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Non-dietary environmental risk factors in prostate cancer

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Abstract

Introduction—The aim is to update and disclose the main environmental risk factors, excluding dietary factors, involved in the etiopathology of prostate cancer.

Materials and methods—Bibliographic review of the last 25 years of non-dietary environmental risk factors associated with prostate cancer between 1985 and 2010, obtained from *MedLine*, *CancerLit*, *Science Citation Index* and *Embase*. The search profiles were *Environmental Risk Factors/Tobacco/Infectious-Inflammatory Factors/Pesticides/Vasectomy/Occupational Exposures/Chemoprevention Agents/Radiation and Prostate Cancer*.

Results—While some non-dietary environmental risk factors increase the risk of acquiring the disease, others decrease it. Of the former, it is worth mentioning exposure to tobacco smoke, chronic infectious-inflammatory prostatic processes and occupational exposure to cadmium, herbicides and pesticides. The first factors that reduce the risk are the use of chemopreventive drugs (Finasteride, Dutasteride) and exposure to ultraviolet solar radiation. With the current data, a vasectomy does not influence the risk of developing the disease.

Conclusions—The slow process of prostate carcinogenesis is the final result of the interaction of constitutional risk and environmental factors. Non-dietary environmental factors play an important role in the etiopathology of this disease. To appropriately assess the risk factors, extensive case studies that include all the possible variables must be analyzed.

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Conflict of interest

The authors declare that they have no conflict of interest.

Resumen

Se pretende actualizar y divulgar los principales factores de riesgo ambientales, excluyendo los dietéticos, implicados en la etiopatogenia del cáncer de próstata.

Revisión bibliográfica de los últimos 25 años de los factores de riesgo ambientales no dietéticos asociados a cáncer de próstata entre 1985 y 2010, obtenida del *MedLine*, *CancerLit*, *Science Citation Index* y *Embase*. Los perfiles de búsqueda han sido *Environmental Risk Factors/Tobacco/Infectious-Inflammation Factors/Pesticides/Vasectomy/Occupational Exposures/Chemoprevention Agents/Radiation* y «Cáncer de Próstata».

Mientras que algunos factores de riesgo ambientales no dietéticos incrementan el riesgo de padecer la enfermedad, otros lo disminuyen. Entre los primeros destacan la exposición al humo del tabaco; los procesos prostáticos infecto-inflamatorios crónicos y la exposición profesional al cadmio, herbicidas y pesticidas. Los principales factores que reducen el riesgo es el empleo de fármacos quimiopreventivos (finasterida, dutasterida) y la exposición a la radiación ultravioleta solar. La vasectomía, con los datos actuales, no influye en el riesgo de desarrollar la enfermedad.

El lento proceso de carcinogénesis prostática es el resultado final de la interacción de factores de riesgo constitucionales y ambientales. Los factores ambientales no dietéticos desempeñan un papel importante en la etiopatogenia de esta enfermedad. Para valorar apropiadamente los factores de riesgo deben analizarse grandes casuísticas que incluyan todas las variables posibles.

Keywords

Prostate cancer; Environmental risk factors; Primary prevention; Epidemiology; Smoking; Pesticides

PALABRAS CLAVE

Cáncer de próstata; Factores de riesgo ambientales; Prevención primaria; Epidemiología; Tabaquismo; Pesticidas

Introduction

In Western countries prostate cancer is a major medical problem due to its high incidence and significant mortality.¹ For these reasons, primary prevention reduces not only the considerable economic burden of diagnosis and treatment but it also the enormous emotional stress of patients and their family and social environment.^{1,2} To this end, we must progress in our current understanding of the risk factors involved in its etiopathogenesis.¹

In this paper, we carry out an updated review of the main non-dietary environmental risk factors associated with prostate cancer, with varying degrees of scientific consistency, in accordance with our bibliographic research.

Smoking

Active and passive exposures to smoke from burning tobacco are considered a carcinogen for many human cancers.³ In spite of this, the process for establishing its causal association with prostate cancer has been slow. With respect to its incidence, most epidemiological studies^{4,5} have not established a causal relationship between tobacco and the disease. Case-control studies have not found a relationship between the various variables of smoking and the incidence of the disease. However, some cohort studies documented a 2–3 times higher risk in smokers of more than a pack a day compared with nonsmokers. However, these studies have not demonstrated a convincing dose-response relationship, neither have they evaluated the influence of possible dietary risk factors that are confusing.⁴

Regarding mortality, the association has been more consistently documented.^{4–6} Several cohort studies have established a direct relationship between smoking and higher mortality due to prostate cancer. Smoking patients double the risk of dying from the disease compared to non-smokers. Most authors found a gradual risk in relation to the number of cigarettes smoked daily and years one has been smoking. However, a convincing article documented a dose-response relationship between the number of packs per year of the smoker 10 years before diagnosis.⁶ Although in several studies ex-smokers did not seem to have a higher risk of dying from prostate cancer, one study documented adverse effects on mortality until a decade after cessation of smoking.⁶

A recently published meta-analysis provides convincing data and statistically significant causal association between exposure to tobacco smoke and the increased incidence and mortality of prostate cancer.⁷ Analyzing 24 epidemiological cohort studies including 21,579 patients, it was found that when stratified by number of cigarettes smoked, current smokers had a higher risk of between 11% and 22% compared to those who had never smoked, and of 9% compared to ex-smokers; these differences were statistically significant. Mortality in active smokers showed statistically significant differences, with an increased risk of 14% compared to those who had never smoked, which increased to 24% and 30% for the most addicted. The authors commented that probably because of their lower case material, studies carried out previously underestimated the true influence of smoking on the incidence and mortality of prostate cancer. They also recommended the need to design studies to review prognosis variables (tumor stage and grade) and medical history of smoking, both in smokers and former smokers.

The causal association with prostate cancer is biologically plausible because smoke carcinogens from tobacco act directly, causing DNA mutations, and indirectly, causing alterations in hormone metabolism. Some authors have found interactions between smoking and certain genetic polymorphisms associated with increased risk of prostate cancer.

Prostatic infectious-inflammatory factors

Substantial epidemiological, genetic, histological and molecular biology data shows the influence of prostate infection and consequent chronic inflammation in the pathogenesis and progression of prostate cancer.^{1,4,8} Potentially, infectious agents can influence

carcinogenesis through the following mechanisms: (a) incorporation of viral oncogenes in the genome of the carrier, (b) inhibition of tumor suppressor genes, (c) stimulation of proliferative signals, and (d) by suppression of the immune surveillance system. Although chronic prostatitis caused by sexually transmitted diseases is associated with increased prostate cancer risk and poorer outcome in treatment, to date, no specific infectious agent has been convincingly associated as a causal agent of the disease.^{4,8}

Human papillomavirus (HPV) has received greater attention due to its association with genitourinary cancers, but its real contribution to prostate cancer is controversial. While some authors have found no association, others have implicated type 16, which corresponds to the variety most linked to anogenital cancers.⁹

Trichomonas vaginalis infection causes adherence of the protozoan to epithelial cells by decreasing the expression of anti-apoptotic genes; it also alters the production of interleukin 6 and monocyte chemotaxis proteins. An extensive case-control study documented that HIV-positive persons had a statistically significant increase of 43% of prostate cancer (95% CI 1.00–2.03) and a 76% increase in high histological grade (95% CI 2.97–3.18).¹⁰

A gammaretrovirus denominated XMRV has recently been identified in radical prostatectomy specimens. Its persistence in mesenchymal stromal cells adjacent to the neoplastic glands is associated with genetic polymorphism R426Q RNASEL. Possible etiopathogenic action would relate to signs and cell transduction pathways between the stroma and the epithelium. If it were ultimately categorized as an oncogenic virus, obtaining a specific vaccine would prevent the number of cases of prostate cancers associated with XMRV.¹¹

Cadmium

During the decades of the 70s and 80s in the twentieth century, some researchers provided evidence on the increased risk of prostate cancer among men occupationally exposed to cadmium (Cd). Subsequently, a review of the International Agency for Research on Cancer and a meta-analysis of 29 epidemiological studies documented a slight, not statistically significant increase in the incidence of prostate cancer associated with exposure to Cd.^{12,13} Toxicologically, a higher tissular concentration of Cd has been found in prostate cancer compared with benign prostatic hypertrophy, with greater amounts in cancers of a higher histological grade. The potentially carcinogenic effect of Cd can be modified by zinc, since both have antagonistic effects on the prostate. Neoplastic tissue has a lower ratio of zinc/Cd than a normal prostate, suggesting that: (a) a high content of zinc in the prostate may protect against carcinogenesis, (b) Cd can act as a weak prostatic carcinogen and is enhanced by a zinc deficiency and, (c) the inability of the prostate to maintain appropriate zinc homeostasis may favor Cd-induced carcinogenesis.¹⁴

Herbicides

These are active chemical compounds that are used to fight plant pests. Agent Orange is a mixture of two herbicides that were used as a defoliant between 1962 and 1971 in the Vietnam War. In 1998, the National Academy of Science of the USA recognized a positive

association between herbicide exposure and many human cancers, but its association with prostate cancer was considered limited and not conclusive.¹⁵ More recent studies suggest a more consistent association. In a review published in 2008, in which 6214 veterans of the Vietnam War were exposed to the herbicide and compared with 6930 non-exposed veterans, the authors found twice as many cases of prostate cancer among the exposed veterans (239 vs. 124), with earlier diagnostic ages, as well as an increased risk of presenting a Gleason score of 8–10 (21.8% vs. 10.5%) and greater likelihood of metastatic disease among exposed veterans (13.4% vs. 4%). Additionally, the authors found no differences between the groups with respect to age, smoking, body mass index, exposure to finasteride and PSA levels. In a multivariate logistic regression model, Agent Orange was the most predictive factor not only of developing prostate cancer but also of a higher histological grade and a greater probability of metastatic disease at diagnosis.¹⁶

Pesticides

They are chemical compounds used to fight animal pests. The difficulties in interpreting the risks associated with prostate cancer lie in the existence of hundreds of different active principles, as well as in the direct chronic and multiple exposure to them in low doses, and particularly indirect exposure, through food, water, air and the environment.⁴

Since the end of the 60s, ecological studies based on deaths showed mortality rates for some cancers, including prostate cancer, which were significantly higher in rural areas of North America, whereas the overall cancer mortality rates were lower in urban areas.⁴ In the decade of the 90s, three meta-analyses^{17–19} documented increased risk, 7%, 8% and 12% respectively, both in the incidence and mortality of prostate cancer in rural areas with high agricultural activity in the U.S. compared with the general population in other areas. However, living in a rural area is not synonymous with the use of pesticides, as potentially, many risk factors related to lifestyle, exposures to other chemicals and biological contaminants are involved.

In the last decade, three meta-analyses have analyzed the use of pesticides in the professional environment.^{20–22} One of them focused on both agricultural and nonagricultural pesticide users, except workers in production facilities.²⁰ Overall, they found a statistically significant and 13% higher risk in pesticide applicators (RR = 1.13, 95% CI 1.04–1.22). The second meta-analysis²¹ focused on pesticide applicators and also found a statistically significant and 12% higher risk of prostate cancer (RR = 1.12, 95% CI 1.03–1.22). The third meta-analysis²² focused on production facility workers and demonstrated a statistically significant and 28% higher risk of developing the disease (RR = 1.28, 95% CI 1.05–1.58). Moreover, after grouping pesticides by chemical group, they found consistent increases in all the groups, however without statistically significant differences.

The *Agricultural Health Study*²³ conducted in the U.S. between 1993 and 2002, is one of the largest prospective cohort studies (89,658 people). It reported a 14% higher risk of prostate cancer among men who used pesticides, as well as three other significant associations between pesticide use and the risk of prostate cancer. On the one hand, a relationship was found between the application of methyl bromide, an alkylating agent classified as a

potential occupational carcinogen by the National Institute for Occupational Safety and Health and the risk of prostate cancer, both in well-differentiated and poorly differentiated tumors. Moreover, a direct relationship was found with the use of organochlorine pesticides, including DDT and heptachlor, but only in those over aged 50 years. A statistically significant association was found with the use of various pesticides only men with a family history of prostate cancer. All this data suggest that exposure to certain pesticides must interact with genetic risk factors, and for several decades, in order to promote prostate carcinogenesis.

Vasectomy

Case-control and cohort studies that have analyzed the association between vasectomy and prostate cancer risk have produced conflicting results. Some authors found increased risks of 40%, 60% and 70% with vasectomy, but others found a lesser risk of developing prostate cancer among vasectomized men.^{4,24,25} In the latter, there is a greater risk among those who were vasectomized before the age of 20 years prior to the study and those who were vasectomized under the age of 35–40 years of age. A meta-analysis in this regard documents an OR = 1.1 (95% CI 0.9–1.4) for cancer risk with vasectomy, but suggested increased risk among those with a positive family history and those who were operated at earlier ages.²⁴ On the other hand, in a very well designed study conducted in New Zealand, the country with the highest global prevalence of vasectomy, the authors found no relationship with these subgroups.²⁵

Socioeconomic factors

All social factors, including economic, lifestyle and educational and academic factors, do not, *per se*, seem to directly influence the risk of developing prostate cancer. Notwithstanding, they are indirectly involved by influencing dietary factors, occupational exposure and access to health systems, both for early detection and appropriate treatment, and they undoubtedly influence the incidence and mortality of this disease.⁴

Sexual activity and marital status

The influence of sexual activity and marital status in the development of prostate cancer has been studied extensively.⁴ Probably, their hypothetical relationship would be subject to the influence of inherent hormonal, infectious and cultural factors.

Several studies have found increased risk of prostate cancer in men with multiple sexual partners and early commencement of sexual activity. However, other authors have documented a lower risk with high sexual activity and early commencement of it. Marital status is not associated with an increased mortality risk of the disease, but some authors have found increased risk among young married couples compared with older couples, as well as increased risk among married couples in comparison with single men.⁴

Other occupational exposures

A cohort study conducted on workers exposed to polychlorinated biphenyls (PCBs) showed a positive trend between incidence and mortality of prostate cancer, with dose and cumulative duration of exposure.²⁶ Another study that examined the levels of PCBs in adipose tissue revealed an association with prostate cancer (OR = 3.15, 95% CI 1.04–9.54), which was higher (OR = 30.3, 95% CI 3.24–284) among men with PSA levels > 16.5 ng/ml.²⁷ *The Netherlands Cohort Study*²⁸ revealed a slight increase of the disease in relation to exposure to metal fumes (RR = 1.11, 95% CI 0.80–1.54), which findings are similar to those obtained in a case-control study in Australia.²⁹ The association between exposure to mineral oils and the risk of the disease has also been analyzed. Increased risk has been reported after exposure exceeding 5 years, and was statistically significant in workers exposed from puberty.³⁰

In a case-control study focused on exposure to polycyclic aromatic hydrocarbons (PAHs), there was no evidence of any significant increase prostate cancer risk in relation to cumulative exposure to different occupational exposures, although the risk was high in exposure due to inhalation of PAHs in petroleum (OR = 1.12, 95% CI 0.73–1.73) or coal (OR = 1.29, 95% CI 0.73–2.30) and in skin exposure to coal (OR = 1.48, 95% CI 0.68–3.20).³¹ However, in this study, an interaction was identified between genetic and environmental factors, showing that men over 60 who had the GSTP1 Val genetic polymorphism, who were exposed to high levels of PAHs, had a significantly higher risk (OR = 4.52, 95% CI 1.96–10.41). Evidence from other studies on exposure to PAHs and prostate cancer is less convincing.^{28,32}

Evidence on the risk associated with solvents is limited. A case-control study found a significant dose-response trend of prostate cancer among workers with low to moderate exposure (OR = 1.3 95% CI 0.8–2.1) and high levels of trichlorethylene (OR = 2.1).³²

Other authors that analyzed various occupations and occupational exposure in relation to the risk of prostate cancer found significant increases in firefighters (OR = 1.22, 95% CI 1.12–1.33), oil workers and workers at semiconductor facilities/laboratories. A meta-analysis found increased risk among commercial pilots. Other studies have associated the risk of prostate cancer with paints, varnishes, soaps and perfumes, leather manufacture, exposure to electromagnetic fields, electricity workers, teachers, police and forestry workers, although other studies did not obtain the same results.³³ Some authors have analyzed the vibrations that the body experiences when certain jobs are performed and in relation to different modes of transport, but have not found a convincing association.³³

Chemoprevention

The administration of drugs to reduce the risk of prostate cancer is a subject of much study and great interest. Chemoprevention must be safe, maintain quality of life, decrease the incidence, impact and severity of the disease and be economically feasible. Of the drugs that have demonstrated greater scientific evidence in clinical trials, worth mention are inhibitors

of the enzyme 5- α reductase, which converts testosterone into dihydrotestosterone and of which two isoforms exist, type 1 and type 2.

In the *Prostate Cancer Prevention Trial (PCPT)*,³⁴ 18,882 men aged as of 55 years, with normal DRE and PSA equal to or less than 3 ng/ml, were assigned to receive finasteride for 7 years (5 mg/day), which inhibits 5- α reductase type 2, or placebo. Prostate cancer was detected in 803 of 4308 men in the finasteride group, compared with 1147 out of 4692 in the placebo group, thus showing a reduction in the risk of disease from 24.8% (95% CI 18.6–30.6, $p < 0.001$). Unexpectedly, there was an increase in the incidence of high-grade prostate cancer in the finasteride group compared with the placebo group (37% vs. 23.2; $p < 0.001$), although later studies have not demonstrated that hormonal changes caused by finasteride enhance the development of aggressive disease.³⁵

In the *Reduction by Dutasteride of Prostate Cancer Events (REDUCE)*,³⁶ 6729 men aged from 50 to 75 years, with serum PSA levels of 2.5–10 ng/ml, and prior negative biopsy, were assigned to receive dutasteride for 4 years (0.5 mg/day) or placebo. The findings, published in 2010, show that dutasteride (0.5 mg/day) reduced the risk of prostate cancer risk in a risk population by 22.8% (95% CI 15.2–29.8, $p < 0.001$) compared with placebo. Dutasteride is a powerful inhibitor of 5- α reductase and is 45 times stronger than finasteride in inhibiting type 1 isoform and twice as strong on isoform 2. No doubt that this is a promising drug in the prevention of prostate cancer on the risk population.

Based on models that show that estrogens have synergy with androgens to induce prostatic hyperplasia, dysplasia and cancer, the role of the modulators of these receptors has been investigated. Toremifene, a selective modulator of estrogen receptors, is being evaluated at doses of 20 mg in a multicenter randomized double-blind, placebo-controlled study in men with high grade intraepithelial neoplasia, to assess the reduction in the incidence of prostate cancer at 12 months after initiation of the study (9.1 vs. 17.4%; $p < 0.05$).³⁵

Initial studies with statins (inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A) suggested a reduction in the risk of prostate cancer; however, different subsequent meta-analyses did not find this reduction.³⁵ Better-designed studies are required to assess the true effect of these agents. Likewise, trials carried out with inhibitors of cyclooxygenase (COX-2) have not documented an actual reduction in risk.³⁵ COX-2 enzyme is involved in inflammatory processes; it promotes angiogenesis and modulates apoptosis. The significant side effects of these drugs at cardiac and cerebrovascular levels make it unlikely that further studies be carried out with these agents. Other studies performed with supplements with selenium and vitamin E (SELECT study), vitamin C or folic acid, compared with placebo showed no significant reduction in the risk of the disease.³⁷

Electromagnetic radiation

Although it presented greater relative risks than expected in unexposed controls, the association between ionizing radiation and prostate cancer, there were no statistically significant increases.³⁸

Exposure to solar UV radiation is inversely associated with both the incidence and mortality of prostate cancer. The biological explanation of this fact is based on the synthesis and physiological actions of vitamin D.^{39,40}

Final comments

Prostate cancer represents the ideal prototype of the slow process of carcinogenesis and the necessary coexistence of constitutional risk factors with environmental risk factors for developing the disease environment. The fact that multiple factors are necessary means that when we analyze a single factor, most of the times we obtain contradictory results or increased risk without statistical significance. We see the most tangible example in exposure to tobacco smoke, given that numerous studies published with disparate results would need a meta-analysis to be performed using extensive patient case material to be able to convincingly determine its causal role. The same occurs with occupational exposure to pesticides, which, in order to obtain statistically significant data, has required large case studies. Even then, its association has only been able to be documented in men aged over 50 years with a family history of prostate cancer. Finally, we would like to point out the promising results that are being obtained with chemoprevention and which heralds its future administration to healthy population subgroups as primary prevention, and to prostate cancer patients for tertiary prevention.

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References

1. Boyle, P.; Levin B. World cancer report 2008. World Health Organization. Lyon: WHO-IARC Publ; 2008.
2. Fourcade RO, Benedict A, Black LK, Stokes ME, Alcaraz A, Castro R. Treatment costs of prostate cancer in the first year after diagnosis: a short-term cost of illness study for France, Germany, Italy, Spain and UK. *BJU Int*. 2010; 105:49–56. [PubMed: 20132102]
3. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks in human. Tobacco smoke and involuntary smoking. Vol. 83. Lyon, Francia: IARC Press; 2004.
4. Platz, EA.; Giovannucci, E. Prostate Cancer. In: Schottenfeld, D.; Fraumeni, JF., Jr, editors. *Cancer epidemiology and prevention*. 3. Oxford: Oxford Univ Press; 2006. p. 1128-1150.
5. Cerhan JR, Torner JC, Lynch CF, Rubenstein LM, Lemke JH, Cohen MB, et al. 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; 8:229–238. [PubMed: 9134247]
6. Giovannucci E, Rimm EB, Ascherio A, Colditz GA, Spiegelman D, Stampfer MJ, et al. Smoking and risk of total and fatal prostate cancer in United States health professionals. *Cancer Epidemiol Biomarkers Prev*. 1999; 8:277–282. [PubMed: 10207628]
7. Huncharek M, Haddock KS, Kupelnick B. Smoking as a risk factor for prostate cancer: a meta-analysis of 24 prospective cohort studies. *Am J Public Health*. 2010; 100:693–701. [PubMed: 19608952]
8. Wagenlehner FM, Elkahwaji JE, Algaba F, Bjerklund-Johansen T, Naber KG, Hartung R, et al. The role of inflammation and infection in the pathogenesis of prostate carcinoma. *BJU Int*. 2007; 100:733–737. [PubMed: 17662075]

9. International Agency for Research on Cancer (IARC). Human papillomaviruses. Vol. 90. Lyon, Francia: IARC Press; 2007. IARC monographs on the evaluation of carcinogenic risks in human.
10. Schlaberg R, Choe DJ, Brown KR, Thaker HM, Singh IR. XMRV is present in malignant prostatic epithelium and is associated with prostate cancer, especially high-grade tumors. *Proc Natl Acad Sci USA*. 2009; 106:16351–16356. [PubMed: 19805305]
11. Sutcliffe S, Giovannucci E, Alderete JF, Chang TH, Gaydos CA, Zenilman JM, et al. Plasma antibodies against *Trichomonas vaginalis* and subsequent risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2006; 15:939–945. [PubMed: 16702374]
12. International Agency for Research on Cancer (IARC). IARC Scientific Publication No 118. Cadmium in the human environment: toxicity and carcinogenicity. Lyon: IARC Press; 1992.
13. Sakhmoun AE, Case LD, Jackson SA, Schwartz GG. Cadmium and prostate cancer: a critical epidemiologic analysis. *Cancer Invest*. 2005; 23:256–263. [PubMed: 15945511]
14. Chen YC, Pu YS, Wu HC, Tony T, Wu TT, Lai MK, et al. Cadmium burden and the risk and phenotype of prostate cancer. *BMC Cancer*. 2009; 9:429. [PubMed: 20003241]
15. Frumkin H. Agent orange and cancer: an overview for clinicians. *CA Cancer J Clin*. 2003; 53:245–255. [PubMed: 12924777]
16. Shah SR, Terris MK. Editorial comment on: agent orange exposure, vietnam war veterans, and the risk of prostate cancer. *Cancer*. 2008; 113:2382–2384. [PubMed: 18661514]
17. Blair A, Zahm SH, Pearce NE, Heineman EF, Fraumeni JF. Clues to cancer etiology from studies of farmers. *Scand J Work Environ Health*. 1992; 18:209–215. [PubMed: 1411362]
18. Keller-Byrne JE, Khuder SA, Schaub EA. Meta-analyses of prostate cancer and farming. *Am J Ind Med*. 1997; 31:580–586. [PubMed: 9099361]
19. Acquavella J, Olsen G, Cole P, Ireland B, Kaneene J, Schuman S, et al. Cancer among farmers: a meta-analysis. *Ann Epidemiol*. 1998; 8:64–74. [PubMed: 9465996]
20. Van Maele-Fabry G, Willems JL. Occupation related pesticide exposure and cancer of the prostate: a meta-analysis. *Occup Environ Med*. 2003; 60:634–642. [PubMed: 12937183]
21. Van Maele-Fabry G, Willems JL. Prostate cancer among pesticide applicators: a meta-analysis. *Int Arch Occup Environ Health*. 2004; 77:559–570. [PubMed: 15688248]
22. Van Maele-Fabry G, Libotte V, Willems J, Lison D. Review and metaanalysis of risk estimates for prostate cancer in pesticide manufacturing workers. *Cancer Causes Control*. 2006; 17:353–373. [PubMed: 16596288]
23. Alavanja MC, Sandler DP, Lynch CF, Knott C, Lubin JH, Tarone R, et al. Cancer incidence in the agricultural health study. *Scand J Work Environ Health*. 2005; 31(S11):39–45. [PubMed: 16190148]
24. Cox B, Sneyd MJ, Paul C, Delahunt B, Skegg DCG. Vasectomy and risk of prostate cancer. *JAMA*. 2002; 287:3110–3115. [PubMed: 12069674]
25. Holt SK, Salinas CA, Stanford JL. Vasectomy and the risk of prostate cancer. *J Urol*. 2008; 180:2565–2567. [PubMed: 18930503]
26. Prince MM, Ruder AM, Hein MJ, Waters MA, Whelan EA, Nilsen N, et al. Mortality and exposure response among 14,458 electrical capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). *Environ Health Perspect*. 2006; 114:1508–1514. [PubMed: 17035134]
27. Hardell L, Andersson SO, Carlberg M, Bohr L, van Bavel B, Lindström G, et al. Adipose tissue concentrations of persistent organic pollutants and the risk of prostate cancer. *J Occup Environ Med*. 2006; 48:700–707. [PubMed: 16832227]
28. Boers D, Zeegers MPA, Swaen GM, Kant I, Van den Brandt PA. The influence of occupational exposure to pesticides, polycyclic aromatic hydrocarbons, diesel exhaust, metal dust, metal fumes, and mineral oil on prostate cancer: a prospective cohort study. *Occup Environ Med*. 2005; 62:531–537. [PubMed: 16046605]
29. Fritschi L, Benke G, Hues AM, Krickler A, Vajdic CM, Grulich A, et al. Risk of non-Hodgkin's lymphoma associated with occupational exposure to solvents, metals, organic dusts and PCBs (Australia). *Cancer Causes Control*. 2005; 16:599–607. [PubMed: 15986116]
30. Agalliu I, Eisen EA, Kriebel D. A biological approach to characterizing exposure to metal working fluids and risk of prostate cancer (United States). *Cancer Causes Control*. 2005; 16:323–331. [PubMed: 15953975]

31. Rybicki BA, Neslund-Dudas C, Nock NL, Schultz LR, Eklund L, Rosbalt J, et al. Prostate cancer risk from occupational exposure to polycyclic aromatic hydrocarbons interacting with the GSTP1 Ile105Val polymorphism. *Cancer Detect Prev.* 2006; 30:412–422. [PubMed: 17067754]
32. Krishnadasan A, Kennedy N, Zhao Y, Morgenstern H, Ritz B. Nested case–control study of occupational chemical exposures and prostate cancer in aerospace and radiation workers. *Am J Ind Med.* 2007; 50:383–390. [PubMed: 17407146]
33. Pukkala E, Martinsen JI, Lyng E, Gunnarsdottir HK, Sparén P, Tryggvadottir L, et al. Occupation and cancer – follow-up of 15 million people in five Nordic countries. *Acta Oncol.* 2009; 48:646–790. [PubMed: 19925375]
34. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med.* 2003; 349:215–224. [PubMed: 12824459]
35. Rittmaster RS, Fleshner NE, Thompson IM. Pharmacological approaches to reducing the risk of prostate cancer. *Eur Urol.* 2009; 55:1064–1073. [PubMed: 19200641]
36. Andriole GL, Bostwick DG, Brawley OW, Gomella LG, Marberger M, Montorsi F, et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med.* 2010; 362:1192–1202. [PubMed: 20357281]
37. Strobe SA, Andriole GL. Update on chemoprevention for prostate cancer. *Curr Opin Urol.* 2010; 20:194–197. [PubMed: 20216317]
38. Ionizing radiation, Part 1, X- and γ -radiation and neutrons. Vol. 75. Lyon: IARC Press; 2000. IARC Monographs on the evaluation of carcinogenic risks to humans.
39. Gilbert R, Metcalfe C, Oliver SE, Whiteman DC, Bain C, Ness A, et al. Life course sun exposure and risk of prostate cancer: population-based nested case–control study and meta-analysis. *Int J Cancer.* 2009; 125:1414–1423. [PubMed: 19444909]
40. Gupta D, Lammersfeld CA, Trukova K, Lis CG. Vitamin D and prostate cancer risk: a review of the epidemiological literature. *Prostate Cancer Prostatic Dis.* 2009; 12:215–226. [PubMed: 19350051]