the UK (approximately 40%), whilst the highest rates (60-70%) occurred in Switzerland, Germany, Iceland, Sweden, France and Finland. The rate in the USA was 86%. It is probable that this much higher survival rate represents the biological non-equivalence of prostate cancers registered in the USA during this time due to different diagnostic procedures (PSA testing as a general diagnostic for PC was introduced in the USA in 1986, but not until the early 1990s in Europe). Survival rates in the USA are lower in black than white men.

The rate for five-year relative survival from PC for cases diagnosed in England and Wales during 1993-95 was 60% (Quinn and Babb, 2002b). Notably, a 17% increase occurred for men diagnosed in 1993-95 as compared with 1986-90. This increase has been attributed to lead-time bias due to increased diagnosis of earlier stage and less invasive tumours. Stratification by age-group showed poorer survival for younger men, with the highest rates occurring in the 60-69 years group. The increasing use of more effective treatments such as hormonal therapy since the early 1990s would be expected to have a beneficial effect on PC survival times.

Mortality

In comparison with the substantial differences seen in incidence and survival rates, mortality due to PC shows less variation between countries (Figure 2b) (Quinn and Babb, 2002a). It is notable that, despite the very high incidence rate, PC mortality in the USA (approximately 25-30 per 100 000 population in the late 1980s/early 1990s) is comparable to that seen in other developed countries, including the UK. Mortality rates in countries such as Singapore, Japan, India and China are, however, low, in accordance with the low incidence rates in these countries. The highest mortality rates are seen in Australia, New Zealand and some Nordic countries. Mortality attributed to PC has increased in many countries over the last few decades, although to a lesser extent than incidence (Figure 5). It has been estimated that inappropriate attribution of PC as the underlying cause of death (for example, in cases where latent carcinomas of the prostate have been diagnosed at biopsy or post-mortem) (attribution bias) would account for some of the increases (Feuer et al., 1999). During the mid to late 1990s, PC mortality rates decreased slightly in the USA, Canada, England, France and Austria. The reasons for these decreases have not been established, but may include earlier diagnosis, improved treatments, and a possible redress of previous attribution bias. It has been estimated that it is still too soon after the widespread introduction of diagnostic PSA testing for this to be a major factor accounting for reduced mortality rates (Etzioni et al., 1999). However, (Etzioni et al., 2002) calculated that the majority of screen-detected cancers diagnosed in the USA since the introduction of PSA-testing would have presented clinically. Large-scale clinical trials are in progress in the USA and Europe to investigate the potential of diagnostic PSA screening to improve PC survival times and to reduce mortality rates.

Figure 6 shows age-specific mortality rates for PC in England and Wales during the second half of the 20th century (Quinn and Babb, 2002b). Rates remained stable in all but the 80+ age groups from the 1950s until the mid-1980s, when increases were observed in all age groups (correlated with increasing incidence rates). Peak mortality

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rates were observed in the early/mid 1990s, since when a decline has been seen in most groups, except the very elderly. The latest available data from UK ONS (for the year 1999) showed PC as the second most common cause of cancer mortality in men in England and Wales, after lung cancer (http://www.statistics.gov.uk/downloads/theme_health/cancertrends_5099.pdf). Latest figures from CRUK (for the year 2001) also showed PC as the second most common cause of cancer death amongst UK males (http://www.cancerresearchuk.org/aboutcancer/statistics/statsmisc/pdfs/cancerstats_mortality.pdf) (Appendix 3).

Risk Factors For Prostate Cancer

Intrinsic factors

Age

The most important factor indicating risk of PC is age. Clinical PC is very rare in men under 40 years, and peaks in the 70s. Data from autopsy studies show latent cancers in 15-30% of men aged over 50 years (figures are relatively consistent across a wide range of countries), and 60-70% of men aged over 80 years (Pienta and Esper, 1993). However, it is thought that the initiating events in PC occur early in life. One report of an autopsy series described histologic evidence of PC in 27% and 34% of men in their 30s and 40s, respectively, whilst prostatic intraepithelial neoplasia (PIN)² was present in 9% of men in their 20s (Sakr et al., 1993).

Family history

PC risk is increased 2- to 3-fold in men who have a first-degree relative affected with the disease. Risk increases if more first-degree relatives are affected, and is greater in the brothers than the sons of affected men. Risk is also greater if the affected relative developed PC at a relatively early age (reviewed by (Bishop and Kiemeny, 1997)). High-penetrance familial PC is estimated to account for ~ 5-10% of all PC cases and a higher proportion of early-onset cases (eg, 55 years) and several susceptibility loci have been proposed (reviewed by (Nupponen and Carpten, 2001; Simard et al., 2002)). Increased PC risk has also been observed in relatives of breast cancer patients in some population-based studies.

Racial background

The general pattern of PC incidence rates worldwide is high in North America and Western Europe, moderate in Africa and low in Asia. Data from numerous studies show consistent variations in PC risk with race. The highest incidence rates in the world occur in African-American men (who also show less favourable survival and mortality rates than white men in the USA). Analyses indicate that the differences between black and white men cannot be explained entirely by socio-economic factors, suggesting racial differences in tumour biology (see (OH et al., 2000; Barista, 2001)

² A description of the biology, histology and pathology of the prostate gland can be found in (OH et al., 2000)

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and refs therein) or other factors (eg, dietary). Low incidence rates are observed amongst Japanese in the USA. However, these rates are still higher than for Japanese in Japan, suggesting that environmental factors may also play a role in prostate carcinogenesis (Shimizu et al., 1991). A study of PC incidence rates in ethnic groups in Los Angeles showed that age at migration did not affect PC risk, suggesting the involvement of a later life factor (or a screening effect) (Shimizu et al., 1991). Histological studies of autopsy series show quite consistent levels of small, latent PCs amongst different racial groups, despite the wide variations in rates of clinically-diagnosed PC (Yatani et al., 1982). It has been suggested that this implies that it is the factors which are associated with the development of clinical PC (ie, the progression of latent to clinical PC, or the *de novo* incidence of clinical PC) that vary between groups, whilst those factors related to the induction of subclinical PC show less variation (Ross and Coetzee, 2002). However, this could also be a reflection of different diagnostic levels in different groups.

Molecular genetic aetiology

Genetic predisposition may facilitate the role of environmental factors in prostate carcinogenesis (Barista, 2001). Genes involved in androgen metabolism and signalling pathways, vitamin D metabolism pathways, insulin-like growth factor (IGF) signalling pathways and clinical carcinogen metabolic pathways are current candidates for analysis in studies of the genetic epidemiology of PC (see review by (Ross and Coetzee, 2002)).

Endocrine factors

Normal growth and function of prostatic tissue is under the control of the androgen steroid hormone, testosterone (T), through conversion to dihydrotestosterone (DHT) by the enzyme 5- α -reductase. The majority of T within the circulation is bound to sex hormone-binding globulin (SHBG). There is substantial evidence that reducing androgens to very low levels can inhibit prostate carcinogenesis. Men who have diminished androgen production due to castration, hypogonadism or enzyme defects of androgen metabolism have very low risk for PC, as compared with the general population (Ross and Schottenfeld, 1996). PC rates are disproportionately low in men with chronic liver disease, which is associated with elevated levels of plasma oestrogens and suppressed testicular androgen secretion (Glantz, 1964). Therapeutically, ablation or antagonism of T production, either through oestrogen administration, orchidectomy or treatment with GnRH superagonists (which act as antagonists, lowering T levels) or antiandrogens, is used to inhibit PC growth and progression, although most cancers eventually become resistant to this treatment (OH et al., 2000).

The role of endogenous steroid hormone levels in contributing to PC risk is less well-defined. Prolonged exposure to androgens has been proposed as a mechanism by which PC may develop. Experimental studies have shown that, although spontaneous prostate and seminal vesicle neoplasms are rare in the majority of laboratory species, prostate cancers can be induced by treatment with pharmacological doses of T, alone or in combination with oestrogen (reviewed by (Shirai et al., 2000)). However, epidemiological studies investigating the role of plasma androgens in the aetiology of

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PC have shown conflicting results, which might reflect the possibility that T is necessary, but not sufficient, for the development of PC in humans. Some case-control studies have shown higher serum T levels in PC patients than in controls who have no known prostatic disease, whilst other studies have shown no difference between cases and controls, or that T levels are lower in PC cases than controls. Studies have also evaluated possible abnormalities in plasma oestrogens, but results have been inconsistent (see reviews by (Ross and Schottenfeld, 1996; Giovannucci and Platz, 2002)). Many of these studies have limitations, including the determination of hormone levels after PC has been identified, inadequate accounting for differences between case and control groups and failure to adjust for other hormones and proteins. Many studies have not adjusted for levels of SHBG, which is important as levels of this protein are likely to modulate the functional availability of steroid hormones. A small number of prospective studies have been reported. Some of these studies have suggested that a higher T:DHT ratio and higher levels of androstanediol glucuronide, a metabolite of DHT, may be related to increased PC risk; however some studies indicated no associations of the plasma hormones tested and PC risk (see (Giovannucci and Platz, 2002) and refs therein). A nested case-control study within the US Physicians' Health Study, in which blood samples were taken from 222 PC cases at least 6 years prior to diagnosis, showed PC relative risks (RR) (top vv. bottom quartile) of 2.6 (95% CI = 1.34-5.02) for T, 0.46 (95% CI = 0.24-0.89) for SHBG and 0.56 for oestradiol (95% CI = 0.32-0.98), indicating that normal variation in androgenicity can influence PC risk (Gann et al., 1996a).

In population-based studies Ross and colleagues found that young African-American men have higher circulating T levels than white Americans (15% higher T, 13% higher nonprotein-bound T) (Ross et al., 1986). The same authors reported that T levels in young Japanese men were not significantly different from those of African-American and white US men, but that the latter 2 groups had higher levels of metabolites indicative of 5 α -reductase activity (3 α ,17 β androstanediol glucuronide and androsterone glucuronide), suggesting that that low PC incidence rates in Japanese men may be related to lower 5 α -reductase activity (Ross et al., 1992). Hill and colleagues reported that African-American and white North American men had similar urinary levels of T and androsterone, but that levels were lower in black South African men. However, feeding of a Western diet to black South African men was associated with a significant increase in urinary oestrogen and androgen levels, whilst feeding a vegetarian diet to African-American and white North American men was associated with decreased urinary oestrogen and androgen levels, suggesting that dietary factors modify testicular hormone activity (Hill et al., 1979).

The concept that variation in androgenicity may influence PC risk may be extended to include evaluation of variation in genes and gene products involved in androgen metabolism or function. For example, an inverse association has been reported between the length of a variable number CAG repeat polymorphism within the amino-terminal-encoding region of the AR (androgen receptor) gene and risk of PC. Smaller repeat number has been associated with increased transactivation of downstream target genes and with higher endogenous androgen levels. Studies have shown that African-American men have a relatively low average number of repeats, white men an intermediate number and Asian men (Chinese or Japanese) have a relatively high number (Edwards et al., 1992; Giovannucci et al., 1997). Epidemiological studies

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have indicated that moderately increased risks for PC or advanced PC may be associated with shorter, as compared with longer, *AR* CAG repeat lengths (Irvine et al., 1995; Giovannucci et al., 1997; Stanford et al., 1997; Hsing et al., 2000). A polymorphism in *SRD5A2* – the gene encoding type II steroid 5 α -reductase – is associated with reduced activity of the enzyme *in vitro*, and has been reported to be more prevalent in Asian men (46%) than other ethnic groups which have been evaluated (22% and 24% in African-American and Caucasian men, respectively) (Makridakis and Reichardt, 2001).

A number of chemicals (eg, organochlorine pesticides) with claimed endocrine-disrupting activities (EDCs) have been identified as possibly being involved in the development of hormone-related cancers. To date, there is little information available regarding the potential involvement of EDCs in PC. This area is reviewed later in this report, in the sections on environmental and occupational risk factors for PC.

IGF-1

Experimental studies *in vitro* and *in vivo* have shown an important role for the IGF (insulinlike growth factor) axis in the control of cell growth and apoptosis in normal and neoplastic prostate tissue. Recent epidemiological studies have also shown a link between the IGF axis and PC. Two case-control studies showed that high IGF-1 levels (the major circulating IGF) were associated with increased PC risk (see review by Djavan et al., 2001). A nested case-control study (152 cases) from the US Physicians' Health Study showed a strong positive association between IGF-1 levels and PC risk; RR for PC [top vs. bottom quartile] 4.3 for IGF-1 (95% CI, 1.8-10.6) (adjusted for IGF-1), and 0.4 for IGF-1 (95% CI, 0.2-1.0) (adjusted for IGF-1) (Chan et al., 1998b).

Vitamin D

Experimental studies have shown that that 1,25(OH)₂D, an active metabolite of vitamin D, can inhibit proliferation and stimulate differentiation of prostatic epithelial cells, and this area is being developed therapeutically. Some epidemiological studies have shown an inverse association between high 1,25(OH)₂D serum concentration and PC risk, although other studies have not revealed such an association (Corder et al., 1993; Gann et al., 1996b). Polymorphic variation of the *VDR* (vitamin D receptor) gene has been suggested to confer differential susceptibility to PC.

In utero and peri-natal factors

Some studies have suggested an association of PC risk with birth weight, which may be a marker of prenatal hormone exposure levels, although other studies have not shown this association. Indirect markers of adolescent hormone levels, such as attained height have also been associated with PC risk in some populations (see (Barista, 2001) and refs therein).

(Golden et al., 1998) noted that early exposure to oestrogens, either *in utero* or shortly after birth, may, theoretically, play a critical role in subsequent prostate neoplasia. In particular, it was noted that compounds identified as environmental oestrogens may

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be able to exert an effect because they do not bind to SHBG. Studies of rats and mice treated pre- or post-natally with diethylstilbestrol (DES) have shown effects on the prostate (eg, hyperplasia, altered response to androgens and oestrogens), but the applicability of these models to humans is not established. *In utero* DES exposure in humans has not shown an increased risk for PC, although a sufficient latency period may not yet have elapsed.

Dietary factors

It has been suggested that an important factor that contributes to varying PC rates around the world is that of dietary and nutritional patterns (Giovannucci and Platz, 2002). This is highlighted by changing PC incidence rates in ethnic groups upon migration (for example in Japanese who have migrated to the USA). National *per capita* consumptions of a number of nutritional variables have been observed to correlate with national PC incidence and mortality rates. Red meat (Michaud et al., 2001), fat (particularly total fat, saturated fat and animal fat), milk and dairy product consumption have been reported to correlate with PC risk (reviewed by (Barista, 2001; Giovannucci and Platz, 2002; Kushi and Giovannucci, 2002) (Table 1). Whether these associations are the result of increased animal and related fat intake, or to other factors unrelated to fat, is not clear. For example, dietary factors that may be associated with red meat intake that may increase prostate cancer risk include formation of polycyclic aromatic hydrocarbons and heterocyclic amines. High-fat and high-red-meat diets also tend to be low in plant foods, which contain constituents that may decrease cancer risk. The correlation with fat intake is supported by experimental studies in rats and mice, which have shown an association of prostate epithelial hyperproliferation and tumour growth with dietary fat intake (cited by (OH et al., 2000)). Some epidemiological studies have shown stronger associations of fat intake with advanced rather than total PC incidence, suggesting that dietary fat influences the later stages of prostate carcinogenesis (or only lesions which would progress to an advanced stage) ((Giovannucci and Platz, 2002) and refs therein). It has been proposed that the association between dairy product intake and PC risk may be an effect of calcium intake levels, and this is supported by the results of studies which have shown elevated PC risk associated with dietary or supplemental calcium intake (Chan et al., 1998a; Giovannucci et al., 1998). It has been hypothesised that high levels of dietary factors such as fat and calcium promote high-risk endocrinologic patterns associated with PC (eg, increased T levels, increased IGF-1/IGFBP-3 ratio, decreased 1,25(OH)₂D levels).

A number of dietary factors and micronutrients have been reported to be protective against PC development (reviewed by (Pathak et al., 2003)). These factors include soy products, fruits and vegetables, vitamin E, selenium, vitamin D, lycopene and β -carotene. Several trials are underway to evaluate the potential roles of nutritional factors in the prevention of PC.

The evidence for an association between diet and risk of PC was reviewed fully by the Working Group on Diet and Cancer of the Committee on Medical Aspects of Food and Nutrition Policy in 1998. The Working Group concluded that the limited data are

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weakly consistent that higher total fat intakes are associated with higher risks of PC. The Working Group also concluded that the limited evidence is moderately consistent that higher vegetable consumption, especially raw and salad vegetables, is associated with a lower risk of PC. The evidence for an association between consumption of fruit and risk of PC is inconsistent. There are insufficient data on intakes of soya products to reach a conclusion on the association of soya products with risk of PC.

Advice on nutritional factors is the responsibility of the Scientific Advisory Committee on Nutrition (<http://www.sacn.gov.uk/>).

Exogenous factors – non-chemical

Vasectomy

Studies have shown either no risk, or modestly increased risk for PC and vasectomy. Some studies have shown increased risk in specific age groups, but these observations have not been consistent. It has been suggested that vasectomy may increase risk because vasectomised men have higher levels of circulating T, or because of the production of anti-sperm antibodies. However, there is concern that detection bias may account for apparent associations. The current consensus of opinion appears to be that an association, if it exists, is weak, and vasectomy is not a factor of concern with regard to PC risk ((Barista, 2001; Giovannucci and Platz, 2002) and refs therein).

Sexual activity and viral exposure

Data regarding potential correlations of PC risk with levels of sexual activity are conflicting, with both positive and negative associations observed in the retrospective studies that have been reported to date ((Barista, 2001; Giovannucci and Platz, 2002) and refs therein). It is theoretically plausible that sexual activity may correlate with PC risk, as a result of exposure to viral infections. (Hayes et al., 2000) reported increased PC risk in men with a history of sexually transmitted diseases (STDs) (syphilis and gonorrhoea, risk directly related to number and range of infectious episodes), sex with prostitutes and unprotected sex. Studies of herpes virus, kaposi's sarcoma virus and human papillomavirus have shown inconsistent findings; this may to some extent be due to assay variability and methodological problems (Hayes, 2000).

Physical activity and lifestyle

Some studies have indicated a small inverse association of physical activity and PC risk, although findings have been inconsistent. In a systematic review, (Friedenreich and Thune, 2001) noted that, among 24 reported studies, 14 studies suggested an inverse association, 6 studies showed no association, whilst 4 studies indicated an increased risk of PC amongst the most physically active men. It was noted that many studies had methodological limitations. A prospective analysis in the US Physicians' Health Study (11.1 years follow-up, ~ 260 000 person-years) indicated that there was no significant association of physical activity levels with risk of PC (Liu et al., 2000).

Exogenous factors - chemical

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Cigarette smoking

Although there is no strong evidence for a link between cigarette smoking and PC incidence, smoking has been associated more consistently with increased PC mortality rates ((Barista, 2001; Giovannucci and Platz, 2002; OH et al., 2000) and refs therein). It is not clear whether this association is an effect of different behavioural characteristics of smokers (ie, delayed diagnosis and treatment seeking) or whether components of cigarette smoke may have a direct effect on tumour progression. However, a recent analysis of the US Health Professionals Follow-Up Study indicated that the effect, at least in part, may be due to the direct biological effects of smoking (Giovannucci et al., 1999).

Alcohol

Some studies have shown a positive association between alcohol intake and risk of PC, whilst others have not supported this relationship. It has been hypothesised that, as alcohol affects T metabolism in the liver (leading to lower circulating T levels), it might be associated with lowered PC risk. In a review of epidemiologic studies of alcohol consumption and PC risk (Breslow and Weed, 1998) concluded that there is little evidence for either a positive or negative association, although most studies had not evaluated extremely high alcohol intake, which might (hypothetically) be inversely related to PC risk. A subsequent review by (Dennis and Hayes, 2001) concluded that moderate alcohol consumption (3 drinks/day) does not appear to influence PC risk, but heavy consumption (7 drinks/day) may be associated with excess risk, as indicated by some studies among alcoholics and other heavy users of alcohol. However, it was noted that the increased risks observed in studies of heavy drinkers were modest and may have been due to confounding factors or other study biases. It is possible that the dose-response curve for alcohol and PC may be affected by different mechanisms at different doses (eg, direct effect of alcohol on T levels; effects of alcoholic liver disease).

Cadmium and cadmium compounds

Cadmium and cadmium compounds are classified by IARC as Group 1 carcinogens (carcinogenic to humans) (IARC, 1993). Cadmium is classified by the US EPA as B1 (a probable human carcinogen) (<http://www.epa.gov/>). Occupational exposure to cadmium is associated with lung cancers. The potential mechanism(s) of cadmium carcinogenesis is unknown. Associations with tumours at other sites, including the prostate, are not definitively established. A number of early studies reported an increased risk for PC among cadmium workers, but the results of later studies have not been consistent.

An increased risk of PC was originally noted in workers at a nickel-cadmium battery plant in the UK (Potts, 1965; Kipling and Waterhouse, 1967; Lemen et al., 1976; Holden, 1980c). However, a subsequent series of cohort analyses did not confirm the excess (RR = 1.36; 95% CI, 0.76-2.25) (Sorahan and Waterhouse, 1983; Sorahan and Waterhouse, 1985). A small cohort study of workers in the same industry in Sweden also found no excess of PC (RR = 1.08; 95% CI, 0.29-2.77) (Elinder et al., 1985).

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Analysis of workers at 2 small copper-cadmium alloy plants in the United Kingdom showed no increase in mortality from PC (RR = 0.63; 95% CI, 0.01-3.52) (Holden, 1980a; Holden, 1980b), while in a similar plant in Sweden a nonsignificant excess was detected (RR = 1.49; 95% CI, 0.40-3.81) (Kjellstrom et al., 1979). Excess mortality from prostatic cancer was initially found among workers employed in a US cadmium recovery plant (overall RR= 3.48; 95% CI, 0.94-8.91; for workers with 20 years latency RR = 4.55, 95% CI, 1.22-11.64) (Lemen et al., 1976), but the risk diminished and became nonsignificant with further follow-up (RR = 2.13; 95% CI, 0.44-6.22) (Thun et al., 1985). In a large cohort of workers from 17 cadmium processing plants in the United Kingdom, a nonsignificant decrease in mortality from PC was observed (RR = 0.75; 95% CI 0.53-1.03) (Armstrong and Kazantzis, 1983; Kazantzis et al., 1988; Kazantzis and Blanks, 1992; Kazantzis et al., 1992). A population-based case-control study of cadmium exposure in the USA showed no evidence of increased PC risk in occupations with potential cadmium exposure, with cigarette smoking or with diet. A composite measure of potentially-high exposure to cadmium from any source was not associated with PC in general (OR = 1.0; 95% CI, 0.7-1.3) but was associated with aggressive tumours (OR = 1.7; 95% CI, 1.0-3.1) (Elghany et al., 1990). However, (Van Der Gulden et al., 1995) observed a significantly elevated risk for PC in men who reported frequent occupational exposure to cadmium (OR = 2.76; 95% CI, 1.05-7.27).

Rodent studies have confirmed human data that chronic inhalation of cadmium causes pulmonary adenocarcinomas. Cadmium can also cause prostatic proliferative lesions, including adenocarcinomas, after systemic or direct exposure; other target tissues include injection sites, adrenals, testes and the haemopoietic system. The association of cadmium administration with the induction prostatic tumours is dependent on the effects of the metal on the testes; doses which are toxic to the testes are associated with prostatic atrophy, rather than proliferation. Analysis of the carcinogenicity of single subcutaneous cadmium injection in rats over 2 years using a wide range of doses (1-40 $\mu\text{mol Cd/kg bw}$) showed dose-related, elevated tumour incidence only at doses that were below the threshold for testicular toxicity ($\sim 5.0 \mu\text{mol Cd/kg bw}$), with no tumour response at higher doses (Waalkes et al., 1988). Oral exposure of rats to cadmium (25-200 ppm in the diet for 77 weeks) produced proliferative lesions (hyperplasia and adenomas) in the prostate of animals in the 50 ppm group (Waalkes and Rehm, 1992), whilst prostatic adenocarcinomas occurred following direct injection of cadmium into the rat prostate (Hoffmann et al., 1985, *cited by* (Waalkes, 2000)). Studies of the effects of cadmium on the prostate in animal models have been reviewed by (Waalkes, 2000). Some treatments modify cadmium carcinogenicity; administration of zinc prevents cadmium-induced injection site and testicular tumours, but facilitates prostatic tumour formation (see review by (Waalkes, 2000) for details and references). Diets deficient in zinc increase the progression of testicular tumours but reduce the progression of prostatic tumours. Species and strain-related differences in sensitivity are observed. The ability of cadmium to induce PC depends on the effects of the metal on the testes; sub-cutaneous cadmium administration to rats resulted in a dose-related increase in tumour incidence, but only at doses of cadmium below the threshold for significant testicular toxicity, whilst there was no response at higher doses. Oral cadmium exposure has been shown to produce proliferative lesions in the rat prostate, whilst direct injection of cadmium into the prostate produced adenocarcinomas. Cadmium treatment also enhanced the appearance of chemically

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induced prostatic tumours in rats. However, it has been noted that the relevance of these studies to prostate carcinogenesis in humans is unclear, because of anatomical differences between the human and rodent prostate (WHO, 2002).

In vitro, cadmium chloride induced malignant transformation of rat and human prostate epithelial cells (Terracio and Nachtigal, 1988; Achanzar et al., 2001; Nakamura et al., 2002). ((Achanzar et al., 2001) estimated that the concentration at which this effect was seen [treatment of human prostate epithelial cells with 10 µM CaCl₂ for 8 weeks] was similar to that estimated to occur in the prostates of men with known occupational exposure to cadmium). Cadmium chloride has been reported to exhibit androgenic effects in prostate epithelial cells (Ye et al., 2000; Martin et al., 2002b).

In summary, a possible association of cadmium exposure and PC was first noted in the 1960s. Subsequent epidemiological studies have shown variable results and the evidence to date does not indicate consistently that occupational exposure to cadmium substantially increases the risk of PC. The development of prostatic tumours in cadmium-treated rats supports, but does not establish, a possible role for cadmium in human PC.

Environmental exposure to pesticides and other endocrine-disrupting chemicals

In vitro and *in vivo* assays have shown that certain chemicals, such as organochlorine pesticides and herbicides, can act as oestrogens and it is hypothesised that these compounds may induce adverse effects through modulation of various complex biochemical and physiologic pathways (Golden et al., 1998; IPCS, 2002). (Golden et al., 1998) discussed the hypothesis that *in utero*/early exposure to oestrogenic compounds may affect PC risk in later life. The possibility that some chemicals may exert their effects *via* the androgen receptor (AR) has been less well-studied. Some compounds (eg, vinclozolin, flutamide, DDE, HPTE, fenitrothion, procymidone) have been shown to act as antiandrogens (reviewed by (IPCS, 2002)). (Schrader and Cooke, 2000), using an *in vitro* reporter gene assay to evaluate the androgenic/anti-androgenic effects of some pesticide and food-additive chemicals, found that *p,p'*-DDE acted as an AR agonist (10-100 µM) in the absence of DHT, but was an antagonist (1-100 µM) in the presence of DHT. 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, kepone, butylated hydroxyanisole and butylated hydroxytoluene (1 and 10 µM) all partially inhibited activation by DHT, but had little or no effect alone. Toxaphene (10 µM) acted as an agonist in the absence of DHT, but decreased cell viability. α- and δ-hexachlorocyclohexanes (HCH) (10 µM) antagonised DHT, whilst β-HCH and α-HCH, mirex, photomirex, oxychlorane, *cis*- and *trans*-nonachlor (concentrations not stated) had no effect. A recent *in vitro* study showed that different pesticides, including β-HCH, *o,p*-DDT, heptachlor epoxide, *trans*-permethrin, and chlorotalonil, could induce progression of androgen-dependent PC cells by activating erbB-2, but this effect did not occur in an androgen-independent cell line. The effect of *o,p'*-DDT was not mediated through direct interaction with the AR (Tessier and Matsumura, 2001). The relevance of results of *in vitro* tests for endocrine effects are uncertain.

Epidemiological studies have not shown an association of PCB, TCDD and DDT with increased risk of PC (IPCS, 2002). No excess risk was seen in PCB-exposed workers

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(Bertazzi et al., 1987; Brown, 1987; Sinks et al., 1992). Environmental exposure to DDE was not positively associated with PC mortality in 22 states of the United States, rather a possible negative correlation was noted (Cocco and Benichou, 1998). It has been suggested that exposure to the anti-oestrogenic compound, TCDD, may be a risk factor for PC (Keller-Byrne et al., 1997). However, an analysis of 20-year mortality in an area of Seveso, Italy, following an industrial accident in which substantial quantities of TCDD were vented into the atmosphere, showed no increase in PC deaths (Bertazzi et al., 2001). A cohort study based on the international registry of workers exposed to TCDD also showed no increase in PC mortality (Saracci et al., 1991).

Environmental herbicide exposure has shown a possible link with PC, but the evidence is weak and the mechanism is unknown (IPCS, 2002). A study in the UK showed a small increase in PC incidence in the area surrounding a pesticide factory, as compared with national rates (observed/expected = 1.10, 95% CI, 1.02-1.18), but there was no decline with distance from the factory (Wilkinson et al., 1997). An ecological study showed a positive correlation between pesticide usage and PC incidence in black men in central California (r [correlation coefficient] = 0.67 and 0.49, respectively, for pounds of atrazine and captan applied annually) (Mills, 1998). However, the US EPA recently concluded that available data do not support a link between atrazine exposure and PC (EPA, 2003). A study of crop production, pesticide use, breast and prostate cancer mortality in Belgium indicated significant associations of both cancer types with cereal and potato cultivation, but no correlation with areas where pesticides are used abundantly, such as fruit-growing areas. Stronger associations were noted for breast than prostate cancer (Janssens et al., 2001). The potential association of pesticide exposure and PC risk is discussed further in the section on occupational risk factors later in this report.

Genotoxic chemicals

Six genotoxic chemical compounds have been found to induce prostate carcinomas in rats: benzo[*a*]pyrene (B[*a*]P), *N*-methyl-*N*-nitrosourea (MNU), *N*-nitrosobis (2-oxopropyl) amine (BOP), 7,12-dimethylbenz(a)anthracene (DMBA), 3,2'-dimethyl-4-amino-biphenyl (DMAB) and 2-amino-1-methyl-6-phenyl-imidazo[4,5-*b*]pyridine (PhIP). Co-administration of T enhances tumour yield, with a latency period of 40-60 weeks (reviewed by (Shirai et al., 2000; Grover and Martin, 2002)). Specific mutations have been identified from PhIP-induced prostate carcinomas in the *lac1* gene of *lac1* transgenic rats (Stuart et al., 2000). Recent studies have suggested that human prostate epithelial cells may be particularly susceptible to the DNA-damaging effects of PhIP, *N*-OH-PhIP and B[*a*]P (Kooiman et al., 2000; Martin et al., 2002a).

(Watanabe et al., 1997) reported that the *p53* gene mutational spectra of prostate cancers varied between different populations, suggesting that different agents may have acted as initiators, or that there is no specific genotoxic factor for PC.

Vitamin supplements

A recent evaluation from the US Health Professionals Follow-Up Study suggested that the risk of advanced PC was increased in men consuming > 100 mg/day

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supplemental zinc (RR = 2.29, 5% CI, 1.06-4.95, as compared with men consuming 0 mg/day supplement) (Leitzmann et al., 2003). There was no increase in risk for men consuming 100 mg/day zinc supplement. It was noted that potential confounding factors, for example increased likelihood of high-dose zinc use by men with long-standing prostate symptoms or residual confounding by intake of other supplements (eg, calcium), could not be ruled out as a possible explanation for these findings. A mechanism for the association has not been proposed.

The available toxicology data on zinc were reviewed fully by the Expert Group on Vitamins and Minerals (EVM) in its report entitled "Safe Upper Limits for Vitamins and Minerals" (<http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf>). The group established a safe upper level of intake for zinc of 25 mg/day (lifetime intake for an adult), based on adverse effects on copper status in subjects taking 50 mg/day zinc supplement. The section of the EVM report summarising data on zinc carcinogenicity and genotoxicity stated that "Zinc has been found to give positive results in some *in vitro* and *in vivo* genotoxicity tests. No data have been identified on the carcinogenicity of zinc." However the genotoxicity tests reviewed related to non-standard tests not routinely used in regulatory assessments. Hence no definitive conclusions have been reached in this review.

PAHs- Occupational studies.

Recent studies in the US have shown positive associations for several occupations involving potential exposure to polycyclic aromatic hydrocarbons (PAHs) (Krstev et al., 1998a; Krstev et al., 1998b). These groups include firefighters (Grimes et al., 1991; Demers et al., 1994; Krstev et al., 1998a; Krstev et al., 1998b; Ma et al., 1998), power plant operators (Krstev et al., 1998a; Krstev et al., 1998b), foundry workers (Sharma-Wagner et al., 2000), coke oven workers (Costantino et al., 1995), furnace, kiln and oven operators (Krstev et al., 1998b), chimney sweeps (Evanoff et al., 1993), railway workers (Aronson et al., 1996; Krstev et al., 1998a; Krstev et al., 1998b; Sharma-Wagner et al., 2000), heavy equipment operators (Krstev et al., 1998a), farm machine operators and paving and stone cutting workers (Sharma-Wagner et al., 2000). (Aronson et al., 1996) found an excess risk of PC with exposure to PAHs as a class, whilst (Seidler et al., 1998) found excess risk in relation to diesel fuel and fumes, soot, tar and pitch. These studies have not been critically assessed for this overview.

Exogenous factors – occupational studies

The majority of studies of occupation and PC have focussed on cadmium, a non-essential trace element which is a zinc antagonist in biological systems (see review by (Brzoska and Moniuszko-Jakoniuk, 2001)) (the potential association between cadmium and PC is discussed earlier in this review), and on farming and farming-related exposures. However, to date no occupational risk factors for PC have been confirmed.

Farming and related exposures

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Farmers and farm-related workers

A number of studies have indicated an excess of PC amongst farmers and farm-related workers, although other studies have failed to confirm this observation. Several reviews and meta-analyses of the epidemiological literature have been published. These generally describe a slight excess of PC, but no clear associations with specific farm exposures have been identified (Blair et al., 1985; Blair et al., 1992; Blair and Zahm, 1995; Blair and Zahm, 1991; Van Der Gulden and Vogelzang, 1996; Cocco, 2002; Acquavella et al., 1998; Keller-Byrne et al., 1997).

In a review of 24 published studies which had evaluated PC risk in farmers, (Blair and Zahm, 1991) noted that 10 of these studies had reported significantly elevated risks (all < 2.0), whilst 1 study had shown a significantly decreased risk (not < 0.9). Blair and colleagues also carried out a meta-analysis of occupational surveys on cancer mortality, including only published studies which had evaluated data on many occupations or many diseases. An overall RR of 1.08 (95% CI, 1.06-1.11) was calculated for death from PC in farmers, based on results from 22 studies (7753 PC cases). Of these, 6 studies showed significantly increased RRs (not > 2.7) whilst 1 showed a significantly decreased RR (not < 0.9) (Blair et al., 1992).

A meta-analysis of 24 studies published between 1988-1994, which had examined the association of PC incidence or mortality with farming, indicated a weak positive association (RR = 1.12; 95% CI, 1.01-1.24). RR for retrospective studies only (n = 13) was 1.29 (95% CI, 1.10-1.51), and the RR calculated from studies reporting standard mortality ratios (SMR) (n = 11) was 0.93 (95% CI, 0.77-1.11). A total of 9 studies showed a negative association between PC and farming (RRs 0.71-0.96, 8-441 cases), whilst 15 studies showed a positive association (RRs 1.06-5.0, 12-4827 cases). (Keller-Byrne et al., 1997).

(Acquavella et al., 1998) also reported a meta-analysis of studies of cancer incidence in farmers, based on data from a total of 37 published (to 1994) and unpublished studies. Analysis of the 30 of these studies which had evaluated PC showed an overall RR for PC (white male farmers) of 1.07 (95% CI, 1.02-1.13). Reanalysis of the studies considered by (Blair et al., 1992) (some of them updated) revealed a RR of 1.09 (95% CI 1.04-1.15) and substantial heterogeneity amongst the studies. Analysis of all 30 studies by study type showed RRs of 0.95 (95% CI, 0.93-0.98) for follow-up studies (n = 11), 1.12 (95% CI, 1.08-1.18) for proportional mortality ratio (PMR) studies (n = 11) and 1.21 (95% CI, 1.15-1.28) for case-control studies (n = 8). The authors noted that, for all cancers except lip cancer, the most homogenous RRs (all close to 1.0) were seen with retrospective follow-up studies and that elevated rates indicated by PMR and case-control studies probably resulted from limitations of these methodologies. They concluded that lip cancer was the only cancer that was clearly elevated amongst farmers.

Studies reported more-recently have shown a moderately increased risk of PC amongst farmers or farm workers. Case-control studies have indicated slightly increased risk for some groups of farm workers, but still no clear correlation with specific farm exposures (Van Der Gulden et al., 1995; Krstev et al., 1998a; Band et al., 1999). Cohort studies of farmers and pesticide applicators have shown more

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consistent positive findings. Fleming and colleagues noted an increase in PC incidence (standard incidence ratio [SIR] = 1.91; 95% CI, 1.72-2.13) (Fleming et al., 1999a) and mortality (SMR = 2.38; 95% CI, 1.83-3.04) (Fleming et al., 1999b) in pesticide applicators in Florida, as compared with the general population. A study of a large Swedish cohort of licensed pesticide applicators showed an excess PC incidence (SIR = 1.13; 95% CI, 1.02-1.24) compared with the general population (Dich and Wiklund, 1998), but no excess risk was found amongst Swedish farmers in general (Wiklund and Dich, 1995). Studies of farmers in IOWA showed increased risk of PC (RR = 1.7; 95% CI, 1.0-2.7) and less-well-differentiated PC (RR = 2.0; 95% CI = 1.1-3.6) in those aged 70+ (Parker et al., 1999), and of death due to PC (PMR = 1.26; 95% CI, 1.19-1.33) (Cerhan et al., 1998). A proportional mortality study also showed increased risk for death from PC in farmers in British Colombia (PMR = 112; 95% CI, 105-120) (Buxton et al., 1999).

(Parent and Siemiatycki, 2001) noted that in most studies of farmers, the epidemiologic analyses were based on job title designations that covered a great variety of occupational circumstances. Therefore, if there is a genuine excess risk for PC which is due to occupational, rather than lifestyle factors, then there should be a much higher RR in some sub-groups of farmers. However, only a small number of studies have attempted to assess risks in relation to specific exposures, the best being that of (Morrison et al., 1993) who evaluated a large Canadian cohort of farmers according to type of farming practice. This study showed increased PC mortality risk associated with the number of acres sprayed with herbicides (RR = 2.23 for 250 or more acres sprayed; 95% CI, 1.30-3.84) (phenoxy acetic acids were the most commonly used herbicides), whilst other farm exposures were not related to PC risk.

Recent data from hospital-based, case control studies showed increased risk of PC in Italian farm workers exposed to some organochlorine pesticides. An initial analysis including 1279 cases indicated a significant association of PC with agricultural work (OR = 1.4; 95% CI, 1.0-2.1), with the excess PC specifically related to the application of pesticides (OR = 1.7; 95% CI, 1.2-2.6) and to fruit growing (OR = 2.0; 95% CI, 1.2-3.5) (Settimi et al., 2001). Analysis of a further 124 cases indicated increased risk of PC with previous exposure of agricultural workers to organochlorine pesticides (OR = 2.5; 95% CI, 1.4-4.2) (Settimi et al., 2003). The most frequently reported organochlorine compound exposures were DDT (OR = 2.0; 95% CI, 1.1-3.0), and dicofol+tetradifon (applied together) (OR = 2.8; 95% CI, 1.5-5.0) (Settimi et al., 2003). No positive correlation was seen with any other pesticide group evaluated. The results of this analysis are shown in Table 2.

(Mills and Yang, 2003) reported increased risk of PC associated with exposure to certain pesticides in a nested case-control study of (mostly Hispanic) farm workers in California. Sixteen specific agricultural chemicals were evaluated. A significantly increased risk was seen with high exposure to simazine (OR = 1.53), whilst high exposures to dichlorvol, heptachlor and lindane were associated with non-significant increases (ORs around 1.3) (Table 3). Risk was positively associated with increasing use for heptachlor and lindane (P for trend = 0.003) and for simazine (P for trend = 0.03).

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As part of the US Agricultural Health Study PC incidence was evaluated in a prospective cohort study of ~ 55 000 male pesticide applicators from Iowa and North Carolina. As compared with the general male population, PC incidence was positively associated with higher-level methyl bromide use (p value for linear trend = 0.004), and with a history of use of chlorinated pesticides among applicators over age 50 years (p value for linear trend = 0.005). The authors also noted that several other pesticides (chlorpyrifos, coumaphos, fonofos, phorate, permethrin and butylate) showed a significantly increased risk of PC among study subjects with a family history of PC, indicating possible gene-exposure interactions for PC (Alavanja et al., 2003).

(Potti et al., 2003) suggested a link between pesticide exposure and early-onset PC. In this study of men with PC onset at age 50 years old in North Dakota, approximately two thirds (37/56) of patients were classified as “exposed to pesticides”. However, in the absence of exposure data in a control population from this highly agricultural part of the US it is not really possible to reach any conclusions re exposure and effect. It is notable that mean survival in the subgroup of patients with pesticide exposure was 11.3 months, as compared with 20.1 months in the unexposed group, however in view of the small numbers and lack of specific information on nature of exposure, it is too preliminary to regard as other than something that should be looked for in similar studies.

In summary, several systematic reviews and meta-analyses have indicated a slightly increased risk of PC amongst farmers and farm-related workers. However, no clear risk factors have been established to date.

Pesticide manufacturers

Some studies have shown non-significant excess risks for PC among pesticide manufacturers: SMR = 190; 95% CI 82-375 for manufacturers of chlorinated dioxins (Ott et al., 1987), SMR = 132; 95% CI 78-208 for workers involved in manufacture, formulation and spraying of phenoxy acid herbicides (Coggon et al., 1986), SMR = 142; 95% CI, 57-293 for workers in a German chemical herbicide-production plant, including processes contaminated with TCDD (Manz et al., 1991). Other studies have shown no excess risk; SMR = 41; 95% CI, 1-229 for workers in production of dieldrin and aldrin (de Jong et al., 1997), observed/expected = 0/0.2 (mortality) 0/0.7 (incidence) for manufacturing workers with potential exposure to alachlor (Acquavella et al., 1996), RR = 0.83 (CIs not given) for workers in 2 phenoxy-herbicide manufacturing factories in Denmark (Lyngø, 1985).

Studies of potential associations of environmental pesticide exposure and PC risk have been discussed earlier in this report.

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Other occupations

There is no consistent evidence for an association of PC with a wide range of other occupations which have been evaluated. Reviews of the extensive literature, and details of more-recent studies, are summarised below.

Reviews of the literature

(Muir and Harriss, 1998) reviewed data from > 200 studies which had evaluated potential associations of occupation and PC. Except for studies of farming or cadmium exposure, which have been discussed in detail in previous sections of this report, their overall findings are summarised in the following paragraph.

Radiation and nuclear fuels – The majority of studies have indicated that the prostate is not a radiosensitive site. No excess risk has been demonstrated for PC and low level radiation exposure. However, a small number of studies have shown possible PC excesses in groups with possible or known internal radionuclide contamination (eg, workers at the UK Atomic Energy Authority (Beral et al., 1985)). Whether this effect is directly related to radiation or to other factors (eg, interference of metal metabolism in the prostate) is not known.

Rubber workers – There is evidence for a possible link between PC and workers in the rubber industry. It is not clear what are the exposures that may be responsible for this effect.

Meat workers – Meat workers may show a small increase in risk for PC. Some potential causal factors are meat, animal bacteria, viruses, nitrosamine and diet.

Exhaust exposure – Studies showed non-significant raised SMRs. It is not known whether any increased risk might be related to a chemical component of exhaust exposure or to other factors such as lack of physical activity.

Chemicals – Studies of this general category have not consistently shown an increased risk for PC.

Other exposures – A cohort study of 2131 men employed for at least 3 months as fertiliser workers showed increased SMRs for those exposed to nitrate fertilisers (SMR for all exposed = 161, 95% CI 107-239; SMR for exposed 10 years = 157, 95% CI, 101-239). Exposure to other fertilisers did not show increased risk for PC (Hagmar et al., 1991). It was noted that the additional intake of nitrates due to occupation would be low as compared with dietary intake. However, intake by inhalation may be more dangerous than dietary intake due to endogenous nitrosification. Further studies are required to confirm these findings. One study (Olin, 1978) showed a significant association of PC and work as a chemist, but the overall number of PC deaths was small and it was not felt that this was a major risk group for PC. There was no overall evidence (in most cases limited data available) for an association of PC with aluminium workers, exposure to dust, grain workers, firemen, printing and pressmen, plastics, coke workers and railway workers.

(Van Der Gulden, 1997) reviewed evidence regarding PC risk in 53 studies including metal workers and 27 studies of mechanics, repairmen and machine operators. Most studies showed slightly increased risks, as have some more recent studies (Park and

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Mirer, 1996; Van Der Gulden and Vogelzang, 1996; Brown and Delzell, 2000). The majority of studies have not identified specific risk factors, although a few studies suggested some evidence of associations with metallic dusts and with metalworking fluids such as solvents, cutting oils, mineral oils, heating oils, hydraulic fluids, lubricating oils and acids (Tolbert et al., 1992; Aronson et al., 1996; Van Der Gulden, 1997). A recent review by the US National Institute for Occupational Safety and Health concluded that the evidence for increased PC risk among workers exposed to metal-working fluids was equivocal (NIOSH, 1998).

(Kogevinas et al., 1998) and (Stewart et al., 1999) have recently reviewed studies of PC risk for workers in the rubber industry, and in both cases concluded that there was little evidence for an association.

(Wong and Raabe, 2000) published a review and meta-analysis of cancer epidemiology in petroleum workers, including > 350 000 workers from the US, UK, Canada, Australia, Finland, Sweden and Italy. PC mortality for the whole group was as expected. Elevated rates were noted in short-term workers at a US refinery and in short-term workers employed in certain crafts at US crude oil operations. However, in the absence of an upward trend by length of employment, it was concluded that there was unlikely to be an association between exposure to petroleum products and PC.

Recent publications

A summary of recent-publications which have evaluated occupation and PC risk is given below.

(Aronson et al., 1996) carried out a population-based, case-control study of occupation and PC in Canada. They found elevated risks amongst those employed in water-transport, aircraft-manufacturing, metal-product fabricators, structural-metal erectors, and railway-transport workers. Exposure assessments indicated increased risks with exposure to metallic dust, liquid fuel combustion products, lubricating oils and greases, and polyaromatic hydrocarbons from coal. The same group also reported a study which, by inference of likely exposures from job titles, indicated increased risk of PC with any exposure to calcium carbonate, and substantial exposure to metallic dust (Weston et al., 2000).

In a proportional mortality study including 216 occupations and 88 industries (Buxton et al., 1999) found increased risk of death from PC among business owners and managers (PMR = 110; 95% CI = 101-118), brokers (PMR = 184; 95% CI = 122-266), farmers and farm managers (PMR = 112; 95% CI = 105-120), and school teachers (PMR = 133; 95% CI = 101-174). Evaluation by industry showed increased PC mortality in the agricultural, financial and transportation equipment and manufacturing industries.

A study of occupational risk factors for PC in Sweden indicated that certain groups – farmers, occupations and industries associated with exposure to cadmium, herbicides and fertilisers, and men with low occupational physical activity levels – had elevated PC risk, although the excess risks were generally small (< 10%) (Sharma-Wagner et al., 2000).

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(Band et al., 2001) reported a significantly increased incidence of PC amongst pulp and paper mill workers in British Columbia (SIR = 1.32; 95% CI, 1.21-1.44).

(Sharpe et al., 2001) reported that the following leisure activities or related exposures were associated with increased PC risk; home or furniture maintenance, exposure to metal dust, exposure to lubricating oils or greases, exposure to pesticides or garden sprays.

Analysis of cancer risk amongst airline pilots and flight personnel has indicated an increased risk of PC, in particular related to long-haul flights (Ballard et al., 2000; Pukkala et al., 2002).

A nested case-control study indicated that men with the highest 10% occupational exposure to electromagnetic fields (EMFs) were twice as likely to die from PC as those exposed to EMFs at lower levels (Charles et al., 2003).

Summary

1- The incidence of PC varies widely around the world. Gradual increases in incidence have occurred in many countries since the 1960s, with larger increases following the introduction of diagnostic PSA screening. Survival rates have improved in recent decades, possibly as a result of earlier diagnosis. Mortality rates have also shown a slight decrease recently. It is thought that this is unlikely to be due, in greater part, to earlier detection, given the slow rate of development of the disease.

2- Well-established indicators of risk for PC are age and family history. Incidence also varies widely depending on ethnicity/country of residence.

3- There is currently no agreement about the involvement of other factors in the aetiology of PC. Credible hypotheses that have been proposed involve hormonal patterns and dietary practices.

4- Farming has been the most consistent occupational risk factor for PC, although the majority of studies have not looked at specific risk factors for farmers and farm-related workers. There is no substantive evidence for an association of other occupations with increased risk of PC.

5- A recent assessment by IPCS noted that the evidence for a link to herbicide or PAH exposure is weak, the mechanism is unknown and more research is needed. (No conclusions have been drawn with regard to PAHs in this overview.). IPCS also concluded that studies on PCB, TCDD and DDT exposures showed no association with increased PC. Data from epidemiological studies of cadmium and PC are inconsistent.

6- Cadmium is one of the few chemicals which has been associated with increased PC risk in animals, but the relevance of tumours in the studies is uncertain. Few other chemicals have been identified that can induce PC in 2-year animal

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bioassay studies. Most of these chemicals are genotoxic carcinogens, and chronic treatment with T is also required to produce a high carcinoma incidence. Transgenic mouse models for PC are being developed and these will allow for the study of hormone-responsive elements and the effects of chemicals on the multistage progression of PC to be evaluated. Future studies using these models may provide additional information on the aetiology of PC.

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