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The Epidemiology of Prostate Cancer

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Prostate cancer is a major cause of disease and mortality among men, and each year 1.6 million men are diagnosed with and 366,000 men die of prostate cancer. In this review, we discuss the state of evidence for specific genetic, lifestyle, and dietary factors associated with prostate cancer risk. Given the biological heterogeneity of this cancer, we focus on risk factors for advanced or fatal prostate cancer. First, we provide descriptive epidemiology statistics and patterns for prostate cancer incidence and mortality around the world. This includes discussion of the impact of prostate-specific antigen screening on prostate cancer epidemiology. Next, we summarize evidence for selected risk factors for which there is strong or probable evidence of an association: genetics, obesity and weight change, physical activity, smoking, lycopene and tomatoes, fish, vitamin D and calcium, and statins. Finally, we highlight future directions for prostate cancer epidemiology research.

DESCRIPTIVE EPIDEMIOLOGY OF PROSTATE CANCER

The global burden of prostate cancer is substantial, ranking among the top five cancers for both incidence and mortality (Ferlay et al. 2015). Prostate cancer is characterized by striking geographical variation in both incidence and mortality rates. An examination of patterns in prostate cancer incidence and mortality across populations and over time provides insights into the role of individual risk factors and population screening behaviors in the epidemiology of this disease.

Incidence

Globally, prostate cancer is the most commonly diagnosed cancer in men, with approximately 1.6 million incident cases in 2015 (Global Burden of Disease Cancer Collaboration 2016). Prostate cancer is particularly common in developed countries. The odds of prostate cancer diagnosis by age 79 years are one in 47 among countries with a low–middle sociodemographic index, compared with one in six among countries with a high sociodemographic index (Global Burden of Disease Cancer Collaboration 2016). In the United States, prostate cancer is the leading cause of incident cancer and it is estimated that 180,890 new cases were diagnosed in 2016 (Howlader et al. 2016).

Prostate cancer incidence is notable for its substantial global variation (Fig. 1). There is a 40-fold difference in age-adjusted incidence rates between men with the highest (African-American men in the United States) and lowest (Asian men living in their native countries) incidence (Ferlay et al. 2013; Howlader et al. 2016). In part, this variation in incidence rates across

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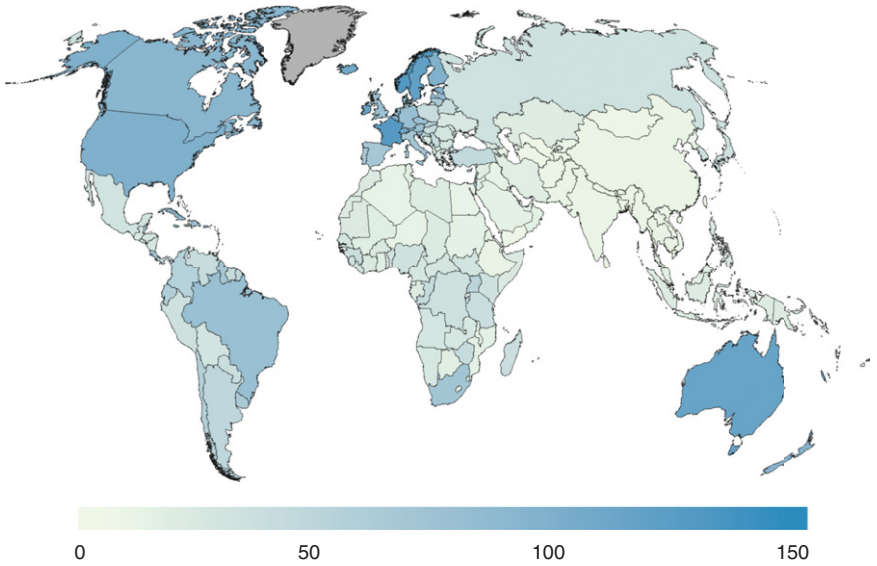

Figure 1. Age-adjusted prostate cancer incidence rates worldwide. Rates are age-adjusted for comparisons across countries and are presented per 100,000 in the population. Gray, no data available. (Figure based on data from Globocan 2012 [globocan.iarc.fr].)

populations can be attributed to differences in diagnostic intensity arising from the practice of prostate-specific antigen (PSA) screening. However, evidence of geographic variation in prostate cancer incidence predating the introduction of PSA screening highlights a potential role of lifestyle factors in disease risk. Furthermore, evidence from migration studies provides support for a role of lifestyle factors. For example, prostate cancer incidence and mortality rates increase among men who migrate from low-risk (e.g., Asia) to high-risk (e.g., United States) countries compared with those in their native countries, although rates remain below the host countries' rates (Shimizu et al. 1991; Yu et al. 1991).

Global patterns of change in incidence rates over time show the impact of PSA screening on prostate cancer epidemiology. During the past 40 years, age-adjusted incidence rates have generally increased across the world (Fig. 2). Notably, this increasing trend has paralleled the uptake of PSA screening in certain regions, such as the United States, Europe, and Australia. In the United States, for example, a large peak in prostate cancer incidence is observed in the early 1990s when PSA screening is first introduced at the population level. The emergence of PSA screening has also led to a shift in the stage at diagnosis, with a higher proportion of men diagnosed with localized disease. Moreover, because of the lead time associated with prostate cancer, estimated to be 3 to 10 years, men are being diagnosed at an earlier age (Etzioni et al. 2008). A further consequence of PSA screening has been an increasing incidence of cancers considered to be overdiagnosis (i.e., cancers that would not have come to light clinically nor led to mortality in the absence of screening) (Etzioni et al. 2002; Ciatto et al. 2005). However, incidence rates have also increased in regions where PSA testing has not yet been widely used, such as in Japan and some other Asian and Eastern European countries (Jemal et al. 2010). The trend in these regions suggests that environmental or lifestyle factors, as discussed later in this chapter, may also influence prostate cancer incidence.

Mortality

Prostate cancer is the fifth most common cause of cancer death globally, accounting for an esti-

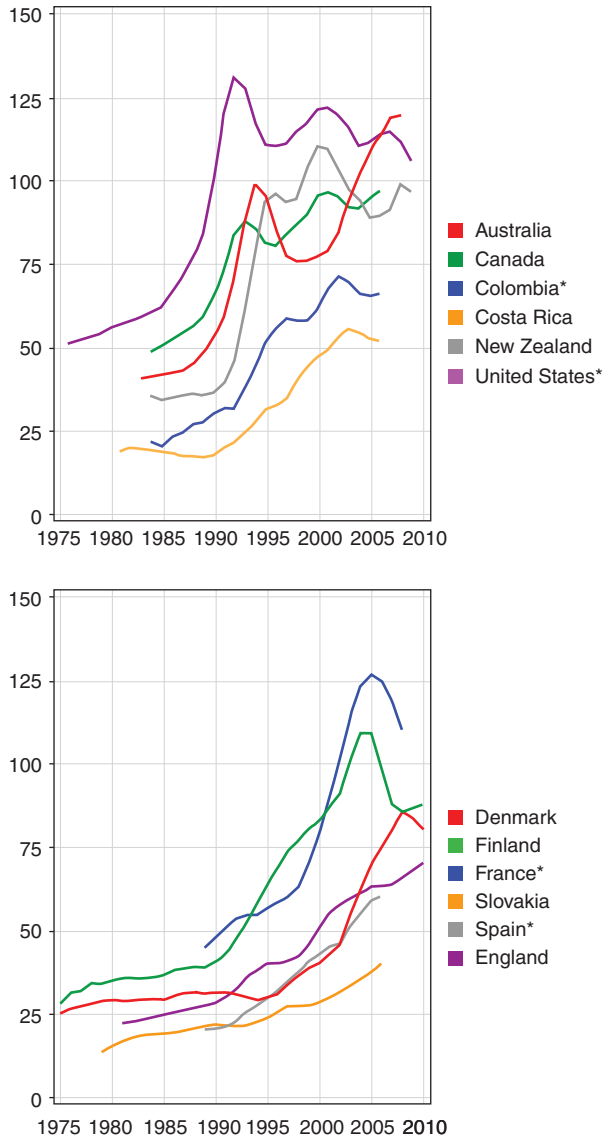

Figure 2. Trends over time in age-adjusted prostate cancer incidence rates (per 100,000). *, Regional data. (Figure based on data from Globocan 2012 [globocan.iarc.fr].)

mated 366,000 deaths and 6.3 million disability-adjusted life years in 2015 (Global Burden of Disease Cancer Collaboration 2016). Compared with prostate cancer incidence rates, there is less global variation in mortality rates, with an approximately 10-fold difference across countries (Fig. 3). Global mortality patterns differ from incidence also in that less-developed regions experience higher mortality caused by prostate cancer than more developed regions. The highest prostate cancer mortality rates are among populations in the Caribbean and in Middle and Southern Africa. In contrast, the lowest prostate cancer mortality rates are observed in Asia, particularly in Eastern and South-Central Asia. Prostate cancer is the second most common cause of cancer death among men in the United States, with 26,120 cancer deaths expect-

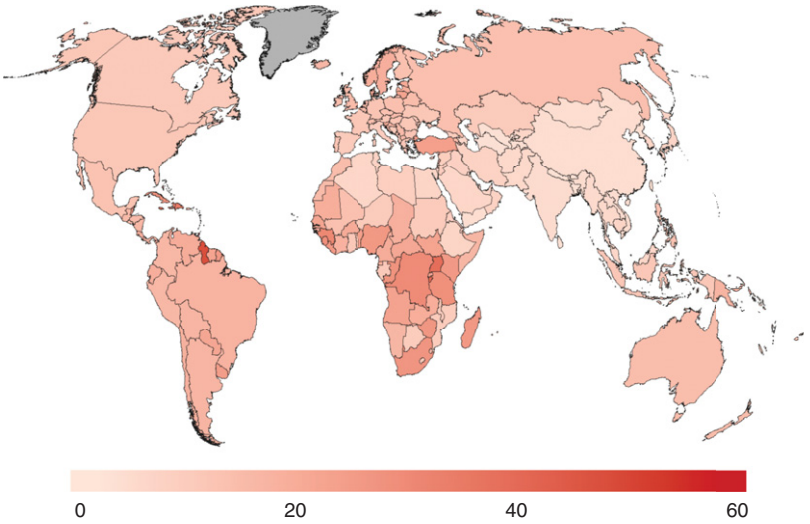

Figure 3. Age-adjusted prostate cancer mortality rates worldwide. Rates are age-adjusted for comparisons across countries and are presented per 100,000 in the population. Gray, no data available. (Figure based on data from Globocan 2012 [globocan.iarc.fr].)

ed in 2016 (Howlader et al. 2016). There have been notable reductions in prostate cancer mortality across a number of Westernized countries including the United States. The reasons underlying this decrease are unclear. However, it is likely that part of the reduction can be explained through the identification of prostate cancer earlier through PSA screening and the resulting earlier treatment (Chu et al. 2003). It is notable that some countries with low or no screening are experiencing increased prostate mortality such as in Africa.

Changes in mortality are a result of both changes in the incidence of prostate cancer as well as survival among patients. There is considerable variability in the ratio of incidence to mortality, with the highest ratio in North America (10:1), lower in Australia (2:1), and almost equal in some countries in the Caribbean and parts of Africa (1.2:1). These differences may be explained in part by a larger proportion of slow-growing cancers diagnosed in countries with PSA screening (Johansson et al. 2004; Albertsen et al. 2005) and, conversely, by later presentation of disease in countries with lower diagnostic intensity. The magnitude of burden attributable to prostate cancer is reflected also in the high prevalence of this disease. As a consequence of its high incidence and long survival, prostate cancer has the highest 5-year prevalence of any cancer type, accounting for 25% of all prevalent cancers (Ferlay et al. 2013). More than four million men are prostate cancer survivors living with a cancer diagnosis around the world, of whom 2.7 million are in the United States (SEER Cancer Statistics Review 1975–2008 2011). This has important implications for the allocation of resources for men who are undergoing treatment or surveillance for this disease.

As shown, several important characteristics of prostate cancer epidemiology can be gleaned from examining incidence and mortality rates across regions and over time. The evidence for specific risk factors associated with prostate cancer will be discussed in detail in the following sections.

RISK FACTORS

Epidemiologic studies of prostate cancer have revealed numerous ways in which individual biology and lifestyle factors influence risk of developing prostate cancer and survival from this disease (Tables 1 and 2). Although many questions remain about the etiology of this common disease, our current understanding of risk fac-

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Table 1. Summary of evidence for selected risk factors of total prostate cancer

Risk factor	Strength of evidence
Increased risk	
Older age	Strong
African descent	Strong
Family history	Strong
Genetic risk loci	Strong
Taller height	Probable

tors points to ways to identify individuals at high risk and use behavior change to reduce the burden of disease. As discussed in the previous section, prostate cancer is a clinically heterogeneous disease. Whereas some men have an aggressive form of prostate cancer, most others have a slow-growing or indolent form of disease. This clinical heterogeneity is reflected also in the underlying etiology of this disease. As detailed in the sections below, several risk factors show different associations for indolent as compared with lethal disease (Jahn et al. 2015). Thus, it is imperative in prostate cancer epidemiology to differentiate between risk factors for total prostate cancer and for advanced or fatal disease.

To evaluate evidence for prostate cancer risk factors, the role of PSA screening in epidemiologic studies must also be considered given its potential to influence the observed associations between risk factors and prostate cancer. On the one hand, risk factors may influence prostate cancer across the pathogenesis of the disease, from cancer initiation to metastases to death. Thus, the association between a factor and prostate cancer risk may differ according to clinical features of the disease, such as stage or tumor grade (Giovannucci et al. 2007). Indeed, it seems biologically plausible that risk factors for prostate cancer overall would differ from those for more aggressive prostate cancer. Moreover, PSA testing can have a potentially confounding effect, because men who engage in regular screening tend to also be healthier in general, and independently with prostate cancer diagnosis. When one is evaluating epidemiological studies in prostate cancer, it is critical to investigate the extent to which a study integrates information on PSA screening.

Table 2. Summary of evidence for selected risk factors of advanced or lethal prostate cancer

Risk factor	Strength of evidence
Increased risk	
Taller height	Strong
Lipid levels	Possible
Obesity	Strong
Smoking	Strong
Dairy, calcium	Possible
Decreased risk	
Physical activity	Strong
Coffee	Limited
Tomatoes	Probable
Fish	Possible
Vitamin D	Possible
Statins	Probable

Risk Factors for Total Prostate Cancer

Established risk factors for total prostate cancer incidence are limited to older age, African-American race, and positive family history of prostate cancer. More recently, genome-wide association studies (GWAS) have provided additional evidence of genetic predisposition to prostate cancer. In populations with ethnically diverse ancestry, more than 180 genetic risk loci have been confirmed (Eeles et al. 2013; Al Olama et al. 2014). Additionally, there is probable evidence that taller height increases risk of total prostate cancer (MacInnis and English 2006). Although these factors are not modifiable, they are illustrative of the possible mechanisms involved in prostate carcinogenesis and could be used to identify individuals at increased risk of developing this disease (risk stratification).

Age is strongly associated with risk of total prostate cancer. Prostate cancer is rare among men younger than 40 years of age. The incidence rate of prostate cancer increases dramatically after 55 years of age, following a similar trend as other epithelial cancers. This trend is evident in global prostate cancer rates, as well as in both low and highly developed regions (Ferlay et al. 2015). It is noteworthy that 10% of U.S. men diagnosed with prostate cancer in 2012 were less than 55 years of age, and early-onset prostate

cancer may have a distinct etiology and clinical phenotype (Salinas et al. 2014). The practice of PSA screening results in a lead time of ~10 years because of detection of prostate cancer before symptom onset. Following the implementation of PSA screening in the United States, the average age at prostate cancer diagnosis shifted earlier and is currently 66 years of age (Howlader et al. 2016).

There are striking differences in prostate cancer incidence and mortality across racial and ethnic groups (Fig. 4). For example, there is a threefold difference in incidence rates of prostate cancer across race/ethnicity groups in the United States, with the highest incidence observed among black men. Moreover, deaths attributable to prostate cancer are 2.4 times greater among black compared to white men in the United States (Howlader et al. 2016). Prostate cancer incidence and mortality rates are lower among Asian/Pacific Islanders, American Indian/Alaskan Natives, and Hispanic men compared with non-Hispanic white men (Howlader et al. 2016). Further study is needed to explain the causes of these disparities. There is some evidence that differences in mortality may be a result, in part, of differences in access to care and stage at diagnosis (Taksler et al. 2012). Observed differences in the prevalence of multiple prostate cancer genetic risk loci across racial/ethnic groups (Haiman et al. 2011) suggests that genetic factors could account for some differences in incidence rates.

There is strong evidence from family studies that family history of prostate cancer influences risk of prostate cancer. Compared with men without a positive family history, men with a father or brother diagnosed with prostate cancer are at a two- to threefold higher risk of being diagnosed, and the risk is nearly ninefold higher for men with both (Hemminki and Czene 2002). A similar association has been observed for risk of lethal prostate cancer. Men with a father or brother who died of prostate cancer have twofold higher risk of death from prostate cancer compared with men diagnosed with prostate cancer without a family history (Brandt et al. 2011). Further evidence from twin studies shows that much of familial aggregation of prostate cancer results from shared genetic factors, with a high heritability estimate of 57% (Lichtenstein et al. 2000; Mucci et al. 2016). The more than 105 prostate cancer risk loci confirmed across multiple studies explain about one-third of the heritability (Eeles et al. 2013; Hoffmann et al. 2015). The majority of identified germline risk

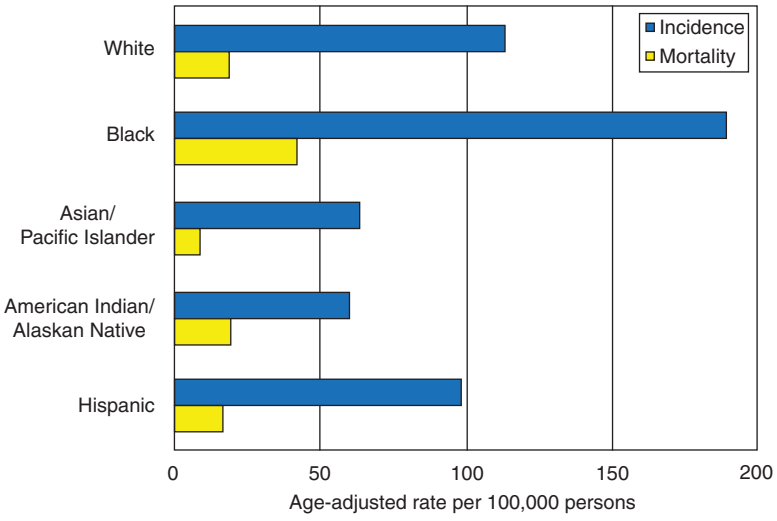

Figure 4. Prostate cancer incidence and mortality rates (per 100,000) by race/ethnicity in the United States, 2010–2014. Rates are age-adjusted. (Figure based on SEER Registry data [seer.cancer.gov/csr/1975-2014/].)

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loci are not strongly associated with lethal or nonlethal prostate cancer (Pomerantz and Freedman 2010; Shui et al. 2014), which suggests that inherited factors may be involved early in prostate carcinogenesis.

Risk Factors for Advanced and Fatal Prostate Cancer

Obesity and Weight Change

Obesity is a growing public health issue because the prevalence of obesity worldwide has more than doubled since 1980 (World Health Organization 2014). In 2014, there were an estimated 1.9 billion overweight adults, of whom 600 million qualified as obese (World Health Organization 2014). Among men worldwide, the prevalence of overweight and obesity is 39% and 11%, respectively. Obesity is implicated in the dysregulation of various hormonal pathways, leading to higher levels of insulin, estradiol, and inflammatory cytokines and lower levels of adiponectin, testosterone, and sex hormone binding globulin (Platz and Giovannucci 2004; De Marzo et al. 2007; Ma et al. 2008; Li et al. 2010).

The relationship between body size and prostate cancer incidence is complex and has been studied extensively (MacInnis and English 2006; Giovannucci et al. 2007; Ma et al. 2008; Robinson et al. 2008; Cao and Ma 2011; Discacciati et al. 2011). Obesity is associated with an increased risk of prostate cancer mortality and recurrence. In a meta-analysis of six postdiagnosis studies of men with prostate cancer, a 5 kg/m^2 increase in body mass index (BMI) was associated with a 20% (RR 1.20, 95% CI: 0.99–1.46) higher risk of death from prostate cancer (Cao and Ma 2011). An association of similar magnitude was observed for risk of biochemical recurrence. Although it has been suggested that differences in screening may explain the association between obesity and worse prostate cancer outcomes, the association remains after accounting for stage and grade at diagnosis as well as PSA screening (Wright et al. 2007; Ma et al. 2008). Biomarkers have been used to identify possible mechanisms through which obesity may affect prostate cancer progression. In a prospective cohort with prediagnostic bloods, men who had high-circulating levels of C-peptide, a marker of insulin secretion, had an increased cancer-specific mortality (Ma et al. 2008). However, this association was not confirmed in two prospective studies for risk of aggressive disease (Ma et al. 2008; Stevens et al. 2014).

Waist circumference is often used as a measure of abdominal obesity and is thought to have more metabolically active adipose tissue. In a prospective study of 150,000 European men, waist circumference was positively associated with risk of advanced prostate cancer (Pischon et al. 2008). This finding was confirmed in the Melbourne Collaborative Cohort Study (MacInnis et al. 2003), but not in the Health Professionals Follow-up Study (HPFS) (Giovannucci et al. 1997; Möller et al. 2016).

Additional studies have investigated the effect of weight across the life course. There appears to be no association between weight gain from early adulthood (age 18 or 21) to midlife and prostate cancer risk (Nomura et al. 1985; Cerhan et al. 1997; Giovannucci et al. 1997; Putnam et al. 2000; Schuurman et al. 2000; Spitz et al. 2000; Jonsson et al. 2003; Friedenreich et al. 2004; Littman et al. 2007) except for one study in the multiethnic cohort (Hernandez et al. 2009). Among prostate cancer patients, men who lost weight in the period from shortly before to after prostate cancer diagnosis had a suggestively lower risk of recurrence, whereas weight gain was positively associated with recurrence after prostatectomy (Joshu et al. 2011b). Further investigation of the mechanisms underlying these associations of obesity and weight change is needed to inform strategies for prostate cancer prevention.

Height

There is probable evidence that taller height may increase risk of overall prostate cancer, and strong evidence for advanced disease. A meta-analysis of 58 studies found a relative risk of 1.09 (95% CI: 1.06–1.12) for prostate cancer overall and 1.12 (95% CI: 1.05–1.19) for advanced prostate cancer per 10 cm of height (Zuccolo et al. 2008). Results were similar when comparing be-

fore and during the PSA era. In the Health-Professionals Follow-up Study, taller height was associated with advanced and fatal prostate cancer but was not associated with total prostate cancer (Möller et al. 2016). However, a prospective study conducted in the multiethnic cohort found no association between height and risk of total or advanced prostate cancer (Hernandez et al. 2009). Although height is not considered a modifiable risk factor, its role in prostate cancer provides insight into the underlying biology of this disease. A potential explanation for this association is that height attained in adult life reflects early-life exposure to growth hormones such as insulin-like growth factor 1 (IGF-1). Birth size is not associated with prostate cancer risk, further suggesting that the etiologically relevant time period may be during puberty when the prostate undergoes maturation and rapid growth (Zuccolo et al. 2008).

Physical Activity

Evidence from prospective cohort studies has shown a moderate inverse association between physical activity and risk of advanced and fatal prostate cancer. Among men >65 years of age in the HPFS cohort, men in the highest quintile of vigorous activity had a 77% lower risk of advanced prostate cancer (Giovannucci et al. 2005). In the CPS-II cohort, men with the highest level of recreational physical activity had a 31% lower risk of aggressive prostate cancer compared with men who did not engage in recreational physical activity (Patel et al. 2005). In contrast, the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort showed an inverse association between occupational activity and risk of advanced prostate cancer but no association for leisure time activity (Johnsen et al. 2009). However, activity levels in the EPIC cohort were substantially higher, and the reference group included men with up to 25 metabolic equivalent (MET)-hours per week.

Among men diagnosed with prostate cancer, physical activity has been linked to improved survival and decreased prostate cancer progression. A study of 2705 men with prostate cancer found that those who exercised vigorously for at least 3 hours per week had a 61% lower risk of prostate cancer–specific mortality compared to those with less than 1 hour per week of vigorous activity (RR 0.4, 95% CI: 0.2–0.8) (Kenfield et al. 2011b). Although the association with prostate cancer–specific mortality was isolated to vigorous activity, both vigorous and nonvigorous activity were linked to lower risk of all-cause mortality in this population. A similar association was observed for brisk walking, with a lower risk of recurrence (RR 0.4, 95% CI: 0.2–0.9) for men engaging in brisk walking at least 3 hours per week compared with easy walking for less than 3 hours per week (Richman et al. 2011). The mechanism through which physical activity may alter prostate cancer risk is yet unclear but may act through changes in sex hormone levels, anti-inflammatory pathways, or the IGF axis (Gann et al. 1996).

Smoking

The role of smoking in cancers, including prostate cancer, is one of great public health significance. The latest 2014 report by the U.S. Surgeon General concluded there is "suggestive" evidence that smoking increases risk of death from prostate cancer, as well as risk of advanced-stage disease and less-well-differentiated cancer (U.S. Department of Health and Human Services 2014). The largest study to examine this question was conducted in HPFS, in which 5366 men diagnosed with prostate cancer were followed prospectively for 22 years and 524 prostate cancer deaths were observed. Compared with men who never smoked, current smokers had a 60% higher risk of prostate cancer mortality (HR 1.61; 95% CI: 1.11–2.32) after adjusting for potential confounders (Kenfield et al. 2011a). The association for current smoking remained elevated after further adjustment for prostate cancer stage and grade. However, attenuation of this association suggests that stage and grade may mediate the effect of smoking on prostate cancer mortality. Current smokers report less PSA testing than nonsmokers (Byrne et al. 2010), and this may contribute to later diagnosis and treatment of cancer among smokers. Another possible mechanism through which smoking may af-

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fect prostate cancer mortality is by influencing response to treatment. There have been consistent findings of worse outcomes among smokers compared to nonsmokers in prostate cancer patients treated by radiation, androgen-deprivation therapy (ADT), and radical prostatectomy (Oefelein and Resnick 2004; Pickles et al. 2004; Pantarotto et al. 2007; Moreira et al. 2010; Joshu et al. 2011a).

Epidemiologic evidence indicates that the effect of smoking on prostate cancer may depend on the time period of exposure. A prospective study in HPFS found that pack-years of smoking 10 years before prostate cancer diagnosis was positively associated with risk of lethal disease, whereas total lifetime smoking was not associated with risk (Giovannucci et al. 1999). A separate study showed that among former smokers who quit 10 or more years before diagnosis, the risk of prostate cancer mortality and recurrence was similar to that of never smokers (Kenfield et al. 2011a). The biological basis for the association between smoking and prostate cancer risk and mortality remains unclear. Several potential mechanisms have been proposed, including tumor promotion through carcinogens contained in tobacco smoke, changes in testosterone levels, and epigenetic and nicotine-induced effects (Kenfield et al. 2011a).

Lycopene and Tomato-Based Products

Oxidative stress may damage molecules, including proteins and DNA, and has been implicated in carcinogenesis. Lycopene is a carotenoid with powerful antioxidant properties and accumulates in high concentrations in prostate tissue. The primary food sources of lycopene include tomatoes and tomato-based products, pink grapefruit, and watermelon (Ilic et al. 2011). Antioxidants such as lycopene may limit the damaging effects of oxidation in animal tissues. The hypothesis that lycopene and lycopene-rich foods may have a protective role in prostate cancer risk has been extensively studied (Mills et al. 1989; Le Marchand et al. 1991; Giovannucci et al. 1995, 2002; Key et al. 1997, 2007; Meyer et al. 1997; Cerhan et al. 1998; Schuurman et al. 1998; Deneo-Pellegrini et al. 1999; Jain et al. 1999, 2007; Vogt et al. 2002; Huang et al. 2003; Bosetti et al. 2004; Kirsh et al. 2006; Peters et al. 2007; Pourmand et al. 2007; Beilby et al. 2010; Kristal et al. 2010, 2011). A 2004 meta-analysis found that high dietary intakes of tomato or tomato-based products were associated with a 10%–20% reduction in risk of incident prostate cancer (Etminan et al. 2004). A separate analysis of studies assessing lycopene in serum or plasma found a 25% lower prostate cancer risk associated with higher concentrations of lycopene. Findings of epidemiologic studies more recently have been inconsistent, with some finding an inverse association between lycopene and prostate cancer (Wu et al. 2004; Jian et al. 2005; Key et al. 2007; Pourmand et al. 2007), whereas others are null (Bosetti et al. 2004; Kirsh et al. 2006; Peters et al. 2007; Karppi et al. 2009; Kristal et al. 2010, 2011).

Epidemiologic studies have also focused on tomatoes as a specific source of lycopene with more consistent findings supporting a protective effect of higher intake of tomatoes on prostate cancer risk. The strongest benefit has been observed for cooked tomatoes, which contain higher levels of bioavailable lycopene than fresh tomatoes (Maiani et al. 2009). A meta-analysis was published in 2004 and included available prospective cohort and nested case control studies (Etminan et al. 2004). Men who consumed higher amounts of raw tomato (5th quintile of intake) had a lower risk of prostate cancer (RR 0.89, 95% CI 0.80–1.00). The association was somewhat stronger for higher intake of cooked tomato products; lycopene is lipophilic and thus cooking allows for more bioavailable sources of lycopene than fresh tomatoes (Maiani et al. 2009). Notably, the associations between tomato products are stronger for risk of advanced or lethal prostate cancer, compared with overall risk, suggesting that tomato products may play a role in disease progression. In a European study, prediagnostic plasma levels of lycopene were not associated with risk overall, although men who had the top quintile of plasma lycopene had lower risk of advanced disease (RR 0.40, 95% CI: 0.19–0.88) (Key et al. 2007). In the HPFS cohort, the relative risk for high lycopene was 0.91 (95% CI: 0.84–1.00) for prostate

cancer risk overall but 0.72 (95% CI: 0.56–0.94) for lethal disease (Zu et al. 2014). Moreover, men who consumed high lycopene also had tumors indicating lower angiogenic potential.

Current epidemiologic evidence is not definitive but suggests that higher intake of tomato-based products is associated with reduced risk of prostate cancer and potentially lower risk of progression. Further study is required to determine whether the effect is because of lycopene or other components of tomatoes. Nonetheless, the association appears to be stronger for advanced prostate cancer than for indolent disease.

Calcium, Dairy Products, and Vitamin D

Calcium intake has been positively associated with prostate cancer in most epidemiological studies. A 2005 meta-analysis reported that men with the highest calcium intake had a relative risk of 1.39 (95% CI: 1.09–1.77), for extreme categories (Gao et al. 2005). Four prospective studies have been published subsequently, each suggesting an increased risk associated with high calcium (Kesse et al. 2006; Mitrou et al. 2007; Park et al. 2007; Allen et al. 2008), whereas five studies found no associations (Ahn et al. 2007; Park et al. 2007; Rohrmann et al. 2007; Kurahashi et al. 2008; Butler et al. 2010; Kristal et al. 2010). There was notable variability in total calcium intake across study populations, with the highest intake ranging from <1000 mg/day in three studies to >2000 mg/day in three other studies (Ahn et al. 2007; Mitrou et al. 2007; Park et al. 2007; Rohrmann et al. 2007; Kurahashi et al. 2008; Butler et al. 2010). In some, but not all, studies, higher calcium intake has been associated with more aggressive prostate cancer defined by high grade or advanced or lethal disease (Tseng et al. 2005; Giovannucci et al. 2006, 2007).

Serum levels of calcium and prostate cancer risk have been examined in several prospective studies. High-serum calcium was associated with a higher risk of fatal prostate cancer in National Health and Nutrition Examination Survey (NHANES) studies, with an RR of 2.68 (95% CI: 1.02–6.99) (Skinner and Schwartz 2008, 2009). Two nested case-control studies of Swedish men found no association with overall risk of prostate cancer (Halthur et al. 2009; Van Hemelrijck et al. 2012); in fact, there was a weak inverse association with overall risk in one study but no association with risk of fatal disease (Van Hemelrijck et al. 2012). The findings on serum calcium must be taken in context, as circulating levels are tightly regulated and are influenced by diet only at high levels of dietary consumption.

Dairy foods are a major source of calcium in the diet, and high intake of dairy has been positively associated with prostate cancer risk. In a meta-analysis, the per-serving RR for total dairy were 1.11 (95% CI: 1.03–1.19), for milk 1.06 (95% CI: 0.91–1.23), and for cheese 1.11 (95% CI: 0.99–1.25) (Gao et al. 2005). Whereas most studies (Rohrmann et al. 2007; Allen et al. 2008; Park et al. 2009) subsequently published also showed a positive association for higher milk or dairy and total prostate cancer (Koh et al. 2006; Park et al. 2007), results for advanced or lethal disease are mixed (Park et al. 2007). The correlation between dairy foods and calcium and other nutrients presents a challenge of distinguishing the independent effects of these compounds. The 2007 expert report from the World Cancer Research Fund on Diet and Cancer stated that calcium is a "probable" risk factor for prostate cancer, but the evidence for dairy was weak/inconclusive (Wiseman 2008). Since the expert report, the EPIC cohort reported a positive association between dairy calcium, but not nondairy calcium, with both total and high-grade prostate cancer (Allen et al. 2008).

A potential mechanism underlying the association with calcium is through suppressing circulating levels of dihydroxyvitamin D (1,25 $(OH)_2D$), the more bioactive vitamin D metabolite. Most vitamin D is from endogenous production in the skin as a result of sun exposure, whereas dietary sources are secondary. Although $1,25(OH)_2D$ is the most biologically active form, 25(OH)D is found in higher concentrations and may be a strong indicator of sun and dietary exposure (Ali and Vaidya 2007). Dairy protein is also associated with increased circulating levels of IGF (Giovannucci et al.

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2003), which has been linked with advanced prostate cancer (Chan et al. 2002).

Studies examining vitamin D through diet or supplemental sources have generally found no association for prostate cancer risk (Chan et al. 1998, 2000; Kristal et al. 2002). Studies using prediagnostic circulating vitamin D have been quite mixed for overall risk, finding no association (Corder et al. 1993; Braun et al. 1995; Gann et al. 1996; Nomura et al. 1998; Jacobs et al. 2004; Platz et al. 2004; Faupel-Badger et al. 2007; Li et al. 2007; Ahn et al. 2008; Travis et al. 2009; Barnett et al. 2010; Park et al. 2010; Gilbert et al. 2012), in addition to significant positive (Albanes et al. 2011), inverse (Meyer et al. 2013), and U-shaped (Kristal et al. 2014) associations. Other lines of evidence point to a role of vitamin D for prostate cancer progression. Inherited genetic variants in the vitamin D pathway, which may influence metabolism or uptake, have been associated with an increased risk of recurrence and prostate cancer mortality (Holt et al. 2010). Moreover, high-protein tumor expression of the vitamin D receptor has been inversely associated with lethal prostate cancer in a survival analysis (Hendrickson et al. 2011). Low pre-diagnostic 25(OH)D levels were associated with higher mortality among prostate cancer patients, with an RR of 1.59 (95% CI: 1.06–2.39) for the highest versus lowest quartiles (Fang et al. 2011).

Fish

Populations with diets rich in fish, such as Japanese and Alaskan Eskimos, tend to have lower incidence of prostate cancer compared to populations following a Western diet low in fish (Zhang et al. 1999; Dewailly et al. 2003). There is some epidemiologic evidence to support a role of fish intake with prostate cancer mortality. A meta-analysis of four cohort studies showed a 63% reduction in prostate cancer–specific mortality associated with higher total fish intake (Szymanski et al. 2010). Although one study found an increased risk of prostate cancer among men with higher blood levels of long-chain omega-3 fatty acids (Brasky et al. 2013), this is likely to have arisen because the cases represented primarily early-stage disease and men with higher fish intake are more likely to receive PSA screening. One study examining fish intake after prostate cancer diagnosis found a 17% reduction in risk of prostate cancer recurrence with two additional servings of fish per week (Chan et al. 2006). A second study of post-diagnostic fish intake found no association (Richman et al. 2010). Although the mechanism is unknown, fish contain long-chain marine omega-3 polyunsaturated fatty acids, which could lower risk of prostate cancer through anti-inflammatory pathways (Chan et al. 2005).

Coffee

Coffee has been studied extensively in prostate cancer epidemiology, although most prior studies focused on total prostate cancer and with generally null results. However, studies investigating risk of fatal or advanced disease support an inverse association (Cao et al. 2014; Discacciati et al. 2014; Lu et al. 2014; Zhong et al. 2014). In addition, meta-analysis by Discacciati et al. (2014) reported an RR of 0.89 (95% CI: 0.82–0.97) for total prostate per three cups/day of coffee and an inverse association with high-grade (Gleason 8–10) disease.

Coffee is composed of a diverse array of biologically active compounds that may underlie the association with prostate cancer progression. For example, coffee is linked with improved glucose metabolism and insulin secretion in observational and animal studies, and it is one of the most potent antioxidant dietary factors.

Statins

Several studies show that higher cholesterol levels are associated with increased risk of total or advanced prostate cancer (Platz et al. 2008, 2009; Kitahara et al. 2011; Shafique et al. 2012). Furthermore, there are several shared genetic risk loci for lipid levels and prostate cancer (Andreassen et al. 2014). The associations between the lipid-lowering class of drugs, statins, has been investigated and consistently suggest an inverse association for advanced disease. The first study was in HPFS, and found the RR of statin users versus nonusers was 0.39 (95% CI:

0.19–0.77) for advanced prostate cancer (Platz et al. 2006). A meta-analysis undertaken in 2012 reported a pooled RR for statin use of 0.93 (95% CI: 0.87–0.99) for total and 0.80 (95% CI: 0.70–0.90) for advanced prostate cancer (Bansal et al. 2012). Six epidemiological studies have been conducted subsequently, all supporting an inverse association between statin use and lethal prostate cancer (Nielsen et al. 2012; Geybels et al. 2013; Margel et al. 2013; Grytli et al. 2014). Among 11,000 prostate cancer patients in the United Kingdom, men who were on postdiagnostic statins had a 34% (95% CI: 0.66–0.88) lower risk of prostate cancer death (Yu et al. 2014). Moreover, the effect was also stronger among men using statins before diagnosis. A retrospective study showed that, during ADT, men using statins experienced longer time-to-progression compared with those not using statins (Harshman et al. 2015). Findings from an in vitro study show statins may act through pathways that decrease available androgen in the tumor (Harshman et al. 2015). Additional studies are needed to elucidate the relevant etiological window as well as identify mechanisms of association.

FUTURE RESEARCH

As discussed in the previous sections, several modifiable risk factors hold promise in reducing risk of aggressive prostate cancer or progression of the disease. To better understand disease heterogeneity, an emerging area of research is the molecular characterization of prostate cancer tumors. A study in The Cancer Genome Atlas showed that most prostate tumors could be classified into seven molecular subtypes based on presence of gene fusions or mutations (Abeshouse et al. 2015). Moreover, growing evidence suggests that prostate tumors defined by molecular features share unique etiology and risk factors (Pettersson et al. 2013). Differences in risk factor associations by prostate cancer phenotype —based on clinical, molecular, or genetic features—could have profound implications for prevention. Future studies should aim to expand and integrate this knowledge to develop targeted interventions that maximize benefit to prostate cancer patients. Furthermore, an improved understanding of underlying biological mechanisms may open the door to identification of biomarkers of susceptibility or early disease.

As highlighted in this review, epidemiologic studies of prostate cancer pose unique methodological challenges. Future studies of prostate cancer epidemiology should focus on clinically relevant prostate cancer, with particular consideration of high-grade and advanced-stage or fatal disease. Additionally, epidemiologic studies of prostate cancer should be designed with consideration of potential biases specific to this disease. For example, the ascertainment of information on PSA screening is required to provide adequate adjustment and avoid potential detection bias.

SUMMARY

Prostate cancer epidemiology is complex, in part because of the biological heterogeneity of the disease as well as PSA screening. Prevention of prostate cancer is challenging given that established risk factors, including age, race/ethnicity, family history, and genetic variants, are primarily nonmodifiable. Smoking cessation, regular exercise, and maintaining healthy weight are important public health targets for intervention. Importantly, several lifestyle modifications may lower risk of developing more aggressive cancer or offer survival benefits to prostate cancer patients. Future research has potential to improve efficacy of these prevention strategies through targeted interventions.

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