

Overview: Prostate Cancer and Hormonally Active Agents

R. Samuel McLaughlin Centre for Population Health Risk Assessment

Institute for Population Health

University of Ottawa

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Abstract

Prostate cancer is by far the most frequent cancer among Canadian and American men with a lifetime risk of about 11% for males in these countries and incidence rates about 14 times those in Hong Kong. Age-adjusted incidence rates have increased substantially in Canada, United States and several other countries since at least 1970 and most rapidly during the late 1980's, in parallel to the introduction of the prostate specific antigen (PSA) test for early detection. Both incidence and death rates appear to have decreased somewhat during the most recent few years for which data are available.

Despite much research, the main proven risk factors for prostate cancer risk are non-modifiable: age, family history, and ethnicity. Genes linked to prostate cancer risk include BRCA1, BRCA2 and several genes involved in sex steroid synthesis, transport, activation, inactivation and function. Polymorphisms of genes such as 5 α -reductase or AR (androgen receptor) may partially explain the high incidence rates among African-American men (the highest rates in the world). Men with high serum testosterone (T) and low sex hormone binding globulin (SHBG) levels appear to have increased prostate cancer risks.

Energy imbalance resulting in abdominal adiposity or elevated body mass index and elevated serum insulin-like growth factor (IGF-1) levels appears to increase risk. There is inconsistent evidence of an inverse relation between exercise and prostate cancer. Dietary factors related to reduced risks include fruits and vegetables, soyfoods, and antioxidants (vitamin A, vitamin E, selenium, lycopene, β -carotene); increased risks have been linked to animal fat, red meat and dairy products. Agricultural and other occupations involving pesticide exposure have been linked quite consistently to increased risks; there is also limited evidence of links to other occupations including metal fabricators, electrical power workers and teachers. There is inconsistent evidence of associations with smoking and alcohol consumption and limited evidence of weak associations with previous sexually transmitted infections and vasectomy. At present, the inconsistencies and inadequacies of the epidemiologic studies do not permit firm conclusions about environmental causes of prostate cancer including the potential role of hormonally active contaminants.

Introduction

Prostate cancer is one of several major hormone-related cancers in humans, the others being breast, endometrium, ovary, testis, thyroid and osteosarcoma ¹. These cancers may share a common mechanism of carcinogenesis, i.e., hormonally-driven cell proliferation that increases the opportunity for occurrence or amplification of genetic errors. Large variations in prostate cancer incidence rates internationally, the similar prevalence rates of latent prostate cancer at autopsy internationally, and the results of migrant studies strongly suggest that environmental determinants are important in the progression of this disease ².

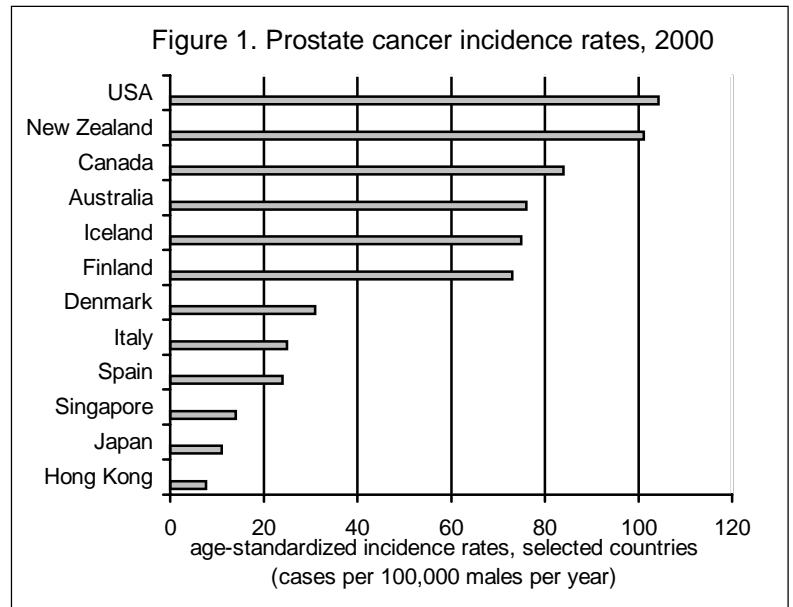
Despite much research, strong external risk factors that could explain prostate cancer risk variations between ethnic groups and increased risks over time have not been identified. The absence of strong socioeconomic risk gradients within ethnic groups suggests that putative environmental causal factors are widespread. Most known or suspected external risk factors could act through hormonal or non-hormonal mechanisms but direct evidence for the former is generally lacking.

Epidemiology

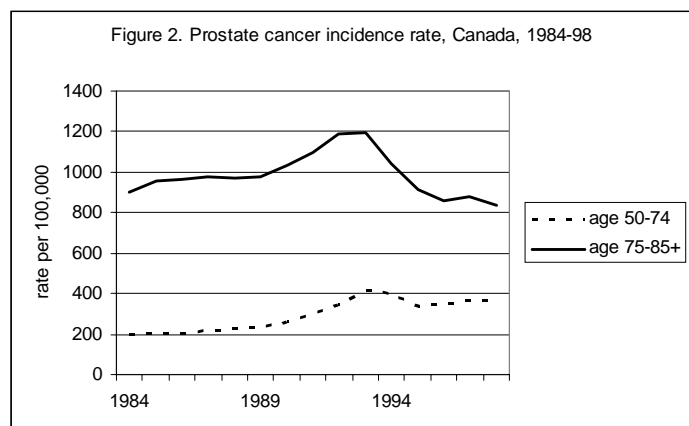
The most important non-modifiable risk factors for prostate cancer are age, family history and ethnicity ¹. Prostate cancer is an androgen-dependent disease that is rare before age 50 years, but thereafter the rate of increase with aging is the greatest for any cancer. The prostate cancer incidence rate in United States is the highest in the world and 14 times that in Hong Kong (Figure 1). Within the United States, African-Americans have about double the risk of Caucasians ³. The lifetime risks of developing or dying from prostate cancer, respectively, are about 11% and 3.6% ⁴. There will be an estimated 189,000 new cases and 30,200 deaths from prostate cancer in United States during 2002

⁵.

Age-adjusted prostate cancer incidence rates have increased substantially in Canada (Figure 2), United States and several other countries since about 1970 but have increased much more rapidly for several years beginning during the late 1980's⁶. This sharp increase was caused by introduction and widespread use of the PSA (prostate-specific antigen) blood test that enables early prostate cancer detection^{7,8}. Age-adjusted prostate cancer death rates have also increased but less dramatically than incidence rates; both incidence and mortality rates appear to have declined slightly during the past few years^{8,9}. The reasons for prostate cancer incidence and mortality rate increases before the late 1980's are unknown but may include a combination of true increased risk and improved diagnosis and reporting. Safer surgical procedures and a more aggressive approach toward treatment of older men likely contributed to improved diagnosis.



Prostate cancer incidence rates in Denmark increased among all age groups over age 50 years during 1943-1992 with no major changes in distribution by age, stage at diagnosis, or diagnostic methods, findings consistent with a true increase in risk¹⁰. In New Mexico, however, the proportion of prostate cancers detected by screening increased from 13% in 1969-1972 to 41% during 1988-1991, a period during which age-adjusted incidence rates almost doubled from 66 to 122 per 100,000 men per year, the proportion of early stage cancers



Source: {Health Canada 2002 #183760}

increased from 78 to 86% and advanced stage cancers decreased from 21 to 10%¹¹. The latter findings suggest that a substantial portion of the upward trend in prostate cancer was caused by earlier detection through screening.

Etiology

Preexisting conditions

Although blood insulin and insulin-like growth factor (IGF) levels are increased in type 2 diabetics and have been associated with prostate cancer (see below), a history of diabetes has not been convincingly linked to prostate cancer risk¹². Findings from the first Cancer Prevention Study showed no overall association between diabetes at baseline and incident prostate cancer but the subgroup of men who had diabetes for at least five years had a relative risk of 1.6 (95% CI 1.0-2.4)¹³. Increased risks have been reported for men with higher blood glucose levels after oral challenge at baseline in a cohort study¹⁴.

A recent meta-analysis of 17 epidemiologic studies of prostate cancer showed a relation with past sexually transmitted infections (pooled RR=1.4, 95% CI 1.2-1.7) and intensity of sexual activity¹⁵. Two early cohort studies showed increased prostate cancer risks after vasectomy^{16,17} and a recent meta-analysis of five cohort and nine case-controls studies showed a marginally elevated pooled relative risk of 1.2 (95% CI 1.0-1.5)¹⁸.

Genetic factors

Family history is a moderately strong risk factor with adjusted relative risks of about 4 for history of prostate cancer in a brother or father^{19,20}; there was a stronger association with family history of both prostate and breast (or ovarian) cancer (RR=5.8, CI 2.4-14)¹⁹. As assessed by studies of familial clusters, genetic factors alone likely explain less than 10% of prostate cancers^{21,22}. Genes potentially important in prostate cancer include those involved in androgen biosynthesis, activation, inactivation and transport: AR (androgen receptor), steroid 5 α -reductase type II (SRD5A2), CYP17 and 3 β -hydroxysteroid dehydrogenase (HSD3B2) genes¹. Increased prostate cancer risks have been linked to polymorphisms in the CYP17 and GSTP I genes; these genes encode

enzymes that can activate or inactivate environmental carcinogens^{23,24}. There are several known polymorphisms in the SRD5A2 gene including two that appear to confer increased rates of testosterone (T) conversion to the more active dihydrotestosterone (DHT) form and increased prostate cancer risk with marked differences in gene variant prevalence rates between ethnic groups¹. The breast cancer genes BRCA1 and BRCA2 also appear to increase prostate cancer risk²⁵. The Framingham cohort study showed an association between prostate cancer and paternal (but not maternal) age at birth (RR=1.7 for highest versus lowest quartile, p for trend = 0.05); this would be consistent with a role for paternal germ cell mutations²⁶.

Steroid hormones

The main male sex steroids are T and DHT. T is produced mainly by testicular Leydig cells and within target tissues is converted to DHT, the latter having about 2.5-fold stronger affinity than T for the androgen receptor (AR). Within prostate cells, T is converted to DHT by type II 5 α -reductase; it has been hypothesized that high levels of this enzyme in prostate tissue may increase cancer risk¹². AR is encoded by a member of the nuclear receptor gene superfamily on the X chromosome, mediates biological actions of T and DHT and is essential for growth, differentiation, and function of the male urogenital tract. T and DHT bind to AR and regulate transcription of several known androgen-responsive genes (including prostate-specific antigen)²⁷. AR also interacts with other signaling pathways including AP-1 (a family of complexes between members of the Fos and Jun transcription factor families) and Ets (a family of transcription factors some of which mediate effects of growth factors on gene expression).

The androgen-dependency of most prostate cancers has been exploited therapeutically in the use of anti-androgen drugs for the treatment of benign prostatic hypertrophy and prostate cancer and in ongoing clinical trials to test the efficacy of such agents in the prevention of prostate cancer. The key role of AR in functioning of normal and malignant prostate cells suggests that environmental endocrine modulators (EMs) or inherited AR gene mutations could modulate prostate cancer risk by modifying AR expression or function. Recent evidence suggests that the elevated risk among U.S. Blacks may be caused in part by reduced CAG repeats in the AR gene²⁸. A preliminary

small clinical trial of the anti-androgen drug finasteride among men with elevated PSA levels showed a more rapid progression to prostate cancer among treated men than in control men; treated men had increased T and decreased DHT levels in serum and this altered hormone balance may have increased prostate cancer risk although it was expected to reduce risk²⁹.

Several epidemiologic studies of serum sex steroids and prostate cancer have produced inconsistent findings. Among cohort studies, positive associations were observed for baseline androstenedione³⁰ and T³¹ and inverse associations with E2³¹. No strong or consistent association with serum sex steroids was observed in several other cohort studies³²⁻³⁷. A recent meta-analysis of prostate cancer and serum hormones indicated a relative risk of 2.3 (95% CI 1.3-4.2) for 4th quartile total serum T levels (relative to 1st quartile) and an inverse association with serum SHBG³⁸. Human prostate epithelial cells express the estrogen receptor ER- β but the role of estrogens in prostate cancer remains controversial³⁹. Diethylstilbestrol (DES) causes proliferative lesions and squamous metaplasia in prostates of humans and experimental animals and estrogen augments prostate carcinogenesis in rodents chronically exposed to androgens²¹.

Growth factors

Insulin-like growth factor I (IGF-I) IGFs are peptide hormones involved in control of cell proliferation, differentiation and apoptosis. Diets high in fat and simple carbohydrates tend to raise insulin and growth hormone levels that, in turn, increase serum IGF-I levels.⁴⁰ Insulin and IGF-I promote sex steroid synthesis and cell proliferation, inhibit apoptosis, and reduce production of SHBG; thus IGF-1 may stimulate proliferation and clonal expansion of partially transformed prostatic epithelial cells and contribute to tumour development or progression⁴¹. A meta-analysis of 14 case-control studies of prostate cancer and IGR-1 yielded a pooled odds ratio of 1.47 (95% CI 1.23-1.77) for high versus low serum or plasma IGF-1 levels⁴⁰. Recent cohort and case-control studies showed about a 3-fold increased prostate cancer risk among men with high IGF-1 levels^{42,43}.

Insulin Although a Swedish cohort study did not find an association between prostate cancer and blood insulin levels⁴⁴, a recent case-control study did show a

moderately strong association with fasting insulin levels that was independent of potential confounders including abdominal adiposity (OR=2.6, 95% CI 1.4-4.8, for highest versus lowest serum insulin tertiles)⁴³. Like IGF-1, insulin stimulates growth of prostatic epithelial cells and inhibits apoptosis⁴⁵.

Kinins

Tissue kallikrein genes encode proteases that form kinins, peptides that play important roles in inflammation and tumour growth. Prostate specific kallikreins, including human glandular kallikrein-1 (hKLK2) and prostate-specific antigen (hKLK3, also known as PSA), are regulated by androgens and other factors; kallikreins and the kinins they generate may facilitate growth and spread of prostate cancer cells^{46,47}.

Diet

An older meta-analysis showed no association with vegetable and fruit consumption⁴⁸. Many recent epidemiologic studies have shown protective effects of vegetables, fruits and antioxidants including vitamin A⁴⁹, vitamin E (protective for metastatic or fatal cancer in smokers)⁵⁰, tomato products and other lycopene-containing foods⁵¹, selenium^{52,53}, foods containing β -carotene^{54,55}, cruciferous vegetables⁵⁵ and fruit⁵⁶. The inverse association with lycopene included evidence of exposure-risk relationships⁵¹. Legumes and soyfoods also appear to be protective, possibly because of their phytoestrogen content^{55,57,58}. Negative findings include no association with serum selenium⁵⁹ or plasma carotenoids other than lycopene⁵¹. A meta-analysis showed a weak association with high linoleic acid intake in case-control but not in cohort studies⁶⁰.

Several studies have linked prostate cancer to animal foods including animal fat or red meats⁶¹⁻⁶⁴, dairy products^{55,63,65}, high calcium combined with low phosphate intake⁶⁵, and cured meat⁶⁶. Five cohort studies of vegetarians did not show reduced prostate cancer risks⁶⁷. Calcium intake (mainly from dairy products) lowers blood 1,25-dihydroxyvitamin D(3), a hormone that appears to decrease cancer risk⁶⁵. There were no significant associations with coffee or tea in a Canadian study⁶⁸ but a study of Japanese-origin men showed an inverse relation with black tea consumption⁶⁹.

Obesity and physical activity

Excessive energy intake relative to total energy expenditure is associated with obesity and increased risks of several types of cancer¹². Although a recent review found no consistent relationship between body mass index (BMI) and prostate cancer risk⁶⁴, some recent studies have shown associations with abdominal adiposity (high ratio of waist to hip circumference)⁷⁰, BMI⁷¹ or percent increase in BMI after age 50 years⁷². In a case-control study, the odds ratio for highest versus lowest quartile waist to hip ratios was 2.7 (95% CI 1.7-4.4, p for trend = 0.0001)⁷⁰.

Reviews of 11 cohort and nine case-control studies of exercise and prostate cancer concluded that the evidence was inconsistent and inconclusive^{73,74}. More recent studies have been inconsistent with negative results from studies of professional athletes⁷⁵ and Iowans⁷² and inverse associations with leisure-time activity^{76,77}. Bouts of exercise and sustained physical activity appear to increase blood IGF-1 levels, possibly complicating the relationship between activity and cancer risk¹².

Occupational exposures

The association between environmental chemicals and prostate cancer has been examined in a limited number of epidemiological studies examining occupational exposure. The occupations most consistently linked to prostate cancer are farming⁷⁸⁻⁸² and other occupations with known exposure to pesticides^{83,84}. If these associations reflect causal relationships, potential mechanisms for at least some pesticides include hormonal modulation⁸⁰. There is also limited evidence for associations with⁸⁵ occupational exposures to metal fabricating, metallic dusts, cutting oils, paints/varnishes⁸⁶⁻⁸⁸, polycyclic aromatic hydrocarbons^{86,89}, calcium carbonate⁸⁸, forest management, tanneries/leather processing, soap/perfume manufacturing⁸¹, oil refinery and crude oil⁹⁰, teachers^{79,91}, electrical power workers⁸⁶ and flight personnel⁹². Although cadmium can cause prostate cancer in rodents, the International Agency for Research on Cancer found inadequate evidence of a role in human prostate cancer⁹³.

Smoking

Smoking has been inconsistently associated with prostate cancer in many well-designed cohort and case-control studies⁹⁴. Several recent studies showed associations with smoking^{3,71,77,95-97} but others showed no convincing relationship^{61,72,98-101}, including a large cohort of U.S. physicians¹⁰⁰. Prostate cancer risk was increased 2-3 times among men with high body mass index who started smoking before age 20 years or were heavy smokers⁹⁷ and by up to 2-fold among heavy smokers^{3,97,97}.

Alcohol

Although the weight of evidence from epidemiologic studies suggests that low to moderate alcohol consumption is likely not a risk factor for prostate cancer^{102,103}, some well-conducted studies have shown associations with alcohol^{72,104,105}. Beverage-specific associations have been observed including liquor¹⁰⁵, beer¹⁰⁶ and wine^{68,107}; others found associations for all types of alcohol⁷². Studies conducted to date provide little information about possible variation in prostate cancer risk by lifetime drinking patterns such as type of beverages and frequency of excessive drinking. Alcohol could affect prostate cancer risk through effects on plasma sex hormone levels, immunosuppression, inhibition of DNA repair or activation of carcinogenic metabolites.

Biologic plausibility

It is known that chronic high-dose exposure to T and E2 cause prostate adenocarcinomas in rodents¹⁰⁸. Prostatic hypertrophy has been reported in rodents following treatment with estrogenic chemicals at relatively low concentrations; it should be noted, however, that other investigators have been unable to reproduce these findings. Moreover, even though the dose levels are below those necessary to induce other adverse effects with these toxicants, the concentrations still considerably exceed those in low dose birth control pills and thus these changes may not necessarily be considered low dose effects. The extent to which chemical effects on rodent prostate gland development can be used to predicting risk of human prostate cancer is not clear, given the differences in gland anatomy and the fact that few rodents spontaneously develop prostate cancer.

Furthermore, the mechanism of environmental contaminant induced changes in prostate gland differentiation and growth have yet to be elucidated.

In the absence of direct human evidence (demonstrated exposure, association between exposure and increased risk of prostate cancer, and evidence of contaminant-induced changes in circulating levels of sex steroids of affected men compared to a reference population), there remains the theoretical possibility that hormonally active chemicals may modulate prostate cancer risk by altering sex steroid balance in men. However, the hypothesis that human exposure to hormonally active environmental chemicals is associated with an increased risk for the development of prostate cancer remains to be tested.

Reference List

1. Henderson BE, Feigelson HS. Hormonal carcinogenesis. *Carcinogenesis* 2000 Mar;21:427-33.
2. Donn AS, Muir CS. Prostatic cancer: some epidemiological features. *Bull Cancer* 1985;72:381-90.
3. Hiatt RA, Armstrong MA, Klatsky AL, Sidney S. Alcohol consumption, smoking, and other risk factors and prostate cancer in a large health plan cohort in California (United States). *Cancer Causes Control* 1994 Jan;5:66-72.
4. National Cancer Institute of Canada. *Canadian Cancer Statistics 2001*. Toronto: 2001.
5. American Cancer Society. *Cancer Facts & Figures 2002*. New York: 2002.
6. Hsing AW, Tsao L, Devesa SS. International trends and patterns of prostate cancer incidence and mortality. *Int J Cancer* 2000 Jan;85:60-7.
7. Mettlin C. Impact of screening on prostate cancer rates and trends. *Microsc Res Tech* 2000 Dec;51:415-8.
8. Sarma AV, Schottenfeld D. Prostate cancer incidence, mortality, and survival trends in the United States: 1981-2001. *Semin Urol Oncol* 2002 Feb;20:3-9.
9. Meyer F, Moore L, Bairati I, Fradet Y. Downward trend in prostate cancer mortality in Quebec and Canada. *J Urol* 1999 Apr;161:1189-91.
10. Brasso K, Friis S, Kjaer SK, Jorgensen T, Iversen P. Prostate cancer in Denmark: a 50-year population-based study. *Urology* 1998 Apr;51:590-4.
11. Gilliland F, Becker TM, Smith A, Key CR, Samet JM. Trends in prostate cancer incidence and mortality in New Mexico are consistent with an increase in effective screening. *Cancer Epidemiol Biomarkers Prev* 1994 Mar;3:105-11.
12. Kaaks R, Lukanova A. Energy balance and cancer: the role of insulin and insulin-like growth factor-I. *Proc Nutr Soc* 2001 Feb;60:91-106.
13. Will JC, Vinicor F, Calle EE. Is diabetes mellitus associated with prostate cancer incidence and survival? *Epidemiology* 1999 May;10:313-8.
14. Gapstur SM, Gann PH, Colangelo LA, Barron-Simpson R, Kopp P, Dyer A, Liu K. Postload plasma

- glucose concentration and 27-year prostate cancer mortality (United States). *Cancer Causes Control* 2001 Oct;12:763-72.
15. Dennis LK, Dawson DV. Meta-analysis of measures of sexual activity and prostate cancer. *Epidemiology* 2002 Jan;13:72-9.
 16. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. A prospective cohort study of vasectomy and prostate cancer in US men. *JAMA* 1993 Feb;269:873-7.
 17. Giovannucci E, Tosteson TD, Speizer FE, Ascherio A, Vessey MP, Colditz GA. A retrospective cohort study of vasectomy and prostate cancer in US men. *JAMA* 1993 Feb;269:878-82.
 18. Bernal-Delgado E, Latour-Perez J, Pradas-Arnal F, Gomez-Lopez LI. The association between vasectomy and prostate cancer: a systematic review of the literature. *Fertil Steril* 1998 Aug;70:191-200.
 19. Cerhan JR, Parker AS, Putnam SD, Chiu BC, Lynch CF, Cohen MB, Torner JC, Cantor KP. Family history and prostate cancer risk in a population-based cohort of Iowa men. *Cancer Epidemiol Biomarkers Prev* 1999 Jan;8:53-60.
 20. Kalish LA, McDougal WS, McKinlay JB. Family history and the risk of prostate cancer. *Urology* 2000 Nov;56:803-6.
 21. Bosland MC. The role of steroid hormones in prostate carcinogenesis. *J Natl Cancer Inst Monogr* 2000;39-66.
 22. Czene K, Lichtenstein P, Hemminki K. Environmental and heritable causes of cancer among 9.6 million individuals in the Swedish family-cancer database. *Int J Cancer* 2002 May;99:260-6.
 23. Gsur A, Bernhofer G, Hinteregger S, Haidinger G, Schatzl G, Madersbacher S, Marberger M, Vutuc C, Micksche M. A polymorphism in the CYP17 gene is associated with prostate cancer risk. *Int J Cancer* 2000 Aug;87:434-7.
 24. Gsur A, Haidinger G, Hinteregger S, Bernhofer G, Schatzl G, Madersbacher S, Marberger M, Vutuc C, Micksche M. Polymorphisms of glutathione-S-transferase genes (GSTP1, GSTM1 and GSTT1) and prostate-cancer risk. *Int J Cancer* 2001 May;95:152-5.
 25. Rosen EM, Fan S, Goldberg ID. BRCA1 and prostate cancer. *Cancer Invest* 2001;19:396-412.
 26. Zhang Y, Kreger BE, Dorgan JF, Cupples LA, Myers RH, Splansky GL, Schatzkin A, Ellison RC. Parental age at child's birth and son's risk of prostate cancer. The Framingham Study. *Am J*

Epidemiol 1999 Dec;150:1208-12.

27. Culig Z, Hobisch A, Bartsch G, Klocker H. Androgen receptor--an update of mechanisms of action in prostate cancer. *Urol Res* 2000 Aug;28:211-9.
28. Platz EA, Rimm EB, Willett WC, Kantoff PW, Giovannucci E. Racial variation in prostate cancer incidence and in hormonal system markers among male health professionals. *J Natl Cancer Inst* 2000 Dec;92:2009-17.
29. Cote RJ, Skinner EC, Salem CE, Mertes SJ, Stanczyk FZ, Henderson BE, Pike MC, Ross RK. The effect of finasteride on the prostate gland in men with elevated serum prostate-specific antigen levels. *Br J Cancer* 1998 Aug;78:413-8.
30. Barrett-Connor E, Friedlander NJ, Khaw KT. Dehydroepiandrosterone sulfate and breast cancer risk. *Cancer Res* 1990 Oct;50:6571-4.
31. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst* 1996 Aug;88:1118-26.
32. Comstock GW, Gordon GB, Hsing AW. The relationship of serum dehydroepiandrosterone and its sulfate to subsequent cancer of the prostate. *Cancer Epidemiol Biomarkers Prev* 1993 May-1993 Jun;2:219-21.
33. Nomura AM, Stemmermann GN, Chyou PH, Henderson BE, Stanczyk FZ. Serum androgens and prostate cancer. *Cancer Epidemiol Biomarkers Prev* 1996 Aug;5:621-5.
34. Guess HA, Friedman GD, Sadler MC, Stanczyk FZ, Vogelman JH, Imperato-McGinley J, Lobo RA, Orentreich N. 5 alpha-reductase activity and prostate cancer: a case-control study using stored sera. *Cancer Epidemiol Biomarkers Prev* 1997 Jan;6:21-4.
35. Vatten LJ, Ursin G, Ross RK, Stanczyk FZ, Lobo RA, Harvei S, Jellum E. Androgens in serum and the risk of prostate cancer: a nested case-control study from the Janus serum bank in Norway. *Cancer Epidemiol Biomarkers Prev* 1997 Nov;6:967-9.
36. Dorgan JF, Albanes D, Virtamo J, Heinonen OP, Chandler DW, Galmarini M, McShane LM, Barrett MJ, Tangrea J, Taylor PR. Relationships of serum androgens and estrogens to prostate cancer risk: results from a prospective study in Finland. *Cancer Epidemiol Biomarkers Prev* 1998 Dec;7:1069-74.
37. Heikkila R, Aho K, Heliövaara M, Hakama M, Marniemi J, Reunanen A, Knekt P. Serum testosterone and sex hormone-binding globulin concentrations and the risk of prostate carcinoma: a

- longitudinal study. *Cancer* 1999 Jul;86:312-5.
38. Shaneyfelt T , Husein R, Bubley G, Mantzoros CS. Hormonal predictors of prostate cancer: a meta-analysis. *J Clin Oncol* 2000 Feb;18:847-53.
 39. Lau KM, LaSpina M, Long J, Ho SM. Expression of estrogen receptor (ER)-alpha and ER-beta in normal and malignant prostatic epithelial cells: regulation by methylation and involvement in growth regulation. *Cancer Res* 2000 Jun;60:3175-82.
 40. Shi R, Berkel HJ, Yu H. Insulin-like growth factor-I and prostate cancer: a meta-analysis. *Br J Cancer* 2001 Sep;85:991-6.
 41. Pollak M, Beamer W, Zhang JC. Insulin-like growth factors and prostate cancer. *Cancer Metastasis Rev* 1998;17:383-90.
 42. Harman SM, Metter EJ, Blackman MR, Landis PK, Carter HB. Serum levels of insulin-like growth factor I (IGF-I), IGF-II, IGF- binding protein-3, and prostate-specific antigen as predictors of clinical prostate cancer. *J Clin Endocrinol Metab* 2000 Nov;85:4258-65.
 43. Hsing AW, Chua S Jr, Gao YT, Gentschein E, Chang L, Deng J, Stanczyk FZ. Prostate cancer risk and serum levels of insulin and leptin: a population-based study. *J Natl Cancer Inst* 2001 May;93:783-9.
 44. Stattin P, Bylund A, Rinaldi S, Biessy C, Dechaud H, Stenman UH, Egevad L, Riboli E, Hallmans G, Kaaks R. Plasma insulin-like growth factor-I, insulin-like growth factor-binding proteins, and prostate cancer risk: a prospective study. *J Natl Cancer Inst* 2000 Dec;92:1910-7.
 45. Peehl DM, Stamey TA. Serum-free growth of adult human prostatic epithelial cells. *In Vitro Cell Dev Biol* 1986 Feb;22:82-90.
 46. Murtha P, Tindall DJ, Young CY. Androgen induction of a human prostate-specific kallikrein, hKLK2: characterization of an androgen response element in the 5' promoter region of the gene. *Biochemistry* 1993 Jun;32:6459-64.
 47. Young CY, Andrews PE, Tindall DJ. Expression and androgenic regulation of human prostate-specific kallikreins. *J Androl* 1995 Mar-1995 Apr;16:97-9.
 48. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. I. Epidemiology. *Cancer Causes Control* 1991 Sep;2:325-57.
 49. Reichman ME, Hayes RB, Ziegler RG, Schatzkin A, Taylor PR, Kahle LL, Fraumeni JF Jr. Serum

vitamin A and subsequent development of prostate cancer in the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Cancer Res* 1990 Apr;50:2311-5.

50. Chan JM, Stampfer MJ, Ma J, Rimm EB, Willett WC, Giovannucci EL. Supplemental vitamin E intake and prostate cancer risk in a large cohort of men in the United States. *Cancer Epidemiol Biomarkers Prev* 1999 Oct;8:893-9.
51. Gann PH, Ma J, Giovannucci E, Willett W, Sacks FM, Hennekens CH, Stampfer MJ. Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. *Cancer Res* 1999 Mar;59:1225-30.
52. Yoshizawa K, Willett WC, Morris SJ, Stampfer MJ, Spiegelman D, Rimm EB, Giovannucci E. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J Natl Cancer Inst* 1998 Aug;90:1219-24.
53. Nomura AM, Lee J, Stemmermann GN, Combs GF Jr. Serum selenium and subsequent risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2000 Sep;9:883-7.
54. Hirayama T. Epidemiology of prostate cancer with special reference to the role of diet. *Natl Cancer Inst Monogr* 1979 Nov;149-55.
55. Kolonel LN, Hankin JH, Whittemore AS, Wu AH, Gallagher RP, Wilkens LR, John EM, Howe GR, Dreon DM, West DW and others. Vegetables, fruits, legumes and prostate cancer: a multiethnic case-control study. *Cancer Epidemiol Biomarkers Prev* 2000 Aug;9:795-804.
56. Giovannucci E, Rimm EB, Wolk A, Ascherio A, Stampfer MJ, Colditz GA, Willett WC. Calcium and fructose intake in relation to risk of prostate cancer. *Cancer Res* 1998 Feb;58:442-7.
57. Severson RK, Nomura AM, Grove JS, Stemmermann GN. A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. *Cancer Res* 1989 Apr;49:1857-60.
58. Jacobsen BK, Knutsen SF, Fraser GE. Does high soy milk intake reduce prostate cancer incidence? The Adventist Health Study (United States). *Cancer Causes Control* 1998 Dec;9:553-7.
59. Goodman GE, Schaffer S, Bankson DD, Hughes MP, Omenn GS. Predictors of serum selenium in cigarette smokers and the lack of association with lung and prostate cancer risk. *Cancer Epidemiol Biomarkers Prev* 2001 Oct;10:1069-76.
60. Zock PL, Katan MB. Linoleic acid intake and cancer risk: a review and meta-analysis. *Am J Clin Nutr* 1998 Jul;68:142-53.

61. Le Marchand L, Kolonel LN, Wilkens LR, Myers BC, Hirohata T. Animal fat consumption and prostate cancer: a prospective study in Hawaii. *Epidemiology* 1994 May; 5:276-82.
62. Hayes RB, Ziegler RG, Gridley G, Swanson C, Greenberg RS, Swanson GM, Schoenberg JB, Silverman DT, Brown LM, Pottern LM and others. Dietary factors and risks for prostate cancer among blacks and whites in the United States. *Cancer Epidemiol Biomarkers Prev* 1999 Jan;8:25-34.
63. Michaud DS, Augustsson K, Rimm EB, Stampfer MJ, Willet WC, Giovannucci E. A prospective study on intake of animal products and risk of prostate cancer. *Cancer Causes Control* 2001 Aug;12:557-67.
64. Kolonel LN. Nutrition and prostate cancer. *Cancer Causes Control* 1996 Jan;7:83-44.
65. Chan JM, Stampfer MJ, Ma J, Gann PH, Gaziano JM, Giovannucci EL. Dairy products, calcium, and prostate cancer risk in the Physicians' Health Study. *Am J Clin Nutr* 2001 Oct;74:549-54.
66. Schuurman AG, van den Brandt PA, Dorant E, Goldbohm RA. Animal products, calcium and protein and prostate cancer risk in The Netherlands Cohort Study. *Br J Cancer* 1999 Jun;80:1107-13.
67. Key TJ, Fraser GE, Thorogood M, Appleby PN, Beral V, Reeves G, Burr ML, Chang-Claude J, Frentzel-Beyme R, Kuzma JW and others. Mortality in vegetarians and nonvegetarians: detailed findings from a collaborative analysis of 5 prospective studies. *Am J Clin Nutr* 1999 Sep;70:516S-24S.
68. Ellison LF. Tea and other beverage consumption and prostate cancer risk: a Canadian retrospective cohort study. *Eur J Cancer Prev* 2000 Apr;9:125-30.
69. Heilbrun LK, Nomura A, Stemmermann GN. Black tea consumption and cancer risk: a prospective study. *Br J Cancer* 1986 Oct;54:677-83.
70. Hsing AW, Deng J, Sesterhenn IA, Mostofi FK, Stanczyk FZ, Benichou J, Xie T, Gao YT. Body size and prostate cancer: a population-based case-control study in China. *Cancer Epidemiol Biomarkers Prev* 2000 Dec;9:1335-41.
71. Cerhan JR, Torner JC, Lynch CF, Rubenstein LM, Lemke JH, Cohen MB, Lubaroff DM, Wallace RB. Association of smoking, body mass, and physical activity with risk of prostate cancer in the Iowa 65+ Rural Health Study (United States). *Cancer Causes Control* 1997 Mar;8:229-38.
72. Putnam SD, Cerhan JR, Parker AS, Bianchi GD, Wallace RB, Cantor KP, Lynch CF. Lifestyle and anthropometric risk factors for prostate cancer in a cohort of Iowa men. *Ann Epidemiol* 2000 Aug;10:361-9.

73. McTiernan A, Ulrich C, Slate S, Potter J. Physical activity and cancer etiology: associations and mechanisms. *Cancer Causes Control* 1998 Oct;9:487-509.
74. Moore MA, Park CB, Tsuda H. Physical exercise: a pillar for cancer prevention? *Eur J Cancer Prev* 1998 Jun;7:177-93.
75. Pukkala E, Kaprio J, Koskenvuo M, Kujala U, Sarna S. Cancer incidence among Finnish world class male athletes. *Int J Sports Med* 2000 Apr;21:216-20.
76. Hartman TJ, Albanes D, Rautalahti M, Tangrea JA, Virtamo J, Stolzenberg R, Taylor PR. Physical activity and prostate cancer in the Alpha-Tocopherol, Beta- Carotene (ATBC) Cancer Prevention Study (Finland). *Cancer Causes Control* 1998 Jan;9:11-8.
77. Lund Nilssen TI, Johnsen R, Vatten LJ. Socio-economic and lifestyle factors associated with the risk of prostate cancer. *Br J Cancer* 2000 Apr;82:1358-63.
78. van der Gulden JW, Vogelzang PF. Farmers at risk for prostate cancer. *Br J Urol* 1996 Jan;77:6-14.
79. Buxton JA, Gallagher RP, Le ND, Band PR, Bert JL. Occupational risk factors for prostate cancer mortality in British Columbia, Canada. *Am J Ind Med* 1999 Jan;35:82-6.
80. Keller-Byrne JE, Khuder SA, Schaub EA. Meta-analyses of prostate cancer and farming. *Am J Ind Med* 1997 May;31:580-6.
81. Sharma-Wagner S, Chokkalingam AP, Malker HS, Stone BJ, McLaughlin JK, Hsing AW. Occupation and prostate cancer risk in Sweden. *J Occup Environ Med* 2000 May;42:517-25.
82. Parker AS, Cerhan JR, Putnam SD, Cantor KP, Lynch CF. A cohort study of farming and risk of prostate cancer in Iowa. *Epidemiology* 1999 Jul;10:452-5.
83. Kross BC, Burmeister LF, Ogilvie LK, Fuortes LJ, Fu CM. Proportionate mortality study of golf course superintendents. *Am J Ind Med* 1996 May;29:501-6.
84. Dich J, Wiklund K. Prostate cancer in pesticide applicators in Swedish agriculture. *Prostate* 1998 Feb;34:100-12.
85. Fleming LE, Bean JA, Rudolph M, Hamilton K. Mortality in a cohort of licensed pesticide applicators in Florida. *Occup Environ Med* 1999 Jan;56:14-21.
86. Aronson KJ, Siemiatycki J, Dewar R, Gerin M. Occupational risk factors for prostate cancer: results from a case-control study in Montreal, Quebec, Canada. *Am J Epidemiol* 1996 Feb;143:363-73.

87. van der Gulden JW. Metal workers and repairmen at risk for prostate cancer: a review. *Prostate* 1997 Feb;30:107-16.
88. Weston TL, Aronson KJ, Siemiatycki J, Howe GR, Nadon L. Cancer mortality among males in relation to exposures assessed through a job-exposure matrix. *Int J Occup Environ Health* 2000 Jul-2000 Sep;6:194-202.
89. Krstev S, Baris D, Stewart PA, Hayes RB, Blair A, Dosemeci M. Risk for prostate cancer by occupation and industry: a 24-state death certificate study. *Am J Ind Med* 1998 Nov;34:413-20.
90. Wong O, Raabe GK. Critical review of cancer epidemiology in petroleum industry employees, with a quantitative meta-analysis by cancer site [see comments]. *Am J Ind Med* 1989;15:283-310.
91. Reynolds P, Elkin EP, Layefsky ME, Lee GM. Cancer in California school employees, 1988-1992. *Am J Ind Med* 1999 Aug;36:271-8.
92. Ballard T, Lagorio S, De Angelis G, Verdecchia A. Cancer incidence and mortality among flight personnel: a meta-analysis. *Aviat Space Environ Med* 2000 Mar;71:216-24.
93. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 58. Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry. France: 1994.
94. Hickey K, Do KA, Green A. Smoking and prostate cancer. *Epidemiol Rev* 2001;23:115-25.
95. Hsing AW, McLaughlin JK, Schuman LM, Bjelke E, Gridley G, Wacholder S, Chien HT, Blot WJ. Diet, tobacco use, and fatal prostate cancer: results from the Lutheran Brotherhood Cohort Study. *Cancer Res* 1990 Nov;50:6836-40.
96. Giovannucci E, Rimm EB, Ascherio A, Colditz GA, Spiegelman D, Stampfer MJ, Willett WC. Smoking and risk of total and fatal prostate cancer in United States health professionals. *Cancer Epidemiol Biomarkers Prev* 1999 Apr;8:277-82.
97. Sharpe CR, Siemiatycki J. Joint effects of smoking and body mass index on prostate cancer risk. *Epidemiology* 2001 Sep;12:546-51.
98. Adami HO, Bergstrom R, Engholm G, Nyren O, Wolk A, Ekblom A, Englund A, Baron J. A prospective study of smoking and risk of prostate cancer. *Int J Cancer* 1996 Sep;67:764-8.
99. Lumey LH, Pittman B, Zang EA, Wynder EL. Cigarette smoking and prostate cancer: no relation with six measures of lifetime smoking habits in a large case-control study among U.S. whites.

- Prostate 1997 Nov;33:195-200.
100. Lotufo PA, Lee IM, Ajani UA, Hennekens CH, Manson JE. Cigarette smoking and risk of prostate cancer in the physicians' health study (United States). *Int J Cancer* 2000 Jul;87:141-4.
 101. Giles GG, Severi G, McCredie MR, English DR, Johnson W, Hopper JL, Boyle P. Smoking and prostate cancer: findings from an Australian case-control study. *Ann Oncol* 2001 Jun;12:761-5.
 102. Breslow RA, Weed DL. Review of epidemiologic studies of alcohol and prostate cancer: 1971-1996. *Nutr Cancer* 1998;30:1-13.
 103. Bagnardi V, Blangiardo M, Vecchia CL, Corrao G. A meta-analysis of alcohol drinking and cancer risk. *Br J Cancer* 2001 Nov;85:1700-5.
 104. Sharpe CR, Siemiatycki J. Case-control study of alcohol consumption and prostate cancer risk in Montreal, Canada. *Cancer Causes Control* 2001 Sep;12:589-98.
 105. Sesso HD, Paffenbarger RS Jr, Lee IM. Alcohol consumption and risk of prostate cancer: The Harvard Alumni Health Study. *Int J Epidemiol* 2001 Aug;30:749-55.
 106. Dennis LK. Meta-analysis for combining relative risks of alcohol consumption and prostate cancer. *Prostate* 2000 Jan;42:56-66.
 107. Schuurman AG, Goldbohm RA, van den Brandt PA. A prospective cohort study on consumption of alcoholic beverages in relation to prostate cancer incidence (The Netherlands). *Cancer Causes Control* 1999 Dec;10:597-605.
 108. Noble RL. Prostate carcinoma of the Nb rat in relation to hormones. *Int Rev Exp Pathol* 1982;23:113-59.