Prostate Cancer: Peer Reviewed Analysis

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Prostate Cancer

Ted Schettler, MD, MPH
Science Director, Science and Environmental Health Network

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Incidence, Mortality, Trends

Prostate cancer is the most commonly diagnosed cancer in men in the US. Over 300,000 new prostate cancer cases are diagnosed annually, constituting about 30% of all new male cancer cases, and more than 40,000 men die from the disease each year. Annual incidence rates average about 155/100,000 for white men and 230/100,000 for black men in the US. The incidence of prostate cancer increased dramatically between 1992 and 1997, largely, but not entirely, as a result of increased screening using prostate specific antigen (PSA) testing. Though mortality rates have not increased as abruptly, a steady upward trend for white and black men continues. Age-adjusted mortality rates for white and black men have declined substantially in recent years because of earlier diagnosis and improved treatment techniques (Chu et al 2003l).

Demographic Factors

The incidence of clinical prostate cancer is lowest in Asian countries and highest in Scandinavia (Lin and Lange 2000). African-American men are at substantially higher risk of developing and dying from prostate cancer than Caucasians in the United States. African-American men living in the San Francisco area have a risk of developing prostate cancer that is 120 times that of Chinese men living in China. It is interesting to note that the incidence of prostate cancer highly correlates with breast cancer incidence in virtually every country studied (Coffey 2001). This suggests that the two kinds of cancer may have causal factors in common. Normal breast and prostate tissue also share some common features. Each is hormonally responsive, containing estrogen, androgen, and progesterone receptors. Prostate specific antigen (PSA), normally present in prostate tissue, is also present in the breast.

Although Asian men are less likely to develop clinical evidence of prostate cancer, an autopsy study shows that Japanese men also develop latent (histologic but clinically unapparent) prostate cancer early in life (Yatani et al. 1988, Shiraishi et al. 1994). Japanese men living in Japan had a marked increase in latent prostate cancer from 1965-1979 to 1982-1986. The risk of developing clinically apparent prostate cancer increases for Japanese men who immigrate to the US, though

prostate cancer incidence among Japanese men in the US remains well below that of Caucasians (Shimizu et al. 1991).

The Natural History of Prostate Cancer

Prostate cancer develops in stages, becomes common in men as they age, and is often present in older men who die of other causes. Clinically apparent cancer is preceded by a sequence of multiple steps that are likely to unfold over many years (Cater et al. 1990). Some tumors, however, behave much more aggressively than others. Early stages of prostate cancer may go undetected for many years, complicating understanding of the natural history of the disease. Although autopsy studies of older men frequently identify prostate cancer as an incidental finding, a study in younger men reported a surprising incidence of prostate cancer (Sakr et al. 1993). In 152 men in California all less than 50 yrs old, who died of other causes, 34 percent of those 40-49 yrs old and 27% of those 30-39 yrs old had microscopic evidence of cancer in their prostate glands. Cellular changes (prostatic intraepithelial neoplasia) that may either progress to cancer or, alternatively, be evidence of susceptibility to cancer were detected in 9 percent of men 20-29 yrs old. An autopsy study in Detroit also identified prostate cancer in a small percentage of men in their 30's, with steady increases in age-associated prostate cancer incidence thereafter (Sakr et al. 1994).

Animal tests discussed below suggest that the earliest stages of what may later become prostate cancer may be traced back to early developmental periods. Genetic and environmental factors that promote the sequence that results in clinical prostate cancer are likely to help explain trends and demographic variability. In fact, even in a single individual, the natural history of early microscopic prostate cancer cells may vary significantly with genetic and environmental factors (Lange 1994).

Together, animal and human data suggest that prostate cancer commonly begins early in life and results from the promotion of a sequence of events, rather than sudden initiation of an outright cancerous tumor in previously normal tissue. The data are consistent with the hypothesis that very early life events influence the risk of developing prostate cancer. It is worth noting that, regarding development of breast cancer in women, a similar hypothesis is supported by a considerable amount of data.

Cause(s) of Prostate Cancer

Genetic Factors: Prostate cancer is a complex disease that results from an interaction of genetic and environmental factors. Approximately 5-10% of cases of prostate cancer may be caused primarily by inherited dominant susceptibility factors (Steinberg et al. 1990). High penetrance and low penetrance susceptibility genes are likely to be involved. The risk of developing prostate cancer increases 2-4 fold with a history of the disease in close relatives and is particularly increased when prostate cancer develops early in the life of a close relative. A study of cancer in monozygotic and dizygotic twins concluded that genetic factors accounted for approximately

42% of prostate cancer risk and suggested that environmental factors account for the remainder (Lichtenstein et al. 2000). Though this is likely to be a somewhat simplistic conclusion about a complex disease with high likelihood of gene-environment interactions, the data emphasize the importance of both genes and the environment.

Genes for which there is some evidence of a causal relationship to prostate cancer include those that code for the enzyme (5-alpha-reductase) that converts testosterone (T) to dihydrotestosterone (DHT), the vitamin D receptor, androgen receptors and their variants, growth factors, and tumor suppressor genes. Some evidence suggests that the breast cancer susceptibility gene, BRAC, also influences prostate cancer risk (Rosen et al. 2001).

Environmental Factors: Historically, studies of environmental variables that may influence cancer risk have focused primarily on the adult environment of people who develop the cancer of interest, including dietary and occupational factors. Demographic differences in cancer incidence also offer clues. Experience with diethylstilbestrol (DES), however, showed the importance of considering the fetal environment. Daughters born to women who took DES during pregnancy are at markedly increased risk of developing cancers of the reproductive tract as adolescents or adults. Animal studies also show that in utero exposures to dioxin can fundamentally alter differentiation of breast tissue so that adult animals are more susceptible to breast carcinogens (Brown 1999). As a result, attention is slowly shifting to include the environment of very early life as it may influence the likelihood of developing cancer many years later. Evaluation of the impact of environmental factors on prostate cancer risk has followed this familiar sequence as summarized here.

Geographical Factors: The probable role of environmental factors in the development of clinically apparent prostate cancer is supported by several kinds of data in addition to the twin study. First, prostate cancer risk increases in men who migrate from low-incidence to higher-incidence countries (Haenzel and Kurihara 1968; Dunn 1975; Angwafo 1998). The data are most persuasive for Asians in whom the risk markedly increases with immigration to the West. Early studies suggested that black men in the US were also at much higher risk of prostate cancer than black men living in Africa (Ahluwalia et al. 1981; Angwafo 1998). However, these may be misleading due to differences in access to health care, disease surveillance, and age distribution of populations. A systematic study of black men in Nigeria found that prostate cancer incidence was actually much higher than previously reported and may be as high as that noted among black men in the US (Osegbe 1997).

Dietary Fat and Red Meat Consumption: A number of epidemiologic studies have identified dietary fat as a risk factor for development of prostate cancer (Lin and Lange 2000; Rose et al. 1986; West et al. 1991). Some studies find animal fat consumption associated with increased prostate cancer risk rather than fat from vegetables and fish (Giovannucci et al. 1993; Gann et al. 1994). High animal fat diets may increase the risk by as much as 3.5 fold.

More recent studies have focused specifically on dietary meat and have found that red meat consumption significantly elevates prostate cancer risk (Kolonel 1996, Michaud et al. 1996, Nelson et al. 2001). The increased risk associated with dietary red meat is larger than for total meat consumption and is, at least in part, independent of total dietary fat. Cooking red meat produces a variety of aromatic amines, many of which are carcinogenic in animal testing. PhIP, one of that family of chemicals, is a potent prostatic carcinogen in rodents.

One theory holds that red meat or animal fat consumption promotes the growth of low-grade unapparent prostate tumors into more aggressive and readily detectable forms. This theory is consistent with the observation that Asian men who eat a Western diet that is higher in animal fat have an increased risk of developing clinically apparent prostate cancer compared to those who remain on a more traditional Asian diet, even though histologic, unapparent prostate cancers occur with roughly the same frequency in Asians and Westerners.

Diet may influence the risk of developing prostate cancer through an effect on the endocrine system. One study showed that serum estrone concentrations decreased in Japanese men who supplemented their normal diet with soy milk when compared to controls (Nagata et al. 2001). Testosterone and estrogen concentrations remained similar and unchanged. In another study, South African prostate cancer patients transferred to a Western diet showed an increase in estrone levels (Hill et al. 1982). Though the significance of these changes is not known, the testosterone:estrogen ratio may be a more significant measure of risk that the absolute values of either hormone alone.

In animal studies, maternal dietary factors also influence the expression of androgen and estrogen receptors in the prostates of male offspring and may, thereby, influence subsequent prostate cancer risk. In a rat study, for example, maternal dietary genistein (an estrogenic component of soy and other plant foods), at levels comparable to humans on a soy diet, decreased both androgen and alpha-and beta-estrogen receptors in the prostates of male offspring (Fritz et al. 2002). Adult male rats fed genistein also showed decreased prostate androgen and estrogen receptor activity.

Cadmium: Cadmium is a known human carcinogen and is linked to prostate cancer in epidemiologic and laboratory animal studies (Agency for Toxics Substances and Disease Registry 1997; Waalkes 2000). The relevance of some rodent studies to humans is uncertain because the prostate glands of some rodent strains do not closely resemble those of humans. However, in a rodent strain with a dorsolateral prostate similar to that in men, dietary cadmium exposure caused dose-dependent proliferative, pre-cancerous appearing lesions in that portion of the prostate (Waalkes et al. 1999). Some studies show an increased concentration of cadmium in prostates with cancer when compared to normal glands (Brys et al. 1997; Waalkes and Rehm

1994). Test tube studies also show the ability of cadmium to cause malignant transformation of human non-malignant prostate cells (Achanzer et al. 2001).

Food and cigarette smoke are the largest sources of cadmium exposure in the general population. Smokers have a daily cadmium intake that may be twice that of non-smokers. Occupational exposures may also occur among welders, metal workers, or those who make cadmium products such as batteries or plastics (Agency for Toxics Substances and Disease Registry 1997). Some people absorb cadmium more readily from the gastrointestinal tract than others, such as those with depleted calcium or iron stores. People with naturally low levels of metallothionein (an inducible substance that sequesters cadmium and other heavy metals) may also be at increased risk of cadmium related toxicity. Cadmium levels are elevated in some foods grown on soil that has been treated with cadmium-containing sewage sludge or fertilizers, or that is naturally high in cadmium (Alloway and Jacson 1991; Piscator 1985).

Pesticides: A number of published studies support a causal relationship between pesticide exposure and prostate cancer. For example, many occupational studies show an increased incidence of prostate cancer incidence and/or mortality among farmers and pesticide applicators (Sharma-Wagner et al. 2000; Dich and Wiklund 1998; van der Gulden et al. 1995; Janssens et al. 2001; Mills 1998; Fleming et al. 1999; Fleming et al. 1999; Keller-Byrne et al. 1997; Kross et al. 1996). Though some of these are correlation studies and, therefore, limited by a lack of actual pesticide exposure data, exposure misclassification in epidemiologic analyses is more likely to bias toward false negatives than false positives. The findings among pesticide applicators are particularly significant since, in general, a healthy-worker effect was noted, and alcohol- and tobacco-related illnesses were reduced among the workers. One in vitro study of human prostate cancer cells showed that several organochlorine pesticides, a pyrethroid, and a fungicide each caused proliferation of androgen-dependent cancer cells (Tessier and Matsumura 2001).

Other Environmental Exposures and Prostate Cancer Risk—The Importance of Timing

In recent years, considerable attention has focused on endocrine disrupting chemicals in the ambient environment and their impacts on human and wildlife health (Colborn and Clement 1992; National Research Council 1999; Colborn et al. 1996; Schettler et al. 1999). An important theme that emerges from these analyses is the particular susceptibility of the developing organism to exposures to hormonally-active substances at levels that have minor, transient, or no impact in adults. Low-level developmental exposures to substances that modulate endocrine activity can have life long impacts if the exposure occurs during window(s) of unique vulnerability.

The fetal prostate develops under the control of maternal and fetal hormones, including testosterone, estrogen, and prolactin. A variety of growth factors also play important roles. Testosterone, enzymatically transformed to dihydrotestosterone (DHT), is essential for normal prostate growth. Estrogens also play a role (Adams et al. 2002). During normal prostate development, squamous metaplasia develops in the prostatic tubules as the fetus matures, but it

normally disappears by birth. However, when the fetus is exposed to excessive estrogen, the condition persists (Shapiro 2000). The role of prolactin in normal prostate growth is not fully understood but it enhances the effects of testosterone and also directly stimulates prostate growth (Jannulis et al. 2000). Prolactin levels are elevated in men with BPH (Saroff et al. 1980).

A 1980 report noted that in utero exposure to diethylstilbestrol (DES) alone or in combination with other hormones in humans correlated with enlargement of prostatic ducts and increased Leydig cells in the testes (Driscoll and Taylor 1980). Studies in rodents show that prenatal exposure to estrogenic agents causes an increase in androgen receptor binding activity and enlargement of the prostate at low doses (Gupta 2000; vom Saal et al. 1997). Higher prenatal doses of DES cause down regulation of androgen receptors and decreased prostate weight, along with other evidence of feminization of males. Postnatal estrogen exposure generally reduces prostate size and androgen sensitivity (Naslund and Coffey 1986). Also in rodents, brief neonatal exposure to estrogens blocks epithelial cells in the prostate from differentiating normally (Habermann et al. 2001). In adulthood, the prostates of animals exposed to estrogens in the neonatal period show precancerous changes (dysplasia). One conclusion that can be drawn from these observations is that the timing of perturbations of normal levels of hormones and growth factors that influence prostate growth and differentiation strongly influences both the nature and magnitude of their effects.

Another "environmental estrogen", bisphenol A (BPA-a component of epoxy resins, polycarbonate plastic, and dental sealants to which the general population is exposed at low levels), caused prostate enlargement in mice exposed to low levels in utero (maternal exposures 20-50 microgms BPA/kg/day) (Nagel et al. 1997; Gupta 2000). Prenatal BPA exposure also alters cellular differentiation in the tissue (stroma) that surrounds the ducts of the prostate (Ramos et al. 2001). Although BPA has a binding affinity for the estrogen receptor that is several orders of magnitude less than estradiol, BPA does not bind to plasma-binding proteins to the same degree as estradiol and therefore, is likely to be more available to cells than estradiol. BPA also stimulated prolactin release in an animal study (Steinmetz et al. 1997). A recent study in prostate cancer cells showed that very low concentrations of BPA activated the androgen receptor and initiated proliferation of cancer cells, independent of testosterone (Wetherill et al. 2002).

Collectively, these studies suggest that prostate growth and development, including organ size, cell differentiation, and hormone receptor levels may be permanently altered by exposure to hormonally-active substances during fetal development. Developmental exposure to estrogen-like substances may increase the risk for later development of prostate cancer, depending on genetic and subsequent environmental factors (Santti et al. 1994). This proposed sequence of events suggests that the investigation of dietary, occupational, and other environmental variables as risk factors for prostate cancer must be examined during fetal life and childhood, as well as in adults.

Summary

Prostate cancer is the most commonly diagnosed cancer in men in the United States and is responsible for more than 40,000 deaths annually. African-American men are at greater risk of developing the disease and dying of it than Caucasians. Asian men living in Asia have a markedly lower risk, but when they move to Western countries, their risk of prostate cancer sharply increases. Autopsy studies show that prostate cancer often begins much earlier in life than previously thought, though usually not becoming clinically apparent until later years.

The causes of prostate cancer are not well understood. Genetic factors play a prominent role in 5-10% of cases, and a lesser role in others. Gene-environment interactions are likely to be important determinants of prostate cancer risk. Known environmental risk factors for prostate cancer include red meat consumption, dietary fat, cadmium, and pesticide exposures.

Recent studies in animals and humans suggest that the lifetime risk for prostate cancer is influenced by fetal, childhood, and adult events, including exposure to environmental contaminants. In particular, contaminants with estrogenic properties may play an important role in early life.

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