Title: Role of hormonal and other factors in human prostate cancer

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Abbreviations:

AHS	Agricultural Health Study
AR	androgen receptor
BMI	body mass index (weight in kg/height in m^2)

CPS	Cancer Prevention Survey
CYP17A	cytochrome P-450c17α
CYP1B1	cytochrome P450 1B1
CYP3A4	cytochrome P450 3A4
DES	diethylstilbestrol
DHT	dihydrotestosterone
ER	estrogen receptor
GSTM1	glutathione S-transferase M1
HPC1	hereditary prostate cancer 1
IGF	insulin-like growth factor
IGFBP	IGF binding protein
MSR1	macrophage scavenger receptor 1
NAT	N-acetyl transferase
NHANES	National Health and Nutrition Examination Survey
PAH	polycyclic aromatic hydrocarbon
PCBs	polychlorinated biphenyls
PON1	paraoxonase 1
PR	progesterone receptor
PSA	prostate-specific antigen
RNASEL	ribonuclease L gene
SHBG	sex hormone binding globulin
SRD5A2	5α-reductase type 2

TGF	transforming growth factor
VDR	vitamin D receptor

Abstract

American men have a lifetime risk of about 18% for prostate cancer diagnosis. Large international variations in prostate cancer risks and increased risks among migrants from low- to high-risk countries indicate important roles for environmental factors. Major known risk factors include age, family history and country/ethnicity. Type 2 diabetes appears to reduce risk while high birth weight and adult height are linked to increased risk of aggressive prostate cancer. Limited evidence supports an association with a history of sexually transmitted infections. A meta-analysis of 8 cohort studies indicated no associations with plasma androgen, estrogen or sex hormone binding globulin (SHBG) levels. However, there were dose-response relationships with baseline plasma testosterone levels in 2 studies that adjusted for other serum hormones and obesity. Finasteride (a drug that blocks testosterone activation) reduced prostate cancer risk by 25%. Low-frequency genes linked to familial prostate cancer only explain a small fraction of all cases. Sporadic cases were linked to relatively common polymorphisms of genes involved in (1) androgen synthesis, activation, inactivation and excretion, (2) hormone and vitamin D receptors, (3) carcinogen metabolism and (4) DNA repair. Epidemiologic evidence supports protective roles for dietary selenium, vitamin E, pulses, tomatoes/lycopene and soy foods and high plasma 1,25-dihydroxyvitamin D levels. There is inadequate evidence that vegetables, fruit, carotenoids and vitamins A and C reduce risk and that animal fat, α-linoleic acid, meat, coffee and tea increase risk. Two major cohort studies found dose-response relationships with dietary calcium intake. Total dietary energy intake may enhance risk. Limited evidence supports a protective role for

physical activity and elevated risk for farmers and other men with occupational pesticide exposure, particularly organochlorine compounds and phenoxy herbicides. There is inadequate evidence for a relationship with alcohol or smoking. Most known or suspected external risk factors may act through hormonal mechanisms but our review found little supporting evidence and substantial further research is needed.

Introduction

Hormone-related cancers occur in the prostate, breast, endometrium, ovary, testis, thyroid and bone (osteosarcoma) (Henderson and Feigelson, 2000). Hormonally-driven cell proliferation may elevate risks of these cancers by increasing the opportunity for genetic errors and epigenetic alterations or by amplifying such changes after they occur. Strong evidence for the role of environmental determinants in the development and progression of prostate cancer include: (1) large international variations in prostate cancer incidence rates, despite similar prevalence rates of latent disease in autopsy series, and (2) increase in prostate cancer risks among men who migrate from low-risk to high-risk countries (Donn and Muir, 1985). Despite much research, external risk factors that might explain most of the variations in prostate cancer risk between countries have not been identified. The absence of strong socioeconomic risk gradients within ethnic groups suggests that putative environmental causal factors are widespread.

The major male sex steroids, testosterone and dihydrotestosterone (DHT), play key roles in prostate gland growth and development. Testosterone is produced mainly by testicular Leydig cells and is converted by type II 5α-reductase in the prostate to DHT. Compared to testosterone, DHT has about 2.5-fold stronger affinity for the androgen receptor (AR). AR regulates transcription of androgen-responsive genes essential for growth, differentiation and function of the male urogenital tract (Culig et al., 2000).

Among U.S. males, the lifetime risk of developing prostate cancer is 18% and about 234,000 new cases and 27,000 deaths occur annually (ACS, 2006). The most important non-modifiable risk factors for prostate cancer are age, family history and ethnicity

(Henderson and Feigelson, 2000). Prostate cancer rarely occurs before age 50 but incidence rates increase steeply thereafter.

Internationally, annual age-adjusted prostate cancer incidence rates vary from about 12 cases per 100,000 males in Japan to over 80 in the USA, Finland, Sweden, Iceland and New Zealand (IARC, 2005). Prostate cancer incidence rates among African-Americans are almost double those for the U.S. white population (Stanford et al., 1999). The introduction of the prostate-specific antigen (PSA) blood test for prostate cancer during the late 1980's enabled detection of asymptomatic cases. U.S. prostate cancer incidence rates increased sharply during the early 1990's (Potosky et al., 1995) and then declined (Chu et al., 2003). This review summarizes results of recent epidemiologic studies on prostate cancer risk factors with a view toward identifying those where endocrine toxicants may play a role.

Risk factors

Preexisting conditions

Diabetes

A meta-analysis of 5 case-control and 9 cohort studies published up to 2003 found a reduced risk (9%) of prostate cancer among diabetics (Bonovas et al., 2004). Subsequently, the Cancer Prevention Study (CPS II) reported a lower risk of incident prostate cancer among men with diabetes diagnosed at least 4 years previously (Rodriguez et al., 2005). A nested case-control study within the US Physicians' Health Study also found a reduced risk of prostate cancer among men with diabetes, independent

of potential confounders (Zhu et al., 2004). A recent meta-analysis of 12 cohort and 7 case-control studies also showed reduced prostate cancer risk among established diabetics (Kasper and Giovannucci 2006). Serum testosterone levels were reduced among men with type 2 diabetes, possibly contributing to reduced prostate cancer risk (Ding et al., 2006). Obesity is a major risk factor for type 2 diabetes and is associated with increased risk of aggressive prostate cancer but reduced risk of nonaggressive disease (Giovannucci and Michaud 2007).

Vasectomy

Two meta-analyses of epidemiologic studies found associations between prostate cancer and vasectomy with increases of 23 and 37% reported respectively (Bernal-Delgado et al., 1998; Dennis et al., 2002). However, both reports found insufficient evidence of a causal relationship. Recent cohorts demonstrated evidence for (Rohrmann et al., 2005) and against (Lynge, 2002; Goldacre et al., 2005) this association. Such inconsistent findings might reflect the influence of uncontrolled confounders such as serum androgen levels (Rohrmann et al., 2005). There is no accepted biological mechanism whereby vasectomy may increase prostate cancer risk.

Infections

Two recent meta-analyses of 17 (Dennis and Dawson, 2002) or 29 (Taylor et al., 2005) epidemiologic studies of prostate cancer found associations with a history of sexually transmitted infections (increases of 40 and 50% reported respectively). Although two studies showed associations between prostate cancer and serum antibodies to HPV

16, 18 or 33 (Adami et al., 2003; Dillner et al., 1998), a large Nordic cohort study found no relationship (Korodi et al., 2005). Thus sexually transmitted agents may play a role in prostate cancer.

Other pre-existing conditions

In the Health Professionals Follow-up Study, there were statistically non-significant increased risks of aggressive prostate cancers among men with birth weights of 3.9-4.5 kg or 4.5 kg, compared to less than 3.2 kg (Platz et al., 1998). Similarly, a Norwegian prospective cohort study observed a positive association between birth weight and metastatic prostate cancer (Nilsen et al., 2005). The association was stronger for combined high birth weight and birth length. A Norwegian cohort study found increased prostate cancer risk among tall men (Engeland et al., 2003). A cohort study of US male health professionals reported a similar association (Giovannucci et al., 2004) but an Australian cohort study revealed no relationship (MacInnis et al., 2003). A meta-analysis of 31 cohort and 25 case-control studies reported a dose-response relationship between adult height and prostate cancer risk (MacInnis and English 2006). Although inconclusive, these findings suggest that factors promoting intrauterine and postnatal growth may produce elevated risks of aggressive prostate cancer.

Endocrine function

Bosland (2000) proposed that prostate carcinogenesis: (1) involves androgen receptor-mediated mechanisms that enhance the carcinogenic activity of genotoxins including estrogen- and prostatitis-generated reactive oxygen species and, possibly, weak environmental carcinogens of unknown nature, and (2) may be modulated by diet and by

genes that encode steroid hormone receptors and enzymes involved in the metabolism and action of steroid hormones..

Androgens

Although human prostate carcinomas are usually androgen sensitive and may be temporarily restrained by hormone therapy before acquiring androgen-independence (Bosland, 2000), epidemiologic studies found inconsistent evidence for associations with plasma androgen levels. In a California cohort study, prostate cancer was positively associated with baseline plasma androstenedione but not with total testosterone or SHBG levels (Barrett-Connor et al., 1990). In the Physician's Health Study, there was a dose-response relationship between prostate cancer risk and baseline plasma testosterone levels, after simultaneous adjustment for other hormone and SHBG levels (Gann et al., 1996).

A meta-analysis of 8 cohort studies concluded that there was no relationship between development of prostate cancer and baseline serum or plasma concentrations of free or total testosterone, DHT, androstenedione or dihydroepiandrosterone sulphate (Eaton et al., 1999). However, a meta-analysis of 2 cohorts (Gann et al., 1996; Hsing and Comstock, 1993) that adjusted for BMI and all measured serum hormones reported a 234% increase in risk for 4^{th} vs 1^{st} quartile total serum or plasma testosterone levels (Shaneyfelt et al., 2000). A case-control study nested with a cohort of Scandinavian men found a weak *inverse* dose-response relationship between prostate cancer and serum or plasma total testosterone and no association with free testosterone (Stattin et al., 2004a). The US Prostate Cancer Prevention Trial showed that healthy men given finasteride, an

inhibitor of 5α-reductase, had an overall 25% reduced risk of prostate cancer during a 7-year follow-up but a significantly higher proportion of aggressive cancers (Thompson et al., 2003). In sum, epidemiologic studies provide inconsistent evidence for a role of endogenous androgen levels in prostate cancer development. However, there remains the possibility that endogenous androgen levels and exposure to exogenous endocrine toxicants during gestation, childhood or adulthood may influence initiation and promotion of prostate cancer.

Estrogens

Prostate cancer was not associated with baseline plasma estrone or 17-beta-estradiol (E2) levels in a California cohort (Barrett-Connor et al., 1990). A case-control study nested within the Physicians' Health Study cohort reported a non-linear inverse association between prostate cancer and plasma E2 (Gann et al., 1996). A meta-analysis of 8 cohort studies concluded that there was no relationship between development of prostate cancer and baseline serum concentrations of estrone or E2 (Eaton et al., 1999). In subsequently published studies, the Carotene and Retinol Efficacy Trial found reduced prostate cancer risks among men in the 4th quartile of baseline total or free serum E2 concentrations (Chen et al., 2003) but an Australian cohort study showed no association with baseline plasma E2 levels (Severi et al., 2006). A large international pooled analysis yielded no evidence for an association with polymorphisms of the HSD17B1 gene, which encodes the 17HSD type 1 enzyme that converts estrone to the more active E2 (Kraft et al., 2005).

Estrogens are metabolized to catechol estrogens by cytochrome P450 enzymes encoded by the genes CYP1A1 and CYP1B1. Until they are inactivated by catechol-O-methyltransferase (COMT), catechol estrogens generate reactive oxygen species (ROS) that produce oxidative DNA damage. In experimental animals, prenatal estrogen exposure imprints the prostate to undergo increased proliferation, inflammation and dysplastic epithelial changes later in life (Harkonen and Makela, 2004; Huang et al., 2004). The latter authors hypothesized a mechanism involving up-regulation of estrogen receptor alpha (ER-α), producing altered steroid receptor expression in the prostate gland, disruption of critical developmental genes and interference with prostate gland growth and differentiation. Ethinyl estradiol (EE) and testosterone acted synergistically to promote prostate cancer induction by 3,2'-dimethyl-4-aminobiphenyl (DMAB) in experimental animals (Mori et al., 1996). Aromatase, the enzyme that converts androgens to estrogens, is expressed in prostate cancer epithelial cells but its potential role in prostate cancer development is undefined (Ellem and Risbridger, 2006). In sum, available evidence indicates that baseline plasma estrogen levels or estrogen-related polymorphisms play a role in human prostate cancer.

Sex hormone binding globulin

No strong or consistent associations with SHBG were observed in several cohort studies (Barrett-Connor et al., 1990; Comstock et al., 1993; Dorgan et al., 1998; Guess et al., 1997; Heikkila et al., 1999; Nomura et al., 1996; Vatten et al., 1997). A meta-analysis of 8 cohort studies found no relationship between prostate cancer and baseline serum or

plasma SHBG concentrations (Eaton et al., 1999). More recently, a Scandinavian nested case-control study found a marginal inverse association with SHBG (Stattin et al., 2004a). Thus there is no evidence that plasma SHBG levels influence the risk of prostate cancer.

Genetic factors

Familial prostate cancer

Studies of familial clusters and sporadic cases indicate that prostate cancer likely involves multiple genes, possibility interacting with each other and environmental factors (Schaid, 2004). Meta-analyses of epidemiologic studies found positive associations between prostate cancer and history of this cancer in first-degree relatives with risk increasing by 250 and 220% respectively (Johns and Houlston, 2003; Bruner et al., 2003). The association with family history was somewhat stronger for cases diagnosed before age 60 and for men with an affected brother. A subsequently published Italian study also reported a positive association between prostate cancer and family history (Negri et al., 2005). Family history of prostate cancer may account for 5-20% of all prostate cancer cases (Hemminki and Czene, 2002; Negri et al., 2005). Familial prostate cancer clusters were linked to low-frequency genes such as hereditary prostate cancer 1 (HPC1), HPC2, HPCX, macrophage scavenger receptor 1 (MSR1) and ribonuclease L gene (RNASEL) (Farnham et al., 2005; Kruger et al., 2005; Noonan-Wheeler et al., 2006; Schaid 2004; Sharpe et al., 1998).

Polymorphisms

Polymorphisms of several genes were associated with increased prostate cancer risk (Gsur et al., 2004; Schaid 2004; Sharpe et al., 1998). Because they are relatively common, such polymorphisms may account for considerably more cases than rare familial genes. As discussed below, there is emerging evidence that polymorphic genes may modulate effects of endogenous androgens or environmental toxicants on prostate cancer risk. However, most studies have lacked the statistical power to evaluate the combined effect of several polymorphisms (Gsur et al., 2004; Salam et al., 2005). This is an important limitation of epidemiologic studies to date in this field including those discussed below.

Androgen-related genes

Epidemiologic studies found limited and inconsistent evidence for associations between prostate cancer and polymorphisms of genes involved in: (1) androgen synthesis (CYP11A1, CYP17A1, CYP19A1, CYP17A2) (Douglas et al., 2005; Kumazawa et al., 2004; Mononen et al., 2006; Ntais et al., 2003a), (2) testosterone activation to DHT in prostate (SRD5A2) (Cicek et al., 2004; Salam et al., 2005), (3) androgen inactivation and excretion (CYP3A4, HSD3B1, HSD3B2) (Chang et al., 2002; Keshava et al., 2004; Zeigler-Johnson et al., 2004), (4) AR (Binnie et al., 2005; Sieh et al., 2006; Zeegers et al., 2004b) and, (5) AR coactivators (AIB1/SRC-3) (Hsing et al., 2002b).

Estrogen and progesterone receptors

The role of estrogen and progesterone receptors in prostate cancer remains relatively unexplored in epidemiologic studies. A Japanese case-control study of familial prostate

cancer found positive associations with the T/T variant of the PvuII site in the ER-α gene, the C/T and T/T variants of the CYP19 gene, the G/A variant of the COMT gene, and the combined occurrence of all 3 variant genes (Suzuki et al., 2003). A Swedish case-control study reported a positive association between prostate cancer and the TC or CC variant alleles of ER-β (Thellenberg-Karlsson et al., 2006). Reduced expression of ER-β and progesterone receptors (PR-A and PR-B) were observed in human prostate cancer cells (Ji et al., 2005). Such findings are consistent with a role for hormone receptor gene expression in prostate cancer.

Vitamin D receptor

Two meta-analyses concluded that prostate cancer was not associated with vitamin D receptor (VDR) gene polymorphisms (Berndt et al., 2006; Ntais et al., 2003b). However, reduced prostate cancer risk was linked to high-activity VDR variants among men with high sun exposure (John et al., 2005). As noted below, vitamin D promotes inhibits proliferation of normal and malignant human prostate cells. Thus both vitamin D intake, solar activation and VDR variants may modify prostate cancer risk..

Genes related to carcinogen metabolism

The cytochrome P450 (CYP) super family includes key enzyme systems involved in bioactivation of chemical carcinogens. Japanese case-control studies reported positive associations between prostate cancer and CYP1B1 Leu432Val (Fukatsu et al., 2004) and the Val/Val CYP1A1 genotype but not with CYP1A2 or CYP2E1 polymorphisms (Murata et al., 2001). A Chilean study observed increased prostate cancer risk among men with both the CYP1A1-M1* and the GSTM1 null polymorphisms but not among

men with CYP1A1-M1* and GSTT1 null polymorphisms (Caceres et al., 2005). A Turkish case-control study observed no association between prostate cancer and CYP1A1 polymorphisms (Silig et al., 2006). Such limited and inconsistent findings preclude firm conclusions about the role of cytochrome P450 variants in prostate cancer.

Although polymorphisms of N-acetyltransferases (NATs) may influence cancer risk by changing the rates of activation or inactivation of carcinogens, there is only limited epidemiologic evidence for their role in prostate cancer. In a European case-control study, prostate cancer risk was reduced among men with a slow acetylator polymorphism (NAT2*6/NAT*6) but not with NAT1 polymorphisms (Costa et al., 2005). No relationship with NAT2 polymorphisms was detected in two other case-control studies (Rovito et al., 2005; Wadelius et al., 1999). The former study found associations with rapid NAT2 and NAT1*10 among men with high intake of heterocyclic amines from meat cooked at high temperatures (Rovito et al., 2005). These findings suggest the potential for interaction between NAT polymorphisms and dietary carcinogens but require confirmation. GSTP1 occurs in normal prostate epithelium but is not expressed in most human prostate cancers and prostatic epithelial neoplasia (PIN) lesions because of somatic CpG DNA methylation (Nelson et al., 2001). These authors proposed that loss of GSTP1 expression increases the susceptibility of the prostate to inflammatory oxidants and other genotoxins. Some studies showed associations between prostate cancer and glutathione S-transferase variants (Agalliu et al., 2006; Nam et al., 2003) but a meta-analysis observed no associations with the GST-T1, -M1 or -P1 polymorphisms (Ntais et al., 2005). In a study using brothers as controls, men with the non-deleted GSTM1 allele

displayed an increased risk of aggressive prostate cancer (Gleason score ≥7 or clinical tumour stage ≥T2c) and reduced risk of less aggressive disease (Nock et al., 2006b). Heavy smoking was associated with increased prostate cancer risk among men with the GSTM1 null genotype but not those with the non-deleted allele (Nock et al., 2006b). A Turkish case-control study reported increased prostate cancer risk among men with the GSTM1 null genotype but not those with GSTT1 null genotype (Silig et al., 2006). In a Japanese case-control study, prostate cancer was not associated with the GSTM1 or GSTT1 polymorphisms (Murata et al., 2001). A Chilean study observed increased prostate cancer risk among men with both the CYP1A1-M1* and the GSTM1 null polymorphisms but not among men with both CYP1A1-M1* and GSTT1 null polymorphisms (Caceres et al., 2005). The complexity and inconsistent findings of these studies preclude firm conclusions. Two case-control studies found associations between incident prostate cancer and PON1[1] mutations (Antognelli et al., 2005; Marchesani et al., 2003). PON1 metabolizes the toxic metabolites of several organophosphate insecticides. Similar to research on other genetic polymorphisms, such findings must be confirmed in much larger studies with adequate statistical power to assess prostate cancer risks in genetically defined subgroups. Until then, firm conclusions about their role in prostate cancer are impossible.

Genes related to DNA repair

Deficient DNA repair may play a role in the age-related increase in prostate cancer risk. Below median nucleotide excision repair was positively associated with prostate

[1]paraoxonase is an enzyme that inactivates arylester compounds including organophosphate pesticide metabolites and certain carcinogenic lipid-soluble radicals arising from lipid peroxidation

cancer in a U.S. case-control study (Hu et al., 2004). A Chinese case-control study of 5 DNA repair markers found positive associations between prostate cancer and the XRCC1-Arg399Gln AA and the MGMT-Leu84Phe CT+TT genotypes (Ritchey et al., 2005). This study also showed interactions between the CT+TT genotype of the XRCC3-241 marker combined with high intake of nitrite-preserved foods. Polymorphisms in DNA repair genes BRAC1/2, CHEK2, SRCC1 and OGG1 were also associated with prostate cancer (Dong et al., 2003; Gayther et al., 2000; van Gils et al., 2002; Xu et al., 2002). A case-control study found an inverse association between aggressive prostate cancer and the 326 Cys/Cys polymorphism of hOGG1 that encodes a key DNA repair enzyme that excises 8-hydroxyguanine, the most common type of oxidative DNA base damage (Nock et al., 2006a). Such findings suggest a role for DNA repair gene polymorphisms in the age-related accumulation of mutations that may explain the steep increase in prostate cancer risk with age but require confirmation.

Multi-gene studies

A meta-analysis of 4 studies employing DNA microarray gene expression technology concluded that 50 genes were over-expressed and 103 genes were under-expressed in prostate cancer (Rhodes et al., 2002). Over-expressed genes included hepsin, a transmembrane serine protease, ornithine decarboxylase, tumor protein D52 (TPD52) and several enzymes involved in polyamine and adenine monophosphate biosynthesis pathways. Under-expressed genes included SPARCL1 (a candidate suppressor gene) and TIMP3 (an inhibitor of metalloproteinases). Over-expression of TPD52 in prostate cancer may be triggered by androgens and genomic amplification

(Rubin et al., 2004). The potential for substantially increased prostate cancer risk among men with multiple polymorphisms is illustrated by a case-control study that found a 1300% increase in risk for the combination of smoking and the polymorphisms p53cd72 Pro and CYP1A1 M1 (Quinones et al., 2006).

DNA methylation

Hypermethylation of CpG islands on gene promoters appears to silence expression in human prostate cancer cells of ER-α (Lau et al., 2000; Li et al., 2004), ER-β (Nojima et al., 2001), TGF-β (Zhao et al., 2005), multidrug resistance 1 (MDR1) (Enokida et al., 2004), RTVP-1 (a tumour suppressor gene) (Ren et al., 2004) and E-cadherin (Li et al., 2001). In contrast, hypomethylation was linked to over-expression in prostate cancer cells of CYP1B1 (Tokizane et al., 2005), transcription factor EGR1 and heparinase (the latter degrades heparin sulfate and was implicated in tumor invasion and metastasis) (Ogishima et al., 2005).

Perinatal exposure to DES produces DNA methylation in the prostate in experimental animals, potentially inducing aberrant gene expression and increased risk of prostate cancer development and progression (Li et al., 2003). Thus environmental endocrine toxicants that affect CpG methylation might also increase prostate cancer risk.

Growth factors

Insulin-like growth factors

The insulin-like growth factor (IGF) system includes ligands, cell membrane receptors, binding proteins and proteases that modulate cell proliferation, differentiation

and apoptosis and were implicated in cancer initiation and progression (Grimberg and Cohen 2000). Diets high in fat and simple carbohydrates tend to raise insulin and growth hormone levels, thereby increasing serum IGF-1 levels (Shi et al., 2001). IGF-1 may stimulate proliferation and clonal expansion of partially transformed prostatic epithelial cells, contributing to tumor development or progression (Pollak et al., 1998-1999). Reduced insulin levels in established diabetics tend to up-regulate insulin-like growth factor binding protein 1 (IGFBP-1), thereby decreasing free IGF-I and possibly reducing prostate cancer risk. In a meta-analysis of 14 case-control studies, a 47 and 26% increase in risk of prostate cancer was reported with elevated plasma IGF-1 and IGFBP-3 levels (Shi et al., 2001). A subsequent meta-analysis of 6 studies (including 3 cohort studies) reported a similar 49% increased prostate cancer risk among mne in the highest compared to the lowest quartiles of IGF-1 (Renehan et al., 2004). A subsequently reported Swedish nested case-control study found a dose-response relationship between prostate cancer and plasma IGF-1 levels; adjustment for plasma IGFBP-3 levels substantially weakened the association levels (Stattin et al., 2004b). The association with IGF-1 was stronger for men below age 59 at baseline and for men with advanced disease. In a cohort of men screened repeatedly for prostate cancer, plasma total IGF-I, free IGF-I and IGFBP-3 levels at baseline were not associated with subsequent development of prostate cancer (Janssen et al., 2004). In sum, available evidence strongly suggests a role for IGF-1 in prostate cancer.

Insulin

Insulin promotes sex steroid hormone synthesis and cell proliferation, inhibits apoptosis and reduces production of SHBG (Peehl and Stamey, 1986) A possible mechanism whereby established diabetes might reduce prostate cancer risk relates to insulin levels that are elevated during development of diabetes but later fall because of reduced pancreatic production (Rodriguez et al., 2005). Although a Swedish cohort study did not find an association between prostate cancer and blood insulin levels (Stattin et al., 2000), a case-control study yielded a moderately strong association with fasting insulin levels, independent of potential confounders including abdominal adiposity (Hsing et al., 2001). Relatively small case-control studies reported that prostate cancer was positively associated with a polymorphism of the insulin gene present in 60% of the general population (Ho et al., 2003) and GR/RR variants of the insulin receptor substrate 1 gene (IRS-1) (Neuhausen et al., 2005). In the latter study, the association with IRS-1 variants was strongest for advanced disease.

Diet

Although dietary components might modify the effect of endogenous hormones or environmental endocrine toxicants on prostate cancer risk, epidemiologic studies to date have not assessed such potential interactions. However, there is some evidence linking diet to endogenous hormone levels. For instance, dietary enterolactone and equol were positively associated with plasma androgen levels in a cross-sectional study of healthy men (Low et al., 2005).

Antioxidants, fruits, vegetables

Epidemiologic studies reported reduced prostate cancer risks among men who reported relatively high intake of certain foods or nutrients including vitamin A (Reichman et al., 1990), vitamin E (Huang et al., 2003; Weinstein et al., 2005), selenium (Etminan et al., 2005; van den Brandt et al., 2003), carotene (Hirayama, 1979; Jian et al., 2005; Kolonel et al., 2000), cruciferous vegetables (Kolonel et al., 2000), garlic and other allium vegetables (Hodge et al., 2004; Hsing et al., 2002a) and lycopene (Etminan et al., 2004; Jian et al., 2005). In a pooled analysis of 16 epidemiologic studies, prostate cancer risk was inversely related to dietary selenium intake (Etminan et al., 2005). A meta-analysis of 21 epidemiologic studies indicated an inverse dose-response relationship between prostate cancer risk and tomato consumption, the major dietary source of lycopene (Etminan et al., 2004). Some cohort studies found no association between prostate cancer and serum vitamin A (Huang et al., 2003; Nomura et al., 1997), serum β-carotene (Huang et al., 2003; Nomura et al., 1997), serum vitamin E (Nomura et al., 1997), serum vitamin C (Berndt et al., 2005; Huang et al., 2003) or self-reported dietary intake of vitamins A, C, D or E, carotene or lycopene (Rodriguez et al., 2004; Schuurman et al., 2002; Tseng et al., 2005). The Cancer Prevention Study II (CPS-II) cohort study reported an *elevated* risk of prostate cancer death among men who used multivitamins at least 15 times/month, compared to non-users (Stevens et al., 2005). Risk was highest during the initial 4 years of follow-up, suggesting that men may have initiated vitamin use after symptoms or diagnosis of prostate cancer. A large European prospective cohort study found no relationship with fruit or vegetable consumption (Gonzalez 2006).

A review of 37 prospective cohort and 4 intervention studies on dietary risk factors for prostate cancer concluded that: (1) evidence supports a protective role for selenium and possibly for vitamin E, pulses and tomatoes/lycopene, (2) vegetables, fruit, carotenoids and vitamins A and C were not consistently related to prostate cancer risk and, (3) β-carotene supplements do not lower prostate cancer risk, except possibly for men with low β-carotene levels at baseline (Dagnelie et al., 2004).

Phytoestrogens

In a meta-analysis of 8 epidemiologic studies (2 cohort, 6 case-control) published up to 2004, prostate cancer risk was inversely related to soy food intake (Yan and Spitznagel, 2005). Among subsequently reported studies, a Swedish nested case-control study found an inverse association between prostate cancer risk and baseline plasma concentrations of enterolactone (a phytoestrogen produced by the intestinal micro flora from precursors in plant foods) (Stattin et al., 2004c). Urinary and serum equol concentrations, proxies for dietary phytoestrogen intake, were positively associated with total and free plasma testosterone among men with the TT but not the CC or CT genotypes of the CYP19 3'-untranslated region (UTR) T-C polymorphism (Low et al., 2005). In a Swedish case-control study, prostate cancer was inversely associated with high dietary intake of phytoestrogens and intermediate serum enterolactone concentrations (Hedelin et al., 2006). The available epidemiologic evidence suggests that soy foods may reduce prostate cancer risk, likely because of their phytoestrogen content. At nanomolar levels *in vitro*, the phytoestrogen genistein blocked induction of matrix metalloproteinase type 2

(MMP-2) by TGF-β and activation of p38 MAPK in prostate cancer cells, thereby inhibiting processes involved in metastasis (Huang et al., 2005).

Tea, coffee, cocoa

Prostate cancer was inversely associated with tea consumption in a cohort study of men of Japanese ancestry (Heilbrun et al., 1986). A case-control study in Utah showed that prostate cancer was not associated with tea consumption but cases over age 67 were positively associated with theobromine intake (Slattery and West, 1993). Tea contains theobromine but cocoa powder is about 2% theobromine and individuals who ingest chocolate or cocoa may consume hundreds of mg of theobromine daily. Theobromine produces dose-related increased sister chromatid exchanges in human lymphocytes *in vitro* (Brusick et al., 1986). A case-control study in Montreal, Canada reported a 2-fold increase in risk of prostate cancer among tea drinkers in the highest tertile of daily consumption (Sharpe and Siemiatycki, 2002). However, another case-control study conducted in Montreal, Toronto and Vancouver found an inverse dose-response relationship between prostate cancer risk and tea consumption (Jain et al., 1998). A Canadian cohort study observed no association with tea consumption (mainly black tea) but did find a weak positive relationship with coffee (Ellison, 2000). In a Chinese case-control study, there were inverse dose-response relationships between prostate cancer risk and green tea consumption (Jian et al., 2004). Dagnelie et al (2004) concluded that coffee and tea were not consistently related to prostate cancer risk..

Fatty acids

Polyunsaturated fatty acids comprise two families, n-6 and n-3 (also known as omega 6 and omega 3) that are derived, respectively, from the essential fatty acids linoleic acid and α-linolenic acid. A meta-analysis of 9 epidemiologic studies (4 cohort, 5 case-control) published up to 2001 revealed a 70% increased prostate cancer risk among men with a high intake or blood level of ALA (Brouwer et al., 2004). Analysis of almost 3000 prostate cancers in the Health Professionals Follow-Up Study showed no overall association with ALA intake but advanced cancers were positively associated with the highest quintile of ALA intake from non-animal and meat/dairy sources (Leitzmann et al., 2004). In contrast, overall prostate cancer risks were reduced among men in the highest quintiles of the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Recent reviews of epidemiologic studies found little evidence of an association between prostate cancer and dietary intake of n-3 fatty acids (Astorg 2004; MacLean et al., 2006). Serum trans fatty acids were associated with increased prostate cancer risk in a large cohort study (King et al., 2005). In experimental animals, n-3 fatty acids (e.g., α-linolenic acid (ALA)) tend to inhibit while n-6 fatty acids generally promote prostate tumor growth (Leitzmann et al., 2004). In mice, the trans-10, cis-12 isomer of conjugated linoleic acid may increase lipid oxidation (Wahle et al., 2004). In sum, the limited and inconsistent evidence precludes firm conclusions about the role of dietary unsaturated fatty acids in prostate cancer.

Meat

Several studies linked prostate cancer to diets high in animal fat (Hayes et al., 1999; Le Marchand et al., 1994), red meat (Kolonel 1996), beef (Le Marchand et al., 1994), dairy products (Gao et al., 2005; Schuurman et al., 1999b) and cured meat (Schuurman et al., 1999b). However, Dagnelie et al (2004) concluded that meat and egg consumption were not consistently related to prostate cancer risk..

Calcium, vitamin D, dairy products

Finnish and U.S. nested case-control studies found inverse associations between prostate cancer risk and plasma 1,25-dihydroxyvitamin D (Chan et al., 2001) or 25-hydroxyvitamin D levels (Ahonen et al., 2000). A Nordic study reported a U-shaped relationship between prostate cancer risk and serum 25-hydroxyvitamin D concentrations (Tuohimaa et al., 2004), while other studies found no relationship (Braun et al., 1995; Jacobs et al., 2004; Nomura et al., 1998; Platz et al., 2004a). Vitamin D promotes differentiation and increases apoptosis, thereby inhibiting proliferation of normal and malignant human prostate cells (Tuohimaa et al., 2005). The limited and inconsistent evidence for associations between prostate cancer and serum or plasma levels of activated vitamin D metabolites precludes firm conclusions. Calcium intake (mainly from dairy products) lowers serum 1,25-dihydroxyvitamin D (vitamin D3) levels. A 2005 meta-analysis reported that men with the highest intake of calcium experienced a 39% increase in risk for prostate cancer (Gao et al., 2005). Two subsequently published cohort studies reported dose-response relationships between higher dietary calcium intake and risk of advanced or fatal prostate cancer and (Giovannucci et al., 2006) or all incident prostate

cancers (Tseng et al., 2005). In sum, available epidemiologic evidence supports an association between dietary calcium intake and increased prostate cancer risk.

Total energy intake

A meta-analysis of case-control studies reported a 60% increase in risk for advanced prostate cancer among those with high energy intake (Platz, 2002). A recent US cohort study of male health professionals found that dietary energy intake was not associated with incident prostate cancer but was positively associated with metastatic or fatal disease (Platz et al., 2003). This association was stronger among men with low BMI or small waist circumference and those who were more physically active. Finally, the association with energy intake was limited to men below age 65 and those with a positive family history.

Obesity and physical activity

Although a review of 23 epidemiologic studies published up to 2000 found inconsistent evidence of a relationship between BMI and prostate cancer (Nomura, 2001), several studies found supportive evidence. In the Cancer Prevention Study II (CPS-II), prostate cancer deaths were positively associated with obesity (Rodriguez et al., 2001). Prostate cancer was positively associated with waist:hip ratio but not BMI in a Chinese case-control study (Hsing et al., 2000). The Baltimore Longitudinal Study of Aging observed a non-linear positive relationship between waist:hip ratio and prostate cancer risk (Hubbard et al., 2004). A Norwegian cohort study revealed a weak overall positive association between prostate cancer and BMI and a stronger relationship among the subgroup age 50-59 (Engeland et al., 2003). An Australian cohort study observed no

overall association between measured BMI and prostate cancer but did find a positive relationship among the subgroup with aggressive disease (MacInnis et al., 2003). A recent meta-analysis reported that each 5 kg/m^2 increase in BMI was associated with a 5% increase in risk for prostate cancer increasing to 12% for those with advanced disease (MacInnis and English, 2006).

A review of 30 epidemiological studies categorized the level of evidence supporting an inverse association between physical activity and prostate cancer as probable (Friedenreich and Orenstein, 2002) Among studies reporting a protective effect, risk for prostate cancer was reduced by about 10-30%. In the Netherlands Cohort Study, overall prostate cancer risk was not related to baseline occupational or non-occupational physical activity or history of sports participation (Zeegers et al., 2005). Both the Health Professionals Follow-up Study and the ACS II cohort found no overall relationship between prostate cancer and physical activity (Giovannucci et al., 2005; Patel et al., 2005). However, the former study observed reduced risk of advanced prostate cancer among men in the highest category of vigorous activity and the latter study reported reduced risk of aggressive disease among physically active men. In sum, available epidemiologic evidence supports associations between prostate cancer and obesity or reduced physical activity.

Occupational exposures

Pesticides

A meta-analysis of 22 epidemiologic studies published by 2003 indicated a 24% increase in risk for prostate cancer associated with employment in farming, a proxy for

occupational pesticide exposure (Van Maele-Fabry and Willems, 2004). Similarly, analysis of 18 studies of pesticide manufacturing workers published by 2004 yielded an overall 28% increase in risk (Van Maele-Fabry et al., 2006). Among subgroups exposed to specific pesticides, prostate cancer risk was significantly elevated for men exposed to phenoxy herbicides likely contaminated with dioxins and furans. The U.S. Agricultural Health Study (AHS) of licensed pesticide applicators reported increased prostate cancer risks among private and commercial applicators (Alavanja et al., 2005). Further analysis of AHS data revealed positive associations between prostate cancer and use of chlorinated pesticides (DDT and several other banned organochlorine insecticides and two banned phenoxy herbicides) among men age 50 or older and methyl bromide and a non-significant relationship with captan use (Alavanja et al., 2003). Among men with a family history of prostate cancer, the AHS found positive associations with several specific pesticides including butylate, carbofuran and coumaphos. However, the odds ratios were not adjusted for use of other specific pesticides. The AHS found no association between prostate cancer and occupational use of metolachlor (Rusiecki et al., 2006) or atrazine (Rusiecki et al., 2004). CONCLUSION??

Other occupational exposures

Other occupations or work-related exposures linked to prostate cancer include metal fabrication, metallic dusts, cutting oils or paints/varnishes (Aronson et al., 1996; van der Gulden, 1997; Weston et al., 2000), polycyclic aromatic hydrocarbons (Aronson et al., 1996; Krstev et al., 1998), calcium carbonate (Weston et al., 2000), electromagnetic fields (Charles et al., 2003), forest management, tanneries/leather processing, soap/perfume

manufacturing (Sharma-Wagner et al., 2000), teachers (Buxton et al., 1999; Reynolds et al., 1999), policemen (Zeegers et al., 2004a), electrical power workers (Aronson et al., 1996), and flight personnel (Ballard et al., 2000; Pukkala et al., 2002). Although cadmium produced prostate cancer in rodents, two reviews found inadequate evidence of a role in human prostate cancer (IARC, 1994; Verougstraete et al., 2003) Meta-analyses of workers in the petroleum industry and the rubber and tire manufacturing industry showed little evidence for an association with prostate cancer (Stewart et al., 1999; Wong and Raabe 2000). An Australian petroleum industry cohort found an increased risk of prostate cancer prostate cancer (Gun et al., 2006). In sum, several specific occupations or work-related exposures are positively associated with prostate cancer in epidemiological studies but the evidence is inconclusive because of methodological limitations, especially the lack of direct exposure measurements (most studies used job titles as proxies for exposure assessment) and low statistical power (Parent and Siemiatycki, 2001). To the extent that any of these associations reflect causal relationships, potential mechanisms for at least some include hormonal modulation but this remains a theoretical possibility (Muir, 2005).

Smoking

Hickey et al (2001) concluded that smoking was inconsistently associated with prostate cancer in many well-designed cohort and case-control studies.. Prostate cancer was positively associated with smoking in two studies (Plaskon et al., 2003; Sharpe and Siemiatycki, 2001). In the former study, the association was stronger for aggressive prostate cancer while the latter study observed the association only among men with a

high BMI An Australian case-control study found no association (Giles et al., 2001). A Finnish cohort study found an increased risk of prostate cancer among smokers (Malila et al., 2006). Although the mechanism whereby smoking might enhance prostate cancer risk is unknown, current smokers had higher serum free and total testosterone levels than non-smokers and testosterone levels decreased after smoking cessation (Trummer et al., 2002). CpG methylation of the genes adenomatous polyposis coli (APC), pi-class glutathione S-transferase (GSTP1) and multidrug resistance (MDR1) was positively associated with prostate cancer Gleason score; current smokers had higher CpG methylation compared to never smokers (Enokida et al., 2006). Two studies found apparent interactions between smoking and polymorphisms including the GSTM1 null genotype (Nock et al., 2006b) and combined occurrence of p53cd72 Pro and CYP1A1 M1 (Quinones et al., 2006). CONCLUSION???

Alcohol

A meta-analysis of 33 epidemiologic studies published by 1998 revealed no overall association between alcohol consumption and prostate cancer but, among the 15 studies that reported amount of alcohol consumed, there was a weak positive association (Dennis, 2000) Reported beverage-specific associations with prostate cancer include liquor (Sesso et al., 2001), beer (Dennis, 2000) and wine (Ellison 2000; Schuurman et al., 1999a). A recent cohort study reported increased prostate cancer risk among men who consumed large amounts of alcohol infrequently (Platz et al., 2004b). An Australian cohort study showed that men who consumed 1-19 g/day of alcohol had a normal risk of non-aggressive prostate cancer and a reduced risk of aggressive disease (Baglietto et al.,

2006). Alcohol (ethanol) is carcinogenic in rodents (Soffritti et al., 2002). Alcohol might increase prostate cancer risk through effects on plasma sex hormone levels, immunosuppression, inhibition of DNA repair or generation of genotoxic metabolites (acetaldehyde, free radicals). A Netherlands cohort study observed a protective effect of α- and β-carotenoids only among non-drinkers (Schuurman et al., 2002). CONCLUSION??

Conclusion

Although prostate cancers are generally androgen-dependent and most known or suspected external risk factors may act through hormonal mechanisms, our review found little supporting evidence from epidemiologic studies and substantial further research is needed. Promising areas for research include: (1) the role of genetic polymorphisms and their potential interaction with environmental factors including diet, energy balance, endogenous hormone levels, smoking and occupational exposures and, (2) development of *in vitro* models of human prostate cells to explore the many molecular mechanisms through which hormonally active substances may influence prostate cancer development and progression.

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