Prostate cancer epidemiology

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1. ABSTRACT

Prostate cancer is the most common non-skin cancer among men in most western populations, and it is the second leading cause of cancer death among U.S. men. Despite its high morbidity, the etiology of prostate cancer remains largely unknown. Advancing age, race, and a family history of prostate cancer are the only established risk factors. Many putative risk factors, including androgens, diet, physical activity, sexual factors, inflammation, and obesity, have been implicated, but their roles in prostate cancer etiology remain unclear. It is estimated that as much as 42% of the risk of prostate cancer may be accounted for by genetic influences, including individual and combined effects of rare, highly penetrant genes, more common weakly penetrant genes, and genes acting in concert with each other. Numerous genetic variants in the androgen biosynthesis/metabolism, carcinogen metabolism, DNA repair, and chronic inflammation pathways, have been explored, but the results are largely inconclusive. The pathogenesis of prostate cancer likely involves interplay between environmental and genetic factors. To unravel these complex relationships, large well-designed interdisciplinary epidemiologic studies are needed. With newly available molecular tools, a new generation of large-scale multidisciplinary population-based studies is beginning to investigate gene-gene and gene-environment interactions. Results of these studies may lead to better detection, treatment, and, ultimately, prevention of prostate cancer.

2. INTRODUCTION

Prostate cancer is the most common cancer among men in most western populations, excluding skin cancer, with 232,090 new cases expected in 2005 (1). Worldwide, incidence rates increased dramatically through the early 1990s (2). In western countries there was a rise in incidence in the late 1970s and early 1980s, in part, due to increased detection with more frequent surgical treatment for benign prostatic hyperplasia (BPH), particularly, transurethral resection of the prostate (TURP) (3). Between 1986 and 1992 there was another sharp rise in incidence largely due to increasing use of prostate specific antigen (PSA) (4). During the mid-1990s, incidence rates in the United States declined, but have recently begun to slowly rise again (5). Incidence rates in Asian countries are generally low, but in recent years have risen proportionally more than in western countries. Part of the increase in incidence has been attributed to increased westernization (2).

Despite prostate cancer's high morbidity, its etiology remains obscure, with the only established risk factors being increasing age, race, and a family history of prostate cancer. Many putative risk factors, including hormones, dietary factors, obesity, physical inactivity, occupation, vasectomy, smoking, sexual factors, and genetic susceptibility, have been implicated, but the epidemiologic evidence is inconclusive. This review presents a current overview of these factors.

3. INCIDENCE AND MORTALITY

Prostate cancer appears to impact the world's populations differently, with widely varying incidence and mortality rates. An examination of these rates can provide meaningful insights into the etiology of the disease, helping generate new hypotheses for further research.

3.1. Incidence

Reported age-adjusted prostate cancer incidence rates vary considerably worldwide (6, 7). Rates among African-Americans are the highest in the world (185.4 per 100,000 person-years), followed by Caucasian-Americans (107.8 per 100,000 person-years) (figure 1). Rates in the Caribbean and in Brazil (92-96 per 100,000 person-years), where there are large populations of African descent, are comparable to the rates among Caucasian-Americans. In contrast, in Central America and other parts of South America, rates are much lower (28-42 per 100,000 person-years). Rates within Europe vary almost 7-fold (15-100 per 100,000 person-years), and are highest in Western Europe, in particular Austria, and lowest in Eastern Europe (15-36 per 100,000 person-years). Although rates in Canada, Oceania (including Australia and New Zealand), Western Europe, and Scandinavia (50-103 per 100,000 person-years) are generally lower than the rates reported in the U.S., they are 2-3 times higher than those reported in Eastern Europe. Asia, the continent having the lowest incidence of prostate cancer, also has considerable variation in reported incidence, with more westernized countries such as Japan, Israel, and the Philippines (22-47 per

100,000 person-years) showing markedly higher rates than Thailand, India, Pakistan, and Shanghai, China (3-7 per 100,000 person-years). Prostate cancer incidence data from Africa are sparse, with only 4 registries from 1994 included in the 2003 IARC report, which showed incidence rates ranging from 5 to 37 per 100,000 person-years (7).

Part of the difference in worldwide incidence rates is related to the extent of prostate cancer screening, especially the less-frequent use of prostate-specific antigen (PSA) testing in developing countries. However, screening practice differences alone are unlikely to explain the nearly 60-fold difference in prostate cancer risk between high- and low-risk populations.

3.2. Mortality

Only one in six American men diagnosed with prostate cancer will eventually die from it. Nevertheless, 30,350 prostate cancer deaths are expected in the U.S. in 2005, making prostate cancer the second leading cause of cancer death among U.S. men, after lung cancer (1). Age-adjusted prostate cancer mortality rates from 38 countries in 1998 are shown in figure 2. Overall, the pattern of mortality worldwide reflects that of incidence, although the mortality rates show less variation between countries. Nevertheless, mortality rates are still higher in Western nations than in lower-risk, Asian countries. Interestingly, the world's highest mortality rates (30.3 to 47.9 per 100,000 person-years) were seen in the Caribbean nations of Barbados, the Bahamas, and Trinidad and Tobago, where there are large populations of men of African descent. Mortality was higher in Scandinavian countries and parts of northern Europe than in the U.S. (18.7-23.6 versus 14.0 per 100,000 person-years), and lowest of all in the Asian countries of South Korea, Philippines, and Japan (1.6-4.4 per 100,000 person-years).

The patterns of incidence and mortality worldwide provide a number of interesting leads. The pronounced excess risk of prostate cancer in western nations suggests that factors associated with westernization, such as diet and obesity, may be positively associated with prostate cancer etiology. In addition, prostate cancer's disproportionate impact on African-Americans and Caribbean men suggests that factors associated with African ancestry may also play a role in prostate cancer etiology. While it is not known whether the risk factors explaining the observed patterns are environmental, lifestyle, or genetic, it is likely that a complex interplay of these factors is associated with prostate cancer development.

4. DEMOGRAPHIC RISK FACTORS

4.1. Age

Over 80% of prostate tumors in the U.S. are diagnosed in men over age 65 (8), and the incidence of prostate cancer increases exponentially with advancing age – an increase that is faster than that for any other malignancy (table 1). Estimates from the Surveillance, Epidemiology, and End Results (SEER) program from 1996-2000 indicate that for U.S. men under 65 years of age
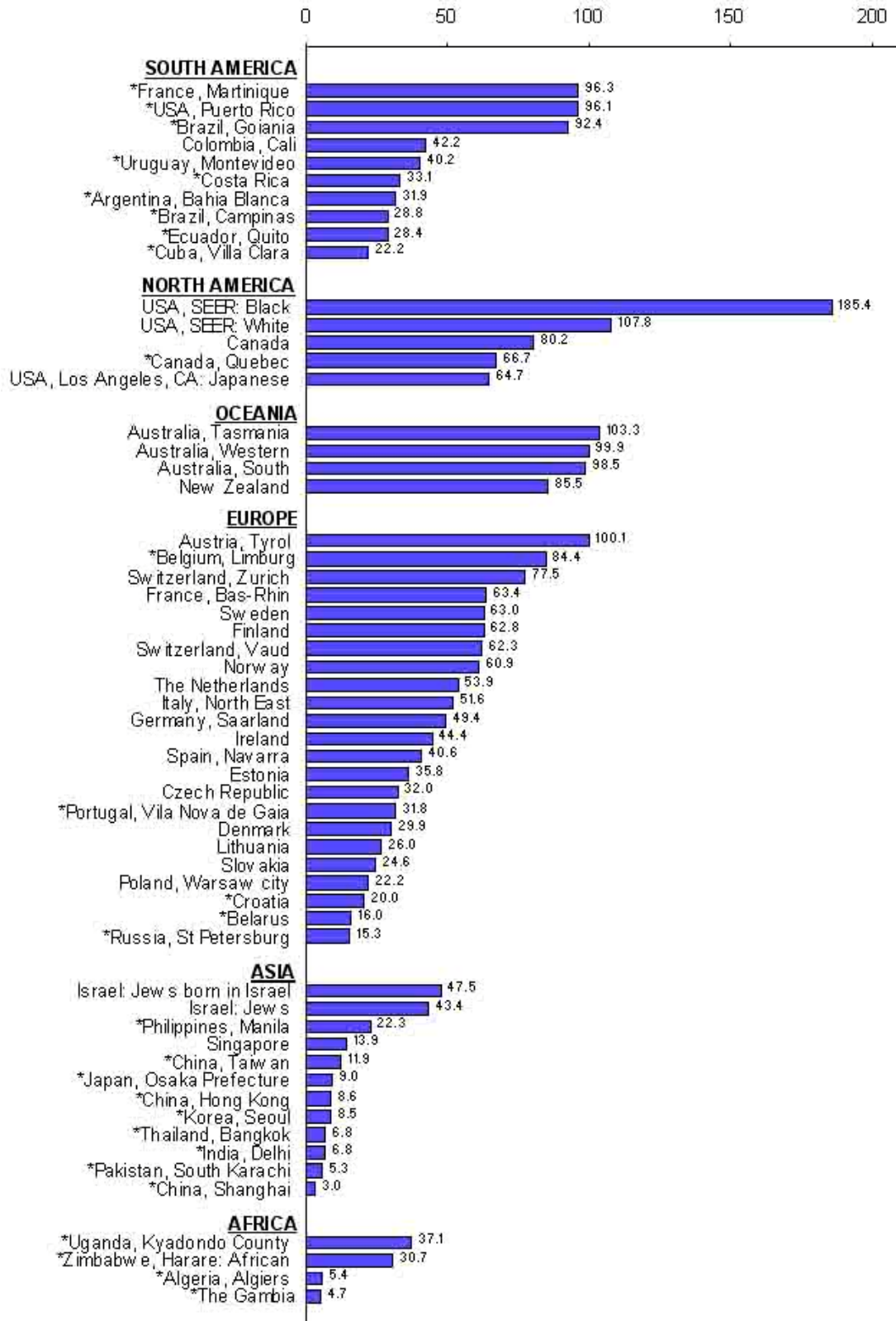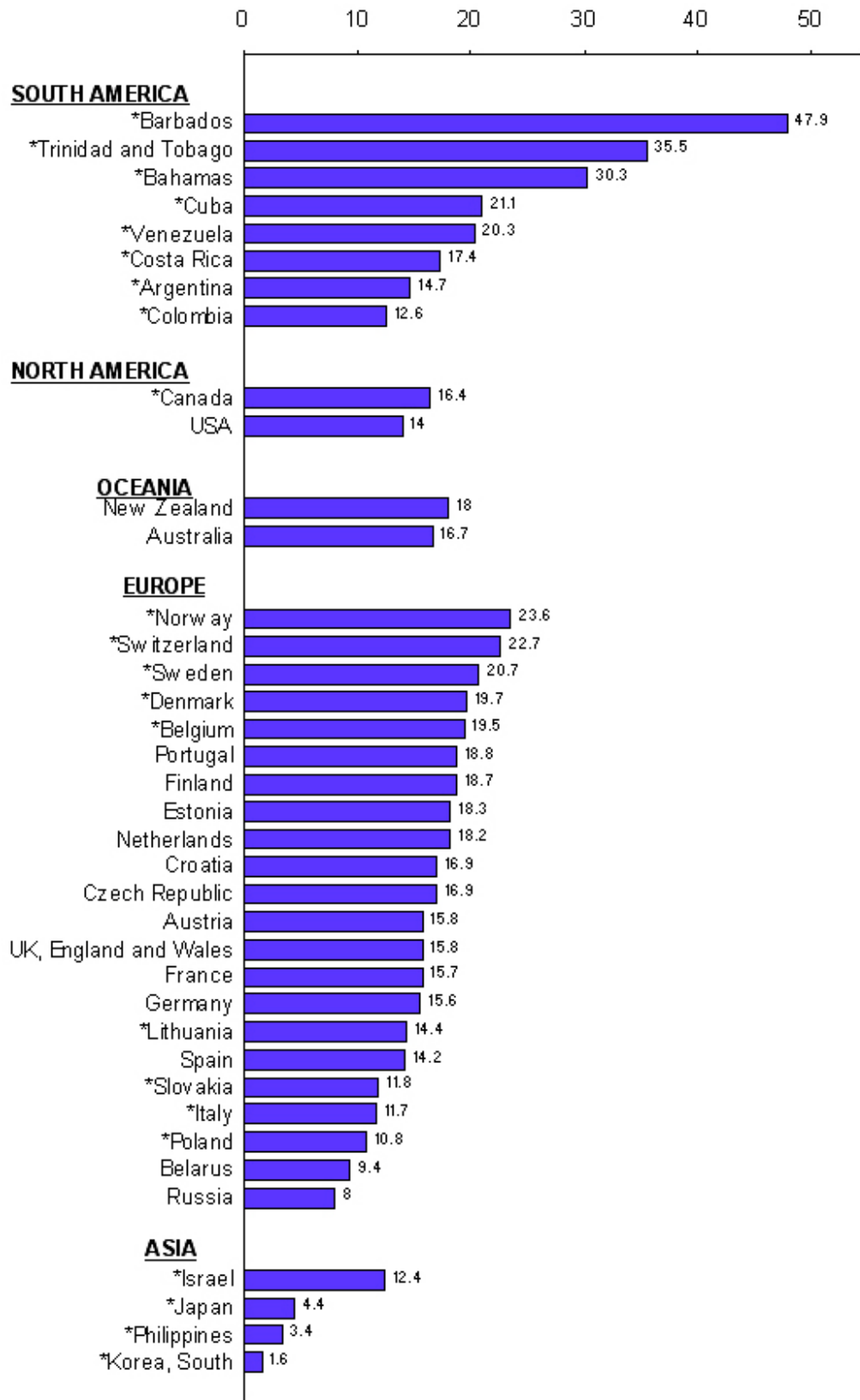
Figure 1. Age-adjusted incidence rates (per 100,000 person-years) for prostate cancer in 48 countries, 1993-1997. Reproduced with permission from (7). * Rates are from 1994

Figure 2. Age-adjusted mortality rates (per 100,000 person-years) for prostate cancer in 38 countries, 1998. Reproduced with permission from http://www.depdb.iarc.fr/who/menu.htm. * Rates are from 1994.

Table 1. Summary of epidemiologic risk factors for prostate cancer

	Observation	Evidence	Implications
Established Factors			
Age	Incidence rises with age	Consistent	Latency is long and progression is slow
Race	African Americans have the highest reported rates in the world, while Chinese men living in China have the lowest reported rates.	Consistent	Suggests both environmental and genetic factors may have a role in prostate cancer
	Migrants have much higher risk than their counterparts in ancestral countries	Consistent	Suggests a role of environmental factors. Suggest westernization may be related to an increased risk
Family history of prostate cancer	Familial aggregation	Consistent	Suggests a role of genetic predisposition
Probable factors			
Diet	Animal fat and red meat intake is associated with an increased risk	Somewhat consistent	Suggests fat or other constituents in meat may contribute to prostate carcinogenesis
	Selenium and vitamin E may be associated with a reduced risk	Somewhat consistent	Suggest anti-carcinogenic effect of these compounds. Chemoprevention trials are underway to evaluate these effects
	Consumption of tomato products is associated with a decreased risk	Somewhat consistent	Lycopene may protect against prostate cancer
	Intake of cruciferous vegetables may be associated with decreased risk	Suggestive	Suggests intake of broccoli, cauliflower, Brussels sprouts, and other cruciferous vegetables may protect against prostate cancer
	Allium vegetable intake may be associated with decreased risk	Needs confirmation	
	Intake of fish and marine fats may be associated with a decreased risk	Needs confirmation	
	Calcium may by associated with increased risk	Inconsistent	
	Intake of total vegetables is associated with decreased risk	Inconsistent	
IGFs	Higher serum/plasma levels of IGF-I and lower levels of IGFBP-3 may be related to an increased risk	Somewhat consistent	Suggest IGFs may be related to the progression of prostate cancer. Clinical utility of IGFs is under evaluation
Occupation	Farmers have ~10% excess risk	Consistent	Suggests exposures to herbicides or pesticides or lifestyles among farmers may be related to prostate cancer risk
	Workers in heavy metal and rubber industry may have an increased risk	Suggestive	Suggests exposures to certain chemicals may increase prostate cancer risk
Androgens	Higher serum levels of androgens are associated with an increased risk	Suggestive	Suggest androgenic action within the prostate gland is involved in prostate carcinogenesis
Obesity	Abdominal obesity may be related to an increased risk	Suggestive	Suggests that alteration of hormone synthesis or metabolisms may have a role in prostate cancer etiology
Chronic inflammation	Inflammation found in prostate biopsies and resected prostate tissue, and pro-inflammatory markers are associated with increased risk	Suggestive	Suggests that factors contributing to inflammatory states may have a role in prostate cancer initiation or promotion
Vitamin D	Higher serum levels of vitamin D may be associated with a reduced risk	Inconsistent	
STDs	Sexually transmitted infections such as HPV infection and syphilis may be related to an increased risk	Inconsistent	
Sexual frequency	Increased sexual frequency, particularly ejaculatory frequency, may be associated with an increased risk	Inconsistent	
Vasectomy	Vasectomy may be associated with an increased risk	Inconsistent	
Physical activity	Long-term physical activity may be associated with a reduced risk of prostate cancer	Inconsistent	
Liver cirrhosis	Patients with liver cirrhosis may have a lower risk	Inconsistent	
Diabetes	Diabetic patients may have a lower risk	Inconsistent	
Smoking	Smoking may be associated with an increased risk	Inconsistent	

vs. 65 years and over, prostate cancer incidence rates were 56.8 vs. 974.7 per 100,000 person-years, respectively (5).

4.2. Racial/ethnic variation

Another consistently observed but poorly understood risk factor is ethnicity. African-Americans have the highest incidence rates in the world: roughly 60 times that of men in Shanghai, China, where the rates are the lowest in the world (2) (figure 1). As noted earlier, it is unlikely that differences in detection (i.e., screening) account for all of the variability in prostate cancer risk between populations. Adjustment of incidence rates for the prevalence of latent disease at autopsy and proportion of localized tumors among all prostate cancers revealed that Japanese men still experience a markedly lower incidence

than Americans, indicating that the large international variation cannot be explained by differences in detection alone (9). This supports the results of migrant studies suggesting that ethnic factors, including genetic, lifestyle, or environmental factors, may affect prostate cancer risk and explain much of the difference in risk between high- and low-risk populations (9, 10).

5. HORMONAL, BEHAVIORAL, AND LIFESTYLE RISK FACTORS

5.1. Hormones and growth factors

Androgens play a key role in the development and maintenance of the prostate gland; however, the precise role of androgens in the etiology of prostate cancer is

unclear. Prostate cancer is notably absent in castrated men, and laboratory studies show that administration of testosterone induces prostate cancer in rats and that androgens promote cell proliferation and inhibit prostate cell death (11-13). Nevertheless, epidemiologic data supporting a role of androgens are inconclusive (14-20). To date, over 17 prospective studies have investigated the role of circulating androgens, and only one observed a significantly higher risk of prostate cancer among men with higher serum testosterone levels (21). More comprehensive reviews of this topic are reported elsewhere (14-16). In addition, studies of genetic markers in genes involved in the androgen pathways offer further insight into this avenue of research – these are reviewed later in this paper.

Vitamin D, another steroid hormone, is obtained primarily from dermal synthesis in response to sunlight exposure. Vitamin D and its analogs have potent anti-proliferative, pro-differentiative, and pro-apoptotic effects on prostate cancer cells. In addition, vitamin D inhibits prostate tumor growth *in vivo*. In general, laboratory data are consistent and support the hypothesis that vitamin D may protect against prostate cancer. However, results from epidemiologic studies investigating serum levels of vitamin D have been inconsistent (22). The reasons for these conflicting results are unclear.

In addition to steroid hormones, insulin-like growth factors (IGFs) have been implicated in prostate cancer. IGF-I and IGF-II are polypeptides that function as both tissue growth factors and endocrine hormones with mitogenic and anti-apoptotic effects on prostate epithelial cells. There are at least six known IGF binding proteins (IGFBPs) that can bind to IGFs and thus prevent activation of the IGF receptor, which mediates IGF effects. At least 13 epidemiologic studies have evaluated the roles of the IGF axis in prostate cancer, and many have reported a positive association with IGF-I and an inverse association with IGFBP3 (23-28). In addition, results from studies, particularly the prospective studies, indicate the IGF-I – prostate cancer association may be strongest for advanced disease (23, 26, 27). However, the roles of IGF-II and the other IGFBPs are less clear.

5.2. Diet
Ecologic studies have shown a strong correlation between the incidence of prostate cancer and dietary fat intake (29). A western diet, typically high in fat, has been linked to a higher risk of prostate cancer, by increasing production and availability of both androgens and estrogens, while Asian and vegetarian diets (low-fat, high-fiber) are associated with lower circulating levels of these hormones (29).

Fat intake is the most studied dietary risk factor for prostate cancer. Most epidemiologic studies have investigated the role of total, saturated, and/or animal fat. Findings from these studies, although mixed, suggest a possible positive association with monounsaturated, animal, and saturated fats, and an inverse association with omega-3 fat. The results for polyunsaturated fat are less consistent (30, 31). Consumption of meat, particularly red meat and processed meat, is also consistently linked to an increased risk of prostate cancer. However, it is unclear whether the excess risk is due to the high-fat content, mutagens such as heterocyclic amines that are induced during high-temperature cooking, animal proteins, or other unidentified factors (32).

Numerous recent epidemiologic studies have also investigated whether intake of fatty fish is associated with reduced prostate cancer risk. Fatty fish are rich in potentially tumor-inhibitory marine fatty acids, such as omega-3. However, a recent review of 17 studies (33), including 8 prospective studies, found suggestive but inconsistent results, possibly due to inadequate assessment of fish intake or lack of information on specific marine fatty acids, particularly the two omega-3 polyunsaturated fatty acids, eicosapentaenoic and docosahexaenoic acids.

Although consumption of fruits and vegetables is associated with a reduced risk of several cancers, their role in prostate cancer is less clear. The only consistent finding is an inverse association with consumption of tomatoes and tomato paste, which has been largely attributed to the antioxidant effect of lycopene (34). Cruciferous and allium vegetables have also been implicated. A recent review concluded that there is modest evidence that intake of cruciferous vegetables, including broccoli, cabbage, cauliflower, and Brussels sprouts, is inversely associated with prostate cancer risk, possibly due to their content of isothiocyanates (35). In addition, intake of allium vegetables, including onions, garlic, and chives, were inversely associated with prostate cancer in a case-control study in China (36). This protective effect may be due to the tumor inhibitory properties of organosulfur compounds.

Dietary calcium, from either dairy products or supplement consumption, has been linked to prostate cancer. Because of its role in the regulation of vitamin D synthesis, calcium may down-regulate vitamin D's anti-proliferative effects on prostate cancer. However, the epidemiologic evidence for calcium is unclear, complicated by differences in the assessment of calcium (dietary intake versus circulating levels) (37) and difficulty in measuring widely varying amounts of intake. Recent data suggest a threshold effect that only very high calcium intake (≥ 2000 mg/day) may be associated with disease (38).

Chronic excess of zinc, a mineral obtained largely through dietary supplements, may be positively associated with prostate cancer risk, although *in vitro* studies demonstrating mitogenic effects of zinc on prostate cancer suggest that it may reduce risk (39).

A large body of epidemiological evidence, including observational, case-control, cohort and randomized controlled clinical trials, support the hypothesis that selenium may reduce prostate cancer risk in humans (40). Molecular data show that selenium prevents clonal expansion of tumors by causing cell cycle arrest, promoting apoptosis, and modulating p53 dependent DNA repair mechanisms. Secondary analyses of clinical trial data have also shown that vitamin E supplementation is associated

with a reduced risk of prostate cancer (41, 42). A clinical trial is currently under way to test the efficacy of these two compounds in chemoprevention of prostate cancer (43).

5.3. Obesity

In epidemiologic studies, overall obesity is usually measured by body mass index (BMI; weight in kg divided by the square of height in meters, kg/m^2) and abdominal obesity by the ratio of waist to hip circumference. Although the findings on overall obesity are mixed, recent data suggest that obesity is more consistently related to aggressive prostate tumors and that abdominal obesity may be associated with an increased risk of prostate cancer even in relatively lean men (44, 45). In addition, higher serum levels of insulin have been linked to an increased risk of prostate cancer (46), and higher serum levels of leptin (the product of the obesity gene *Ob*) have been linked to larger tumor volume (>5 cm^3) (47). Although obesity's role in prostate cancer is not clearly defined, it is linked to numerous putative prostate cancer risk factors, including high meat and fat intake, hormone metabolism, and insulin metabolism. Furthermore, the prevalence of obesity correlates with prostate cancer risk across populations. Thus, it is likely that obesity may provide a link between westernization and increased prostate cancer risk. With the growing epidemic of obesity in both developed and developing countries, the role of obesity in prostate cancer needs to be clarified further.

5.4. Physical activity

Physical activity may decrease levels of total and free testosterone, reduce obesity, and enhance immune function (48), all of which may lead to protection from prostate cancer. However, perhaps due to challenges in classifying physical activity and/or identifying the age/time periods during which such activity may be most protective, results from numerous epidemiologic studies are equivocal (48, 49).

5.5. Occupation

Occupation is highly correlated with socioeconomic status and lifestyle factors. There is a large body of literature on prostate cancer and occupation, and one consistent result from these studies is that farmers and other agricultural workers have a 7-12% increased risk. (50, 51). While this excess could reflect lifestyle factors such as increased intake of meat and fats, exposures to chemicals may also play a role. Chemicals commonly encountered in agriculture include fertilizers, solvents, pesticides, and herbicides, which have a wide variety of poorly characterized effects (52). Organochlorines present in many pesticides and herbicides can affect circulating hormone levels; however the epidemiologic evidence linking specific pesticide or herbicide exposures to prostate cancer is weak. In addition to agriculture, workers in heavy industry, rubber manufacturing, and newspaper printing may be at elevated risk (50), suggesting that exposure to certain chemicals or other factors common in these work environments may increase the risk of prostate cancer.

5.6. Chronic inflammation

Evidence for a role of chronic inflammation in prostate cancer is beginning to emerge (53), but an association of prostate cancer with chronic inflammation of the prostate (chronic prostatitis) has long been suspected. A recent meta-analysis of 11 studies of prostatitis and prostate cancer reported an overall relative risk of 1.6 (54). Inflammation is frequently found in prostate biopsy specimens obtained from both radical prostatectomy and surgical treatment for benign prostatic hyperplasia (55, 56); however, epidemiologic findings have been mixed.

Results from pathologic and molecular surveys suggest that the earliest stages of prostate cancer may develop in lesions generally associated with chronic inflammation (57, 58). De Marzo *et al.* showed that almost all forms of focal prostatic glandular atrophy are proliferative, and that such proliferative inflammatory atrophy (PIA) lesions often contain inflammatory infiltrates and are frequently found adjacent to or near high-grade prostatic intraepithelial neoplasia (PIN), a precursor of prostate cancer (57, 58). Inflammation may lead to tumorigenesis by stimulating angiogenesis, enhancing cell proliferation, and damaging DNA through radical oxygen species such as nitric oxide.

Additional support for a role for chronic inflammation in prostate cancer comes from the observation that a higher intake of fish and use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with reduced prostate cancer risk (59). In two large prospective studies, higher intake of fish was associated with a lower risk of total prostate cancer and metastatic prostate cancer (60, 61). Abundant in fatty fish, omega-3 fatty acids are known antagonists of arachidonic acid and suppress the production of pro-inflammatory cytokines (62). In addition, use of anti-inflammatory agents, especially NSAIDs such as ibuprofen or aspirin, has also been related to lower prostate cancer risk in epidemiologic studies (63-66), and a recent meta-analysis of 12 of these studies concluded that aspirin use was associated with a 15% reduction in prostate cancer risk (67). Taken together, these data suggest chronic inflammation may increase the risk of prostate cancer. However, there are few epidemiologic studies investigating this directly, possibly due to the difficulty in diagnosing chronic prostatitis and in measuring cytokine levels reliably in serum samples. This is likely to be a fruitful area for future research.

5.7. Sexually transmitted diseases

Sexually transmitted diseases (STDs) have been linked to prostate cancer. One recent large, population-based study showed 2-3-fold prostate cancer risks associated with STDs, particularly syphilis and recurrent gonorrhea infections (68). Other studies reported associations of human papillomavirus-16, -18, and -33 serology with an increased risk of prostate cancer (69, 70), while a study of a human immunodeficiency virus (HIV)-infected population found that duration of HIV infection was associated with increased prostate cancer risk (71). In addition, epidemiological data associating sexual history and behavior with prostate cancer risk are accumulating (72-74). A recent meta-analysis of 17 studies concluded that a higher number of sexual partners is associated with

increased prostate cancer risk, possibly through increased opportunity for sexually transmitted infections (54). Although the mechanisms are not clear, sexually transmitted bacterial or viral agents have been implicated with the induction of chronic inflammation of the prostate, potentially leading to prostate cancer.

5.8. Sexual frequency

Recent studies have indicated that increased sexual frequency may be associated with an increased risk of prostate cancer, because it may serve as an indicator for either a greater opportunity of infection or higher androgenic activity (54, 72, 74). However, most studies of sexual behavior are case-control studies, and given the sensitive nature of sexual history/behaviors, such studies are strongly susceptible to bias in recall between cases and controls. A recent prospective study, which is not as vulnerable to recall bias as case-control studies, reported that ejaculation frequency is not associated with risk; in fact, there was some suggestion that very high ejaculation frequency during a man's 20's (>21 times per month) is associated with reduced risk (75).

5.9. Vasectomy

Several, but not all studies investigating the association between vasectomy and prostate cancer risk suggest a modest positive association (76). However, the role of vasectomy remains controversial, since most studies are unable to exclude the possible effect of detection bias, i.e., men undergoing vasectomies are more likely to have prostate cancer detected than men who do not. Vasectomy is linked to elevations in anti-spermatozoa antibodies, reduced hormone concentrations in the semen, and reduced prostatic secretion (77). Whether these conditions can influence prostate carcinogenesis needs to be clarified.

5.10. Benign prostatic hyperplasia

The relationship between benign prostatic hyperplasia (BPH) and prostate cancer is not well established. BPH is currently not considered a precursor to prostate cancer, since prostate cancer occurs mostly in the external, peripheral zone of the prostate and BPH is more common in the internal transition and periurethral zones. Nevertheless, because both conditions are common in elderly men, and because they may coexist within the prostate, they appear to share risk profiles, making it difficult to elucidate the independent role, if any, of BPH in prostate cancer etiology. Again, detection bias complicates this investigation, as higher prostate cancer incidence in men who are symptomatic for BPH may simply be a reflection of the increased evaluation and medical surveillance in these patients. In addition, in most epidemiologic studies, it has been difficult to completely rule out the presence of BPH in control populations, since the prevalence of BPH is very common in elderly men. Due in part to these limitations, the epidemiologic evidence for BPH as a risk factor for prostate cancer remains weak and inconsistent (78), with the largest study to date (over 85,000 BPH patients) showing only a marginally elevated age-adjusted risk of prostate cancer among BPH patients versus the general population (<2% in 10 years) (79).

5.11. Other factors

Several other risk factors, such as smoking, use of alcohol, diabetes, and liver cirrhosis, have been investigated, but their roles in prostate cancer are weak or unclear based on data in the current literature (80-82).

6. GENETIC FACTORS

6.1. Family history of cancer

Numerous studies have consistently reported familial aggregation of prostate cancer, showing a 2- to 3-fold increased risk of prostate cancer among men who have a first-degree male relative (father, brother, son) with a history of prostate cancer (83). Recent data from a large twin study suggest that as much as 42% (95% CI 29-50%) of the risk of prostate cancer may be accounted for by genetic factors (84). Genetic factors involved in prostate cancer include individual and combined effects of rare, highly penetrant genes, more common weakly penetrant genes, and genes acting in concert with each other.

6.2. High-penetrance markers

Segregation and linkage analyses have shown that certain early-onset prostate cancers may be inherited in an autosomal dominant fashion (85), and it is estimated that such hereditary prostate cancers (HPCs) due to highly penetrant genes may account for about 10% of all prostate cancer cases (84). Several family studies are currently underway to identify hereditary prostate cancer candidate genes. However, these investigations have proven to be difficult for several reasons (86). One is that, due to both the high incidence of prostate cancer and the heterogeneity of tumors (which makes it difficult to detect preclinical disease), it is possible that sporadic cases are included in HPC families, thereby reducing the statistical power to detect genes for HPC. In addition, because prostate cancer is generally diagnosed at a late age, it is often impossible to obtain DNA specimens from fathers of HPC cases, and sons of HPC cases are too young to have developed prostate cancer. Therefore, studies of HPC families are often unable to include more than one generation. Finally, the genetic heterogeneity of prostate cancer makes it difficult to devise appropriate statistical transmission models that account for multiple susceptibility genes, many of which may have only moderate penetrance. Despite these challenges, seven loci have been described to date, including *HPC1, HPC2, HPCX, HPC20, CAPB, PCAP*, and an unnamed locus at 8p22-23 (table 2), and fine mapping has led to the identification of a number of candidate genes, including *RNASEL, ELAC2 (HPC2),* and *MSR-1* (87, 88). The results of studies of these loci (89-113), which have been extensively reviewed elsewhere (88), have largely been mixed, with subsequent studies failing to replicate promising earlier findings. An exception is the *HPC1* locus, for which most studies have shown positive results among HPC cases, with mixed findings for sporadic disease. The absence of strong, consistent results for high penetrance markers strongly suggests that the heritable component of prostate cancer largely comprises effects of multiple factors, including common, weakly penetrant markers, possibly interacting with one another and with environmental factors.

Table 2. Summary of epidemiologic studies of rare, high penetrance genes and prostate cancer

Region	Gene	Markers	Studies (reference), no. of cases studied, population	Results
1q24-25 (HPC1)	*RNASEL*	E265X, R462Q, D541E, I97L, 471delAAAG	Rokman *et al*, 2002 (92), N=116 HPC [1] cases, Finns	Positive association
			Nakazato *et al*, 2003 (90), N=101 HPC cases, Japanese	Positive association
			Wang *et al*, 2002 (96), N=438 HPC cases, US Caucasians	Positive association
			Casey *et al.*, 2002 (89), N=423 HPC cases, US subjects	Positive association
			Rennert *et al*, 2002 (111), N=85 Ashkenazi Jewish cases	Positive association
			Rennert *et al*, 2005 (111), N=888 US Caucasian cases, 131 African-American cases	Positive association
			Maier *et al*, 2005 (110), N=227 cases, Germans	Null association
				Overall, consistent positive association
17p11 (HPC2)	*ELAC2*	A541T, S217L	Rebbeck *et al*, 2000 (91), N=359 cases, U.S. subjects	Positive association
			Suarez *et al*, 2001 (93), N=257 HPC cases, U.S. Caucasians	Positive association
			Tavtigian *et al*, 2001 (94), N=429 HPC cases, U.S. Caucasians	Positive association
			Vesprini *et al*, 2001 (95), N=431 cases, Canadians	Null association
			Wang *et al*, 2001 (96), N=446 HPC cases, U.S. Caucasians	Null association
			Xu *et al*, 2001 (98), N=249 cases, 159 HPC cases, U.S. Caucasians	Null association
			Rokman *et al*, 2001 (103), N=467 cases, 107 HPC cases, Finns	Null association
			Meitz *et al*, 2002 (101), N=432 cases, UK subjects	Null association
			Adler *et al*, 2003 (99), N=199 cases, Canadians	Positive association
			Stanford *et al*, 2003 (105), N= 591 cases, U.S. subjects	Positive association
			Takahashi *et al*, 2003 (106), N=98 cases (BPH controls), Japanese	Positive association
			Severi *et al*, 2003 (104), N=825 cases, Australians	Null association
			Rennert *et al*, 2005 (111), N=888 US Caucasian cases, 131 African-American cases	Null association
			Meta-analysis: Camp and Tavtigian, 2002 (100)	Association only for HPC
				Overall, weak, inconsistent associations. May be associated only with HPC, not sporadic disease
xq27-28 (HPCX)	none		No epidemiologic studies	AR (also on X chromosome) unlikely to be HPCX susceptibility gene
20q13 (HPC20)	none		No epidemiologic studies	Linkage studies need further confirmation
1p36 (CAPB)	none		No epidemiologic studies	Most consistent linkage to strong family history with early onset disease
1q42.2-43 (PCAP)	*PCTA-1*		No epidemiologic studies	PCTA is possible candidate gene, but no functional markers
8p22-23	*MSR1*	PRO3, P275A, D174Y, IVS5-59, R293X , IVS7delTTA, IVS5-57	Xu *et al*, 2003 (107), N=301 cases, U.S. Caucasians	Positive association
			Miller *et al*, 2003 (102), N=134 cases, African-Americans	Positive association
			Wang *et al*, 2003 (113), N=499 cases, 438 HPC cases, U.S. Caucasians	Null association
			Seppala *et al*, 2003 (112), N=537 cases, Finns	Null association
			Rennert *et al*, 2005 (111), N=888 US Caucasian cases, 131 African-American cases	Positive association
			Hope *et al*, 2005 (108), N=2943 cases with invasive cancer, all from Western countries	Null association
			Lindmark *et al*, 2004 (109), N=215 cases, 83 HPC cases, Swedes	Positive association
				Overall, weak results, with larger studies showing null associations even for HPC

[1] HPC, hereditary prostate cancer

6.3. Common low-penetrance markers

Results of epidemiologic studies of common polymorphisms are summarized below and in table 3 by biological pathway. For the sake of simplicity, this section has been organized by gene and reports only whether the studies showed positive or null results. More thorough reviews of several of these markers and genes can be found elsewhere (88, 114-119). It is important to note that, as with any other epidemiologic exposure, replication of findings is critical to establishing causality. This is particularly true for genetic association studies, because the recent explosion of genetic data has increased the potential for false discoveries due to multiple hypothesis testing, and also publication bias as investigators and publishers become more selective about publishing findings.

6.3.1. Androgen biosynthesis and metabolism pathway

Because prostate cancer is an androgen-dependent tumor, it is likely that markers in genes whose products are involved in androgen biosynthesis and metabolism (figure 3) may be associated with prostate disease. This is supported by evidence that there is racial/ethnic variation in polymorphisms of genes involved in the androgen pathways (120, 121). Recent epidemiologic studies have investigated the role of polymorphisms of at least 9 genes involved in androgen biosynthesis, metabolism, transport, and regulation. Though these data are promising and accumulating at a remarkable pace, they are still too sparse to support a strong role for any particular gene.

Results for the androgen receptor (*AR*), involved in androgen binding and transport, are fairly consistent, showing that shorter CAG repeat lengths are associated with increased risk in many but not all populations (122-147). However, a recent meta-analysis notes that *AR* CAG or GGN repeat length is unlikely to have a major biological role in prostate cancer because the pooled effect size is not large, and the absolute difference in number of CAG or GGN repeats between cases and controls is less than one (119). For the type II steroid 5α-reductase (*SRD5A2*),

**Table 3.** Summary of epidemiologic studies of common, low penetrance genes and prostate cancer

Gene	Marker	Studies (reference), no. of cases studied, population	Results and comments
Androgen biosynthesis/metabolism			
CYP17	MspA1	Lunn et al, 1999 (154), N=108 cases, U.S. subjects	Positive association for Caucasians, null for African-Americans
		Wadelius et al, 1999 (174), N=178 cases, Swedish Caucasians	Positive association
		Gsur et al, 2000 (167), N=63 cases, Austrians	Positive association
		Habuchi et al, 2000 (168), N=252 cases, Japanese	Positive association
		Haiman et al, 2001 (169), N=600 cases, U.S. Caucasians	Null association
		Yamada et al, 2001 (161), N=105 cases, Japanese	Positive association
		Kittles et al, 2001 (170), N=71 cases, African-Americans	Positive association
		Latil et al, 2001 (137), N=226 cases, French Caucasians	Null association
		Chang et al, 2001 (166), N=225 cases, U.S. Caucasians	Null association
		Stanford et al, 2002 (173), N=596 cases, U.S. Caucasians and African-Americans	Null association overall, positive association among Caucasians with family history
		Madigan et al, 2003 (172), N=174 cases, Chinese	Null association
		Lin et al, 2003 (171), N=93 cases, Taiwanese	Null association
		Nam et al, 2003 (140), N=483 cases, Canadians	Null association
		Cicek et al, 2004 (143), N=440 cases, US subjects	Null association
		Antognelli et al, 2005 (165), N=384 cases, Italians	Positive association
		Forrest et al, 2005 (144), N=288 early onset cases, UK subjects	Null association
		Review: Ntais et al, 2003 (115)	Meta-analysis indicates no overall association, but A2 allele may be associated with risk in African-Americans (115). A1 is reported to be risk allele in Asians
CYP19	TTTA repeats, N264C	Latil et al, 2001 (137), N=226 cases, French Caucasians	Positive association
		Modugno et al, 2001 (138), N=88 cases, U.S. Caucasians	Positive association
		Suzuki et al, 2003 (164), N=99 HPC[1] cases, Japanese	Positive association
		Fukatsu et al, 2004 (162), N=147 cases, Japanese	Null association
		Li et al, 2004 (163), N=439 cases, US subjects (90% Caucasian)	Null association
			Suggestive but mixed results - longer TTTA alleles associated with higher risk in Caucasians, but lower risk in Asians. Further investigation needed.
SRD5A2	V89L, A49T, R227Q, TA repeats	Lunn et al, 1999 (154), N=108 cases, U.S. Caucasians and African-Americans	Null association
		Kantoff et al, 1997 (151), N=590 cases, U.S. Caucasians	Null association
		Febbo et al, 1999 (149), N=592 cases, U.S. Caucasians	Null association
		Makridakis et al, 1999 (155), N=388 cases, U.S. Hispanics and African-Americans	Positive association
		Margiotti et al, 2000 (156), N=108 cases, Italians	Positive association
		Yamada et al, 2001 (161), N=105 cases, Japanese	Null association
		Nam et al, 2001 (158), N=158 cases, Canadians	Positive association
		Latil et al, 2001 (137), 226 cases, French	Null association
		Mononen et al, 2001 (157), N=449 cases, Finns	Null association
		Hsing et al, 2001 (158), N=191 cases, Chinese	Null association
		Pearce et al, 2002 (159), N=921 cases, U.S. subjects	Null association
		Soderstrom et al, 2002 (160), N=176 cases, Swedes	Null association
		Lamharzi et al, 2003 (161), N=300 cases, U.S. subjects	Positive association
		Chang et al, 2003 (162), N=245 cases, 159 HPC cases, U.S. Caucasians	Null association
		Li et al, 2003 (163), N=302 cases, Japanese	Positive association
		Nam et al, 2003 (143), N=483 cases, Canadians	Null association
		Cicek et al, 2004 (144), N=440 cases, US subjects	Positive association
		Forrest et al, 2005 (145), N=288 early onset cases, UK subjects	Positive association
		Review: Ntais et al, 2003 (116)	Overall, the T allele of A49T (associated with higher enzymatic activity) and shorter TA repeats may be associated with a modest increase in risk. While results are mixed, the V89L marker's LL genotype, which is associated with lower serum levels of androgens, may be associated with a reduced risk. R227Q is very rare, observed only in Asians.
AR	CAG repeats, GGN repeats, E211 G>A	Ingles et al, 1997 (128), N=57 cases, U.S. Caucasians	Positive association
		Stanford et al, 1997 (131), N=301 cases, U.S. Caucasians	Positive association
		Giovannucci et al, 1997 (126), N=587 cases, U.S. Caucasians (and Platz et al, 1998 (127), N=582 cases)	Positive association
		Correa-Cerro et al, 1999 (123), N=132 cases, French and Germans	Null association
		Ekman et al, 1999 (125), N=93 cases, 59 HPC cases, Swedes and Japanese	Positive association
		Edwards et al, 1999 (124), N=178 U.K. Caucasians	Positive association
		Hsing et al, 2000 (127), N=190 cases, Chinese	Positive association
		Miller et al, 2001 (129), N=140 cases, U.S. subjects	Null association
		Beilin et al, 2001 (122), N=445 cases, Australians	Null association
		Latil et al, 2001 (137), N=226 cases, French	Null association
		Modugno et al, 2001 (138), N=88 cases, U.S. Caucasians	Positive association
		Chang et al, 2002 (133), N=245 cases, 159 HPC cases	Positive association
		Mononen et al, 2002 (139), N=449 cases, Finns	Positive association
		Gsur et al, 2002 (135), N=190 cases, Austrians	Null association
		Chen et al, 2002 (134), N=300 cases, U.S. subjects	Null association
		Balic et al, 2002 (132), N=82 Hispanics	Positive association
		Santos et al, 2003 (141), N=133 cases, Brazilians	Null association
		Huang et al, 2003 (136), N=66 cases Taiwanese	Null association
		Nam et al, 2003 (140), N=483 cases, Canadians	Null association
		Cicek et al, 2004 (143), N=440 cases, US subjects	Null association
		Forrest et al, 2005 (144), N=288 early onset cases, UK subjects	Positive association
		Hayes et al, 2005 (146), N=815 cases, Australians	Positive association for metastatic disease
		Salinas et al, 2005 (147), N=591 cases, US subjects	Null association

Gene	Polymorphism	Study	Result
		Binnie *et al*, 2004 (142), N=100 cases, Scottish subjects	Null association
		Gilligan *et al*, 2004 (145), N=118 cases, African-Americans	Null association
		Review: Zeegers *et al*, 2004 (119)	Although results of individual studies are mixed, overall, shorter CAG and GGN repeats are associated with modestly increased risk. However, absolute number of repeat differences is < 1; biological impact of *AR* trinucleotide repeats is unlikely to be large.
HSD3B1	N367T, c7062t	Chang *et al*, 2002 (175), N=245 cases, 159 HPC cases, U.S. Caucasians	Positive association
HSD3B2	c7159g, c7474t	Chang *et al*, 2002 (175), N=245 cases, 159 HPC cases, U.S. Caucasians	Null association
HSD17B3	G289S	Margiotti *et al*, 2002 (176), N=103 cases, Italians	Positive association
ER-alpha	XbaI, PvuII	Fukatsu *et al*, 2004 (162), N=147 cases, Japanese	Null association
ER-beta	RsaI	Fukatsu *et al*, 2004 (162), N=147 cases, Japanese	Null association

Growth factors and non-androgenic hormone pathways

Gene	Polymorphism	Study	Result
VDR	BsmI, TaqI, polyA, ApaI, FokI,	Taylor *et al*. 1996 (201), N=108 cases, U.S. Caucasians	Positive association
		Ingles *et al*. 1997 (128), N=57 cases, U.S. Caucasians	Positive association
		Ingles *et al*. 1998 (184), N=151 cases, African-Americans	Null association
		Ma *et al*. 1998 (195), N=372 cases, U.S. Caucasians	Null association
		Correa-Cerro *et al*. 1999 (189), N=131 cases, European	Null association
		Habuchi *et al*. 2000 (192), N=222 cases, Japanese	Positive association
		Furuya *et al.*, 1999 (190), N=66 cases, Japanese	Null association
		Watanabe *et al.*, 1999 (202), N=100 cases, Japanese	Null association
		Blazer *et al.*, 2000 (186), N=77 cases, U.S. Caucasians	Null association
		Chokkalingam *et al*, 2001 (188), N=191 cases, Chinese	Null association
		Gsur *et al*, 2002 (191), N=190 cases, Austrians	Null association
		Hamasaki *et al*, 2002 (193), N=110 cases, Japanese	Positive association for aggressive disease
		Medieros *et al*, 2002 (197), N=163 cases, Portugese	Positive association for late-onset disease
		Suzuki *et al*, 2003 (200), N=81 HPC cases, Japanese	Null association
		Nam *et al*, 2003 (140), N=483 cases, Canadians	Null association
		Forrest *et al*, 2005 (144), N=288 early onset cases, UK subjects	Null association
		Mishra *et al*, 2005 (198), N=128 cases, Indians	Positive association
		Hayes *et al*, 2005 (146), N=812 cases, Australians	Null association
		Maistro *et al*, 2004 (196), N=165 cases, Brazilians	Null association
		Oakley-Girvan *et al*, 2004 (199), N=113 African-American cases, 232 Caucasian-American cases	Null association
		Cheteri *et al*, 2004 (187), N=559 cases, U.S. subjects	Null association
		Huang *et al*, 2004 (194), N=160 cases, Taiwanese	Positive association
		Review: Ntais *et al*, 2003 (117)	Overall, meta-analysis (117) shows null association for all markers. 3' markers (BsmI, Taq1, ApaI, and polyA) are non-functional, 5' FokI marker is functional.
INS	+1127PstI	Ho *et al*, 2003 (178), N=126 cases, U.S. subjects	Positive association
		Neuhausen *et al*, 2005 (179), N=199 cases, US subjects	Null association
		Claeys *et al*, 2005 (177), N=233 cases, African-Americans	Positive association
TH	-4217PstI	Ho *et al*, 2003 (178), N=126 cases, U.S. subjects	Null association
IRS1	G972R	Neuhausen *et al*, 2005 (179), N=199 cases, US subjects	Positive association
IRS2	G1079D	Neuhausen *et al*, 2005 (179), N=199 cases, US subjects	Null association
IGF-I	CA repeats	Nam *et al*, 2003 (140), N=483 cases, Canadians	Positive association
		Neuhausen *et al*, 2005 (179), N=199 cases, US subjects	Null association
		Friedrichsen *et al*, 2005 (180), N=591 cases, US subjects	Positive association
		Schildkraut *et al*, 2005 (182), N=100 cases, US subjects	Positive association
		Tsuchiya *et al*, 2005 (183), N=303 cases, Japanese	Positive association
		Li *et al*, 2004 (181), N=440 cases, US subjects (90% Caucasian)	Null association
			Overall, results mostly positive
IGF-II	MspI	Ho *et al*, 2003 (178), N=126, U.S. subjects	Null association
IGFBP-3	-a202c, A32G	Wang *et al*, 2003 (113), N=307 cases, Japanese	Null association
		Nam *et al*, 2003 (140), N=483 cases, Canadians	Null association
		Friedrichsen *et al*, 2005 (180), N=591 cases, US subjects	Null association
		Schildkraut *et al*, 2005 (182), N=100 cases, US subjects	Null association
		Li *et al*, 2004 (181), N=440 cases, US subjects (90% Caucasian)	Null association

Carcinogen metabolism pathway

Gene	Polymorphism	Study	Result
GSTT1	Deletion	Medeiros *et al*, 2004 (197), N=150 cases, Portugese	Null association
		Nakazato *et al*, 2003 (90), N=81 cases, Japanese	Null association
		Kidd *et al*, 2003 (240), N=206, Finns	Null association
		Kote-Jarai *et al*, 2001 (241), N=275 cases, U.K Caucasians	Null association
		Gsur *et al*, 2001, (242), N=166 cases, Austrians	Null association
		Murata *et al*, 2001, (213), N=115 casese, Japanese	Null association
		Steinhoff *et al*, 2000 (243), N=91 cases, Germans	Positive association
		Autrup *et al*, 1999 (203), N=153 cases, Dutch subjects	Null association
		Nam *et al*, 2003 (140), N=483 cases, Canadians	Positive association
		Kelada *et al*, 2000 (206), N=276 cases, U.S. subjects	Positive association
		Joseph *et al*, 2004 (205), N=428 cases, US subjects	Positive association
		Komiya *et al*, 2005 (207), N=190 cases, Japanese	Positive association
		Review: Ntais *et al*, 2005 (118)	Overall, GSTT1 unlikely to be a major susceptibility determinant on a population-wide basis
GSTM1	Deletion	Medeiros *et al*, 2004 (197), N=150 cases, Portugese	Null association
		Nakazato *et al*, 2003 (90), N=81 cases, Japanese	Null association
		Kidd *et al*, 2003 (240), N=206, Finnish subjects	Positive association
		Kote-Jarai *et al*, 2001 (241), N=275 cases, U.K Caucasians	Null association
		Gsur *et al*, 2001, (242), N=166 cases, Austrians	Null association
		Murata *et al*, 2001, (213), N=115 casese, Japanese	Positive association
		Steinhoff *et al*, 2000 (243), N=91 cases, Germans	Null association
		Autrup *et al*, 1999 (203), N=153 cases, Dutch subjects	Null association
		Nam *et al*, 2003 (140), N=483 cases, Canadians	Null association

		Kelada *et al*, 2000 (206), N=276 cases, U.S. subjects	Null association
		Joseph *et al*, 2004 (205), N=428 cases, US subjects	Null association
		Komiya *et al*, 2005 (207), N=190 cases, Japanese	Null association
		Review: Ntais *et al*, 2005 (118)	Overall, GSTM1 unlikely to be a major susceptibility determinant on a population-wide basis
GSTM3		Medeiros *et al*, 2004 (197), N=150 cases, Portugese	Positive association
GSTP1	I105V	Nakazato *et al*, 2003 (90), N=81 cases, Japanese	Positive association
		Kidd *et al*, 2003 (240), N=206, Finns	Null association
		Kote-Jarai *et al*, 2001 (241), N=275 cases, U.K Caucasians	Positive association
		Gsur *et al*, 2001, (242), N=166 cases, Austrians	Positive association
		Steinhoff *et al*, 2000 (243), N=91 cases, Germans	Null association
		Shepard *et al*, 2000 (208), N=590 cases, U.S. Caucasians	Null association
		Autrup *et al*, 1999 (203), N=153 cases, Dutch	Null association
		Wadelius *et al*, 1999 (174), N=850 subjects, Swedes and Danes	Null association
		Antognelli *et al*, 2005 (165), N=384 cases, Italians	Positive association
		Nam *et al*, 2003 (140), N=483 cases, Canadians	Null association
		Srivastava *et al*, 2005 (209), N=127 cases, Indians	Positive association
		Komiya *et al*, 2005 (207), N=190 cases, Japanese	Null association
		Debes *et al*, 2004 (204), N=499 cases, 438 HPC cases, US subjects	Null association
		Review: Ntais *et al*, 2005 (118)	Overall, GSTP1 unlikely to be a major susceptibility determinant on a population-wide basis
NAT1		Costa *et al*, 2005 (218), N=146 cases, Portugese	Null association
		Rovito *et al*, 2005 (219), N=152 cases, US subjects	Null association
NAT2		Wadelius *et al*, 1999 (174), N=850 subjects, Swedes and Danes	Null association
		Costa *et al*, 2005 (218), N=146 cases, Portugese	Positive association
		Rovito *et al*, 2005 (219), N=152 cases, US subjects	Null association
PON1	I102V, Q192R, L55M	Marchesani *et al*, 2003 (211), N=20 cases, Finns	Positive association
		Antognelli *et al*, 2005 (165), N=384 cases, Italians	Positive association
CYP1A1	2455A>G, 3801T>C, 2453C>A	Murata *et al*, 1998 (213), N=115 cases, Japanese	Positive association
		Suzuki *et al*, 2003 (214), N=81 HPC cases, Japanese	Positive association
		Chang *et al*, 2003 (212), N=245 cases, U.S. Caucasians	Positive association
CYP3A4	5' promoter variant *1B	Rebbeck *et al*, 1998 (216), N=230 cases, U.S. Caucasians	Positive association
		Paris *et al*, 1999 (215), N=174 cases, African-Americans	Positive association
		Nam *et al*, 2003 (140), N=483 cases, Canadians	Null association
		Zeigler-Johnson *et al*, 2004 (217), N=622 cases, US subjects	Positive association
CYP3A5	intron 3 missense variant *1	Zeigler-Johnson *et al*, 2004 (217), N=622 cases, US subjects	Null association
CYP3A43	exon 10 A>P variant *3	Zeigler-Johnson *et al*, 2004 (217), N=622 cases, US subjects	Positive association
CYP1B1	L432V	Fukatsu *et al*, 2004 (162), N=147 cases, Japanese	Positive association
CYP2D6	* 4	Fukatsu *et al*, 2004 (162), N=147 cases, Japanese	Null association
MnSOD	V→ A	Li *et al*, 2005 (220), N=567 cases, US subjects	Null association
DNA repair pathway			
XRCC1	R399Q, R194W, R280H	Rybicki *et al*, 2004 (225), N=637 cases, U.S. Caucasians	Null association
		van Gils *et al*, 2002 (226), N=77 cases, U.S. subjects	Positive association
		Ritchey *et al*, 2005 (224), N=162 cases, Chinese	Positive association
XRCC3	T241M	Ritchey *et al*, 2005 (224), N=162 cases, Chinese	Null association
XPD	D312N, K751Q	Rybicki *et al*, 2004 (225), N=637 cases, U.S. Caucasians	Positive association
		Ritchey *et al*, 2005 (224), N=162 cases, Chinese	Null association
hOGG1	S326C, +11657A/G	Xu *et al*, 2002 (227), N=245 cases, U.S. Caucasians	Positive association
		Chen *et al*, 2003 (223) N=84 cases, U.S.Caucasians	Positive association
MGMT	L84F, I143V	Ritchey *et al*, 2005 (224), N=162 cases, Chinese	Positive association
ATM	D1853N, D1853V, ivs38-8t>c, ivs38-15g>c, P1054R	Angele *et al*, 2004 (222), N=637 cases, French subjects	Positive association
Inflammation/Angiogenesis/Cytokines			
TGF-beta	L10P, c509t	Li *et al*, 2004 (229), N=351 cases, Japanese	Positive association
		Ewart-Toland *et al*, 2004 (228), N=492 cases, US subjects	Positive association for advanced stage only
COX-2	-1285A/G, -1265G/A, -899G/C, -297C/G	Panguluri *et al*, 2004 (230), N=288, 264, and 184 cases African-Americans, Nigerians, and U.S. Caucasians	Positive association in all ethnic groups
TNF-alpha	TNF-alpha-308	McCarron *et al*, 2002 (231), N=247 cases, U.K. Caucasians	Null association
		Wu *et al*, 2004 (232), N=96 cases, Taiwanese	Null association
IL-1-beta	IL-1-beta-511	McCarron *et al*, 2002 (231), N=247 cases, U.K. Caucasians	Null association
PPAR-gamma	P12A	Paltoo *et al*, 2003 (233), N=193 cases, Finns	Null association
VEGF	VEGF-1154, VEGF-460	McCarron *et al*, 2002 (231), N=247 cases, U.K. Caucasians	Positive association
		Lin *et al*, 2003 (171), N=96 cases, Taiwanese	Positive association
IL-8	IL-8-251	McCarron *et al*, 2002 (231), N=247 cases, U.K. Caucasians	Positive association
IL-10	IL-10-1082	McCarron *et al*, 2002 (231), N=247 cases, U.K. Caucasians	Positive association
Other genes			
PSA	ARE1-158	Salinas *et al*, 2005 (147), N=591 cases, US subjects	Null association
		Binnie *et al*, 2004 (142), N=100 cases, Scottish men	Positive association

[1] HPC, hereditary prostate cancer
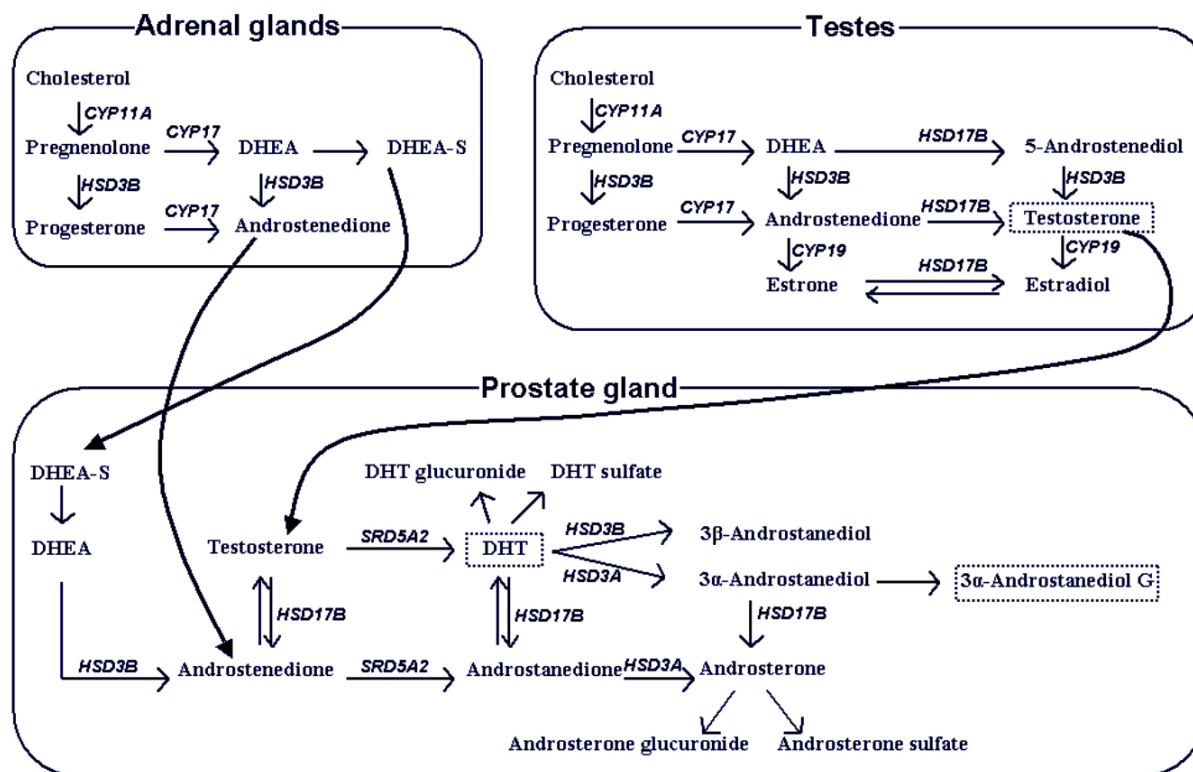
Figure 3. Androgen Biosynthesis and Metabolism Pathway.

which converts testosterone to the more active androgen dihydrotestosterone, the results are mixed (137, 140, 143, 144, 148-161), with a recent meta-analysis showing modest risk increases associated with shorter TA repeats and the T allele of the A49T marker, but not for other studied markers (115). Markers in other genes, including cytochrome p450-17 (*CYP17*) (137, 138, 162-164) and cytochrome p450-19 aromatase (*CYP19*) (115, 137, 140, 143, 144, 154, 161, 165-174) have shown promising initial results, but often do not replicate. Furthermore, recent initial studies of 17-beta-hydroxysteroid dehydrogenase 3 (*HSD17B3*) and 3-beta-hydroxysteroid dehydrogenase 1 (*HSD3B1*) have shown promising results (175, 176), while initial studies of polymorphisms in the estrogen receptors alpha and beta (*ER-alpha* and *ER-beta*) have been null (162). Further studies are needed to elucidate the role these androgen-related markers may play in prostate cancer.

6.3.2. Growth factor and non-androgenic hormone pathways

Due to serological evidence linking them to prostate cancer, a number of studies have explored the prostate cancer risk associated with polymorphic markers in genes involved in the insulin and insulin-like growth factor (IGF) signaling pathways. Two of three early studies of the insulin gene (*INS*) have shown promising results (177-179), and most studies of the CA repeat marker in the gene encoding IGF-I have been positive as well (140, 179-183). However, early studies of markers in the IGF-II and IGF binding protein-3 (IGFBP-3) genes have been null (113, 140, 178, 180-182).

Strong laboratory evidence showing chemoprotection of vitamin D against prostate cancer, in addition to the suggestive but inconsistent results of sero-epidemiological studies, has led to numerous studies of the vitamin D receptor gene (*VDR*) (140, 144, 184-202). However, despite promising early studies, results for *VDR* have been largely mixed, and a recent comprehensive meta-analysis showed no overall associations and concluded that markers in the *VDR* gene are unlikely to be major genetic determinants of prostate cancer risk (117).

6.3.3. Carcinogen metabolism pathway

Genes encoding enzymes that metabolize carcinogens and other toxins may play a role in prostate cancer. However, results from several studies of markers in different glutathione-*S*-transferases (GSTs), responsible for detoxifying a variety of carcinogens and including *GSTT1*, *GSTP1*, and *GSTM1*, have mostly been null (90, 140, 174, 203-209) and a recent review concluded that these genes are unlikely to comprise a major susceptibility locus across populations (118). Recent initial epidemiologic studies of other genes in these pathways, including *GSTM3* (210), paraoxonase 1 (*PON1*) (165, 211), cytochrome p450-1A1 (*CYP1A1*) (212-214), *CYP3A4* (140, 215-217), *CYP3A43* (217), and *CYP1B1* (162) have shown mostly positive results for these genes. In contrast, results for *N*-acetyl transferase 1 (*NAT1*) (218, 219), *NAT2* (174, 218, 219), *CYP3A5* (217), *CYP2D6* (162), and manganese superoxide dismutase (*MnSOD*) (220) have been mostly negative. With the exception of the GSTs, genes in the carcinogen metabolizing pathways have been studied in

only a limited number of populations and therefore require confirmation.

6.3.4. DNA repair pathway

Genes in the DNA repair pathway prevent disruptions in DNA integrity which may otherwise lead to gene rearrangements, translocations, amplifications, and deletions, contributing to cancer initiation (221). Initial reports of markers in genes encoding DNA repair enzymes, including the X-ray repair cross-complementing groups 1 and 3 (*XRCC1* and *XRCC3*), human 8-oxoguanine glycosylase I (*hOGG1*), xeroderma pigmentosum group D (*XPD*), methylguanine DNA methyltransferase (*MGMT*, also known as alkylguanine DNA alkyltransferase, or *AGT*), and ataxia telangiectasia mutated protein (*ATM*, involved in DNA damage signalling)) show promising results (222-227). These results, combined with strong biological plausibility, suggest that this may be a fruitful area for further research.

6.3.5. Chronic inflammation pathway

Several lines of evidence point to a role of inflammation in prostate cancer etiology, and studies of markers in the genes involved in inflammation are emerging. Initial studies show positive results for transforming growth factor-beta (*TGF-beta*) and *COX-2* (228-230) and negative results for tumor necrosis factor-alpha-308 (*TNF-alpha-308*) (231, 232), interleukin-1-beta (*IL-1-beta*) (231), and peroxisome proliferator-activated receptor-gamma (*PPAR-gamma*) (233). Evidence for a role of inflammation markers in prostate cancer is increasing, and given the biological plausibility of this hypothesis, this should be a fruitful area for future research.

6.3.6. Angiogenesis pathways

The need for increased vasculature to support cancer growth forms an area of research that is currently gaining momentum. Genetic investigations of angiogenesis in prostate cancer have involved the vascular endothelial growth factor (*VEGF*) gene as well as the genes for *IL-8* and *IL-10*, and thus far have shown positive results (231, 234). These findings await further confirmation, and support the notion that angiogenesis may indeed be involved in prostate cancer.

6.3.7. Biological pathways related to dietary factors

It is clear that genetic susceptibility to both Phase I and II enzymes (cytochrome p450) affects the association between certain dietary factors and prostate cancer risk. For example, the effect of cruciferous vegetables is related to both their high glycosinolate content and functional variations in enzymes, particularly *GSTM1* and *GSTT1*, which metabolize glycosinolates to isothiocyanates (ITCs) (35). Thus, to better assess the role of ITCs in prostate cancer, it is important to examine intake of cruciferous vegetables (measured in a comprehensive and reliable manner) in conjunction with genetic polymorphisms in *GSTM1* and *GSTT1*. An early exploration of this hypothesis suggests that men with *GSTM1*-present genotypes and high cruciferous vegetables intake have a greatly reduced risk (205). Moreover, genetic polymorphisms in receptors and transcription factors that interact with these compounds may contribute to variation in response to cruciferous vegetable intake. With sufficiently large sample size and careful assessment of diet and genetic factors, this important area should be investigated further.

6.3.8. Challenges of studies with common polymorphisms

Currently, the totality of data suggests that racial/ethnic variation exists in common polymorphisms of certain genes, such as the *SRD5A2*, *AR*, and *ELAC2/HPC2* genes, but a clear contribution to prostate cancer susceptibility is not yet evident. There are a number of challenges in genetic epidemiology studies of common polymorphisms, including the selection of relevant single nucleotide polymorphisms (SNPs) for genotyping and the difficulty in replicating results. The difficulty in replicating earlier findings in subsequent association studies is due, in part, to 1) the relatively small to modest effects of most common polymorphisms, with risk differences ranging from 10% to 80%; 2) the relatively small sample size in most previous studies, ranging from 100 to 500 cases, and the limited power (10-50%) of many of these studies to detect modest effects; 3) the tendency of small studies to produce false positive findings; and 4) differences in study design and populations, including differences in the severity of cases. Thus, studies with large sample sizes (>1,000 cases) are needed to clarify further the role of these polymorphic markers. In addition, it is becoming clear that because a single common gene or SNP alone is unlikely to explain a substantial part of the variation in prostate cancer susceptibility, even larger sample sizes (>3,000 cases) will be required to evaluate the effect of multiple variants.

Another challenge in epidemiologic studies investigating the role of genetic variants in complex disease (e.g., prostate cancer) is the limited ability to identify 'causal SNPs' through association studies. This is partly related to two factors: 1) the difficulty in selecting biologically relevant SNPs for genotyping; and 2) the inability to tease out causal SNPs from blocks of SNPs that are in high linkage disequilibrium (LD) with one another. There may be a dozen to a few hundred known SNPs within each gene of interest, and there may be many other SNPs that are unknown. The conventional approach to genotyping is to choose known SNPs with functional significance. However, this is a difficult task in practice, given the very large pool of known SNPs and the limited functional information of many of them. In some studies, the haplotype-tagging approach has been used to identify limited numbers of informative SNPs by exploiting blocks of SNPs that are in high LD with one another (235-237).

Rapid progress in genetic epidemiology during the next few years is likely to hinge upon several factors, including the availability of large, well-designed interdisciplinary epidemiologic studies, development of novel analytical approaches and statistical methods to deal with the vast amounts of data generated from genotyping studies, and innovative laboratory methods, such as DNA pooling (238) or whole genome scans, that enable the typing of multiple genetic markers in a high throughput fashion at a much lower cost and lower biospecimen depletion.

7. FUTURE STUDIES

It is clear that prostate cancer etiology involves an intricate interplay between lifestyle and genetic factors. To fully explore the complexity of interrelationships between the numerous elements in these pathways, large cohort studies collecting data and biospecimens prior to diagnosis will be required. Such studies will be important for identifying the modifiable lifestyle factors, such as diet, obesity, physical activity, that can be targeted for prevention and risk reduction. To this end, entities such as the Cohort Consortium, a collaborative agreement launched in 2003 involving over 10 large, prospective cohorts with a combined total of over 9,000 incident prostate cancer cases, have been organized to provide unique opportunities to evaluate the complex lifestyle and genetic relationships in prostate cancer etiology with sufficient statistical power.

The widespread use of PSA testing in western populations has changed the composition of prostate cancer cases included in epidemiologic studies (239). Prostate cancer cases diagnosed in the PSA era are more likely to have early lesions, which may differ in etiology from advanced lesions and more aggressive tumors. Therefore, risk estimates from the newer studies that include a large number of early-stage cases may differ substantially from older studies including mostly clinically relevant tumors. This is also frequently seen in recent epidemiologic investigations that include a large of number of cases with both early and advanced lesions, where positive associations are detected for advanced stage or more aggressive tumors but not for early stage or localized tumors. It is important that future studies include prostate tumor subclassification, such as methods of detection, markers of biological aggressiveness, and genetic changes, in order to provide more accurate and comparable risk estimates for specific risk factors.

8. SUMMARY

Epidemiologic observations provide important clues to the etiology of prostate cancer. Although the causes of prostate cancer still remain unclear, epidemiologic studies have revealed many intriguing leads, including both environmental and genetic factors. The pathogenesis of prostate cancer reflects complex interactions between environmental and genetic factors. With newly available tools in molecular biology and genomics, a new generation of large-scale multidisciplinary population-based studies is beginning to investigate the individual and combined effects of these factors. These studies are likely to provide strong evidence for risk factors that may help identify subsets of the population that are more susceptible to prostate cancer.

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