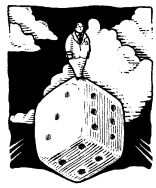

Prostate cancer: 3. Individual risk factors

Richard P. Gallagher, PhD; Neil Fleshner, MD

The case

A 42-year-old lawyer makes an appointment to see his family physician. His father (age 67) has just been diagnosed with metastatic prostate cancer. The patient has no significant medical history and has not seen a doctor since he had a vasectomy 7 years ago. He is an admitted junk-food addict, has a sedentary life-style and is moderately overweight. Palpation reveals no abnormalities of the prostate. The patient asks the physician's advice about reducing his risk of prostate cancer.

Rising incidence rates and increased public awareness of prostate cancer have created an explosion of scientific interest in the epidemiology of this disease.[1] Although a number of studies are shedding light on risk factors, the data are not firm enough to support widescale primary prevention trials. Nevertheless, the importance of several factors is becoming clear (Fig. 1).

National and ethnic differences

In Canada, the incidence rates for prostate cancer are among the highest in the world, although they are still below those in the United States and Sweden.[1,2] The highest incidence rates occur among black American men, for whom the age-standardized rates are 50% to 60% higher than those for white American men.[2] The lowest rates of prostate cancer are typically found in Asian countries; the rates in China are only 4% of those in Canada.[3] Although variations in case-finding strategies may provide a partial explanation, these differences are much too pronounced to be an artifact due entirely to ascertainment procedures.

Studies of migrating populations are often useful in determining the relative contributions of genetics and environment to disease causation. Among Asian men who have immigrated to North America, for example, prostate cancer incidence rates remain low. Within long-standing Chinese and Japanese communities in North America, these rates, although much higher than in Asia, are only about half those for white men living in the same areas.[2] Although these racial differences suggest a genetic component to disease causation, cultural practices, such as dietary habits, may also explain the variations. Furthermore, the fact that incidence rates increase significantly in groups who immigrate to North America indicates that life-style factors play a major role in the etiology of the disease.

Family history and genetic predisposition

Apart from age, the most consistent risk factor for prostate cancer found to date is the occurrence of the disease in a close relative.[4] Having a first-degree rel-

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Education

Éducation

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The members of the Prostate Cancer Alliance of Canada, an umbrella group formed to carry out the recommendations of the 1997 National Prostate Cancer Forum, are pleased to support the intent to inform both health care professionals and lay people about the detection, diagnosis and treatment of prostate cancer through this 13-part series.

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ative (i.e., a father, son or brother) with prostate cancer increases the risk of the disease by about 2 to 2.5 times among black, white and Asian men in North America.[4–7] If 2 or more first-degree relatives have prostate cancer, the risk increases by more than 4 times among white and Asian men and by perhaps as much as 10 times among black North American men.[6] A recent Canadian study[8] found that the risk associated with having 1 or more relatives with the disease was midway between the risks associated with having 1 relative and having 2 or more relatives affected. The risk associated with having a first-degree relative with the disease may be even higher if that relative's diagnosis is made before age 65, although this is still to be confirmed.[7]

Teaching points

- A diet high in fat has been associated with an increased risk of prostate cancer.
- Dietary fat may be particularly associated with aggressive cancers, which suggests a role in disease progression.
- Vitamin E and selenium may reduce the incidence of prostate cancer.
- The potential preventive properties of soy products and lycopenes are being investigated.

Elevation of risk of prostate cancer among relatives may be attributed to genetic predisposition, shared exposures or bias. Genetic factors appear to be partly responsible for familial clustering, and a recent segregation analysis[9] suggested that an autosomal dominant gene might be responsible. The proposed model suggests that about 0.6% of white men inherit a mutated allele of one or more predisposing genes, which confers a lifetime risk of prostate cancer for these men of about 88%, as opposed to about 5% for men without the mutated allele. The model suggests a relative risk of about 1.6 for men whose fathers have prostate cancer compared with men whose fathers do not have the disease; this estimate is similar to, although slightly lower than, what has been seen in recent studies.[4,6]

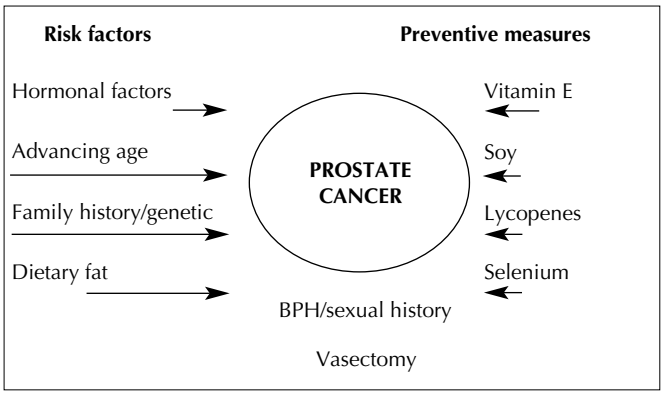

Fig. 1: Common risk factors and preventive factors for prostate cancer. Arrow length is proportional to the degree of supporting evidence. Factors listed to the left and right of the circle indicate risks and preventive factors, respectively. For benign prostatic hyperplasia (BPH) or sexual history and vasectomy, there is very little evidence supporting the association.

Clustering of prostate cancer has also been reported in more distant relative pairs, such as grandfather–grandson, uncle–nephew, first cousins and second cousins.[10] It is unlikely that this effect is due to detection bias or shared environmental factors.

A number of groups have provided evidence of a "prostate cancer gene," *HPC1*, on the short arm of chromosome 1.[11,12] A great deal more work is needed to identify the specific mutated locus within this region, which contains 20 million base pairs, and to determine the function of the gene. The fact that at least one group[13] studying large numbers of high-risk families has not confirmed the importance of *HPC1* suggests that this marker is not the only gene predisposing men to familial prostate cancer. Other studies have pointed to different candidates, including several genes on the X chromosome[14] such as the androgen receptor gene[15] and the vitamin D receptor gene.[16]

Diet

Descriptive data suggest that diet plays a major role in prostate cancer. Internationally, the incidence of prostate cancer is highly correlated with that of colon, breast and endometrial cancers, which are thought to be related to diet.[17] Mortality from prostate cancer among Japanese men increases when they immigrate to North America, and dietary changes are thought to be a significant factor in these increases.[18]

Dietary fat

Data from analytic studies suggest a positive relation between high fat consumption and prostate cancer[19–34] (Appendix 1). Although some of the early studies[19,21,22] revealed no association, dietary assessment became more sophisticated in later investigations. The first study to include both large numbers of cases and controls and a dietary assessment questionnaire that identified the majority (85%) of normal intake[24] showed that prostate cancer incidence increased with consumption of saturated fat in most of the ethnic groups studied.

The association between dietary fat and aggressiveness of the cancer raises the possibility that fat primarily affects disease progression within established tumours. A recent study[35] carried out in mice with established transplanted human prostate tumours and raised on a diet with 40% of

calories from fat suggested that reduction to 20% of calories from fat slowed tumour growth velocity relative to mice maintained on the high-fat diet. If these observations are confirmed, reducing dietary fat may reduce the risk of prostate cancer risk, even relatively late in life.

Micronutrients

Many studies[20–24,28,29,32,34,36–40] have reported on the putative relation between vitamin A or beta-carotene intake and prostate cancer (Appendix 2). These compounds are potent antioxidants and may exert a protective effect against epithelial tumours. Unfortunately, there is no consistent evidence of protection from prostate cancer and, in fact, several studies[24,39] suggest that these nutrients increase the risk of this disease.

Vitamin E

Although there is relatively little information on the effect of vitamin E, or alpha-tocopherol (its most common form), some recent findings[34,41] suggest that it may reduce the risk of prostate cancer. However, other results[37,39] have not been convincing, and more work is necessary to assess this potential association.

Lycopene and tomato products

Consumption of tomatoes and tomato-based products may reduce the risk of prostate cancer.[27,39] Researchers have concluded that lycopene, a potent antioxidant found in tomatoes, may be responsible. Recent evidence also indicates that levels of lycopene in the prostate are at high enough concentrations to be equivalent to those that are biologically active in laboratory studies.[42] More research is needed to clarify the role of lycopene in prostate cancer.

Selenium

Glutathione peroxidase, an enzyme that protects cells from oxidative damage, is selenium dependent,[43] and several epidemiologic studies have confirmed an inverse association between selenium intake and various human cancers, including prostate cancer.[43] Recently, the efficacy of 200 µg/day of selenomethionine in a placebo-controlled intervention study of 1312 patients with non-melanoma skin cancer was reported.[44] After 8269 patient-years of follow-up, there was a 3- to 4-fold lower incidence of prostate cancer among those who received the selenium (relative risk 0.29, $p < 0.001$). No toxic effects of selenium were observed. Although the incidence of prostate cancer was not an intended outcome variable in this study, these highly significant findings call for further investigation.

Soy products

The incidence of prostate cancer is significantly lower in Asia than in North America,[2] and some of this difference is thought to be due to diet. A recent investigation of serum levels of 2 isoflavones, daidizein and genistein, in normal Japanese and Finnish men revealed substantially higher concentrations in the Japanese men.[45] Isoflavones are phytochemicals that possess a wide range of anticancer properties. Genistein, which occurs in lentils and soy products such as tofu, inhibits the growth of androgen-dependent and androgen-independent prostate cancer cells in culture.[46]

To date only one study[26] of tofu consumption has shown a protective effect in terms of prostate cancer risk. Another study[27] demonstrated that lentils and beans, which are known to contain isoflavones, have a protective effect. Currently, there is insufficient evidence to recommend an increase in consumption of isoflavinoids, but further research may well identify a chemopreventive effect for prostate cancer.

Body mass and physical activity

Case–control studies[47–50] have suggested that men with high body mass and those who are obese as adults have an increased risk of prostate cancer; however, others[27,29,32] have failed to confirm this association. Level of physical activity has been found to be inversely associated with risk,[31,51] but the data are inconsistent with other studies showing an association or a positive relation.[29,32,48] This association may have to be examined in young men, in whom physical activity is known to affect hormonal profiles.[52]

Vasectomy

Evidence for a relation between prostate cancer and vasectomy is inconclusive. Currently, the consensus appears to be that even if vasectomy is a risk factor for prostate cancer, it is a weak one, and its effect is not strong enough to influence public health policy regarding vasectomy.[53]

Hormonal and sexual factors

Sex hormones are probably related to the development of prostate cancer for several reasons: the prostate gland is androgen dependent,[54] prostate cancer does not occur in eunuchs,[55] administration of male sex hormones can induce prostate cancer in animal models,[54] and castration induces programmed cell death — apoptosis — in prostate cancer cells.[56]

A recent study of normal, older, black, white and Asian men[57] — groups known to be at high, medium and low risk for prostate cancer respectively — showed that after

adjustment for age and body mass, the levels of total and bioavailable testosterone were highest in Asian men, intermediate in white men and lowest in black men. However, the ratio of dihydrotestosterone to testosterone was the reverse (i.e., highest in black men, intermediate in white men and lowest in Asian men). Also, sex hormone binding globulin (SHBG) levels were higher in men reporting one or more first-degree relatives with prostate cancer. A prospective cohort study[58] revealed that high plasma levels of testosterone before diagnosis were associated with increased risk of prostate cancer, and an inverse trend was seen with levels of SHBG. Thus, data in this area are contradictory and further study is necessary.

Several studies[59,60] have suggested that subjects with shorter polymorphic CAG repeat sequences in the androgen receptor gene are at higher risk for prostate cancer than those with longer sequences. This finding suggests that male sex hormone regulation is critical in the development of prostate cancer, which might account for the lower risk of prostate cancer in Asian men.

Because sex hormone levels decline with age,[57] investigators are beginning to evaluate the hormonal profiles of young men, reasoning that the etiologically relevant period may be at a much younger age than the age at which the cancer develops. Serum testosterone levels in college-aged black men have been found to be 15% higher, and free testosterone levels 13% higher, than in their white counterparts.[61] These differences are substantially greater than in older black, white and Asian men. In another study that included young Japanese men as well as black and white American men,[62] the expected low levels of testosterone in the Japanese men were not found. However, there was indirect evidence of reduced 5 α-reductase activity in the Japanese men, which may account for the low rate of clinically evident prostate cancer in Japan.

Because diet and levels of physical activity can affect male serum hormone levels,[63] more research is needed on these factors, particularly among young men of various ethnic groups. It would also be useful to compare dietary patterns and serum hormone levels in young men whose fathers or grandfathers have prostate cancer with those of young men without a family history of the disease.

Teaching points

- Physical activity and obesity have not been consistently associated with prostate cancer.
- Evidence does not support the suggestion that vasectomy is a risk factor.
- Hormonal milieu is important in the development of prostate cancer; however, additional work is needed to determine which steroidal metabolites are important and at what ages.

Sexual history

Studies of sexual history in men with and without prostate cancer have not, by and large, revealed consistent differences. Several investigations[64,65] have suggested that men with prostate cancer were sexually active earlier and had more partners than the control group, but other evidence appears to indicate the opposite.[66] History of sexual activity seems to be open to substantial misclassification, and because the information gathered is impossible to validate, it is difficult to imagine that this will be a fruitful area for future study.

Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) is common in older men; it varies considerably in onset and severity and is difficult to study because of the lack of standardized pathologic criteria for its diagnosis. Several epidemiologic investigations have been conducted to evaluate whether men with BPH are at higher risk for prostate cancer. One of these studies[67] identified a higher risk of prostate cancer among those with BPH, but another,[68] a follow-up comparison of a cohort of patients who underwent subtotal prostatectomy for BPH with a group of other surgical patients, found no increase in risk.

Historically, men with symptomatic BPH have undergone transurethral prostate surgery, and in 10% of cases cancer has been discovered incidentally. Given this detection bias, only death from prostate cancer could serve as an adequate endpoint. Fortunately, the detailed embryologic and anatomic studies of McNeal[69] have shed some light on this issue. Benign prostate disease is restricted to the transition zone compartment of the prostate gland. Conversely, prostate cancer originates principally in the peripheral zone compartment. This critical difference in disease ontogeny suggests that a causal relation between these 2 conditions is unlikely.

Occupational exposure

The role of occupational exposure in the etiology of prostate cancer has been explored. Several cohort investigations have found an elevated risk among workers exposed to cadmium,[70] although other studies,[71–73] including expanded analyses[72,73] for one of the occupational groups for which a positive association had previously been found, have shown no increased risk.

Although potential biologic mechanisms for carcino-

genesis have been suggested,[72] it seems unlikely that cadmium exposure alone could explain much of the current prevalence of prostate cancer. Using sound data on exposure, Aronson and co-workers[74] found elevated risks among those employed in the water-transport and aircraft manufacturing industries. Other groups at elevated risk include metal product fabricators, structural metal erectors and railway transport workers. The difficulty with these associations is that no dose–response relation is seen, with the possible exception of exposure to aluminum dust and to liquid fuel combustion products.

Farming and agricultural work have been associated with elevated prostate cancer mortality in several studies[75,76]; however, others have failed to validate these observations.[74,77] Recent investigations have revealed high incidence of and mortality rates from cancer among airline pilots[78] and chemical workers exposed to perfluorooctanoic acid.[79] However, with the possible exception of perfluorooctanoic acid, even if the higher rates observed are "real," primary prevention programs in the workplace would be difficult to implement because specific carcinogens have not been identified.

Conclusion

The aging of the Canadian population and the longer life expectancy of men have made prostate cancer a major public health issue. Thus, the research community must intensify efforts to elucidate the etiology of this disease in the expectation that many of the risk factors identified will be modifiable. Several research areas look promising:

- Studies of the cascade of mutations that mark the transformation of normal prostatic tissue to frank carcinoma may help to identify specific loci of action for carcinogens in sporadic prostate cancer.
- Studies aimed at isolating germline mutations that predispose to familial prostate cancer will help identify men at high risk long before the disease occurs.
- Dietary studies with emphasis on the early years of life, coupled with investigation of physical activity levels and serum hormone levels, might reveal more about early events critical in the occurrence of the disease.
- Studies of hormone profiles in young men of various ethnic groups, particularly in families with a strong history of prostate cancer, could identify early hormonal anomalies leading to higher risk later in life.

The patient described in the case at the beginning of this article is at elevated risk for prostate cancer. The main risk relates to his father's disease, but other factors, in order of diminishing significance, are his high-fat diet and his sedentary life-style. In terms of clinical recommendations, there are as yet no evidence-based guidelines. However, in terms of overall health, the patient would be wise to decrease his fat intake and begin an exercise program. Consumption of vitamin E and tofu are unlikely to cause harm and may provide beneficial effects. Although there are no firm guidelines regarding screening, the American Urological Association recommends that digital rectal examination and testing for prostate-specific antigen begin at age 40.

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Appendix 1: Studies of dietary fat and prostate cancer

Place of study	Diagnosis period	Type of study	No. of subjects		Source of fat (intake)	Summary RR (and 95% CI) in highest exposure group
			Cases	Controls		
Japan[19]	1966–1975	Cohort	63		Meat	0.9 (NS)
New York[20]	1957–1965	Case–control	311	294	Total fat	2.04 (CI not given, $p < 0.05$)
Kyoto, Japan[21]	1981–1984	Case–control	100	100	Total fat	1.33 (NS, $p > 0.05$)
Washington, DC[22]	1982–1984	Case–control	55	55	Total fat	No difference, RR not given
California[23]	1977–1980	Case–control	142	142	Total fat	1.9 (CI not given, $p < 0.05$)
Hawaii[24]	1977–1983	Case–control	452	899	Saturated fat	1.70 (1.0–2.8)
New York[25]	1982–1988	Case–control	371	371	Annual fat	1.26 (0.76–2.07)
Hawaii[26]	1965–1986	Cohort	174	–	Saturated fat	1.00 (0.75–1.60)
California[27]	1976–1982	Cohort	180	–	Beef	1.21 (0.83–1.75)
Minnesota[28]	1966–1986	Cohort	149	–	Meat	0.8 (0.5–1.3)
Utah[29]	1984–1985	Case–control	358	679	Total fat	Aggressive cases 2.9 (1.0–8.4)
US[30]	1986–1990	Cohort	300	–	Total fat Red meat	Advanced cases 1.79 (1.04–3.07) Advanced cases 2.6 (1.21–5.77)
Sweden[31]	1989–1992	Case–control	256	252	Total fat	0.7 (0.4–1.1)
US and Canada[32]	1987–1991	Case–control	1655	1645	Saturated fat	Aggressive cases 2.8 (1.5–5.2)
Ontario[33]	1990–1992	Case–control	207	207	Total fat	0.7 (0.4–1.3)
Serbia[34]	1990–1994	Case–control	101	202	Total fat	1.95 (0.68–5.57)

Note: RR = relative risk, CI = confidence interval, NS = not significant.

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Appendix 2: Studies of beta-carotene or vitamin A and prostate cancer

Place of study	Diagnosis period	Type of study	No. of subjects: Cases	No. of subjects: Controls	Source (intake or level)	Summary RR (and 95% CI) in highest exposure group
New York[20]	1957–1965	Case–control	311	294	Vitamin A	Age < 70, 1.64 (CI not given) Age ≥ 70, 1.97 (CI not given)
Washington, DC[22]	1982–1984	Case–control	55	55	Vitamin A	NS, RR not given
California[23]	1977–1980	Case–control	142	142	Vitamin A	Black men 0.8 (NS) White men 0.9 (NS)
					Carotene	Black men 0.6 (NS) Whites men 1.0 (NS)
Hawaii[24]	1977–1983	Case–control	452	899	Vitamin A	Age < 70, 0.8 (0.5–1.3) Age ≥ 70, 2.0 (1.3–3.1)
					Carotene	Age < 70, 1.0 (0.6–1.6) Age ≥ 70, 1.5 (0.9–2.3)
California[36]	1981–1986	Cohort	93	–	Total vitamin Dietary carotene	1.2* 1.0*
Rotterdam, Netherlands[37]	1982–1985	Case–control	133	130	Serum retinol level Serum carotene level	0.36 ($p = 0.04$) 0.77 (NS)
Kyoto, Japan[21]	1981–1984	Case–control	100	100	Dietary carotene	0.34 ($p < 0.05$)*
US[38]	1971–1988	Cohort	84	–	Prospective serum vitamin A level	0.4*
Minnesota[28]	1966–1986	Cohort	149	–	Vitamin A	Age < 75, 2.8 (1.4–5.8) Age ≥ 75, 0.4 (0.2–0.9)
					Carotene	Age < 75, 1.9 (1.0–3.7) Age ≥ 75, 0.2 (0.1–0.6)
Utah[29]	1984–1985	Case–control	358	679	Vitamin A	Age 45–67, 1.0 (0.6–1.7) Age 68–74, 1.6 (0.9–2.7)
					Carotene	Age 45–67, 0.8 (0.5–1.2) Age 68–74, 1.4 (0.9–2.4)
US and Canada[32]	1987–1991	Case–control	1655	1645	Vitamin A	No association, RR not given
US[39]	1986–1992	Cohort	773	–	Total retinol equivalents Retinol without supplements	1.13 (0.88–1.44) 1.30 (1.03–1.66)
Serbia[34]	1990–1994	Case–control	101	202	Retinol Retinol equivalent	0.69 (0.50–1.24) 1.64 (1.01–2.67)
Chicago[40]	1957–1989	Cohort	132	–	Carotene	1.03 (0.59–1.60)

*Calculated from data provided in paper.