Epidemiology and Prevention of Prostate Cancer

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2.1 Historical Facts on Prostate Cancer (Marx and Karenberg 2010; Josef and Karenberg 2009; Androutsos 2005)

The first knowledge of the prostate as an anatomic entity dates back to the third century BC, when *Herophilus of Chalcedon* (*c. 330–260 BC*) first described the anatomical features of the prostatic gland as we know it today.

In 1817, *George Langstaff* (*1780–1846*), a London physician, provided the first genuine description of prostate cancer to appear in the medical literature. Later that same century, the French surgeon *Stanislas Tanchou* observed that only 5 of 9,118 cancer deaths in Paris from 1830 to 1840 were due to prostate cancer. *John Adams* (*1806–1877*), a surgeon at the London Hospital, described in 1853 the first case of prostate cancer established by histological examination. Adams noted in his report that this condition was "a very rare disease" and also stated, "…of the treatment, unfortunately, little of a satisfactory nature can be said".

The works of the English urologist *Sir Henry Thompson* (*1820–1904*), collected in his book "Bladder Tumors", were for over 40 years the most important reference in terms of urological pathology. He was the first to identify that cancerous cells in

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urine were associated with a positive diagnosis of cancer. In 1859 he was awarded the *Jackson Prize* by the Royal College of Surgeons of England for his contribution to the understanding of the prostate's anatomy, physiology, pathology, and cancer.

In 1867, a German-Austrian surgeon, *Christian Albert Theodor Billroth* (*1829–1894*), performed the first perineal prostatectomy for prostate cancer, and from then on, numerous surgical techniques for the prostatic surgery appeared, drastically reducing mortality rates for these types of interventions. *Billroth* also described several surgical procedures not only for urological diseases but for digestive and gynaecological disorders.

A British surgeon, Arthur *Ferguson McGill* (*1850–1890*), performed in 1867 the first suprapubic prostatectomy, reaching in a few years 37 cases with promising results. A few years later, the North American surgeon *William Belfield* (*1856–1929*) provided some interesting new surgical approaches for prostate cancer, having reached in 1890 up to 80 cases with low complication rate.

The North American surgeon *Hugh Hampton Young* (*1870–1945*) was the last of the nineteenth century's celebrities to contribute to the urological field. He is considered the pioneer of modern urology, having introduced numerous surgical procedures and devices, like "the punch", a type of urethroscope with an inner cutting steel tube, which gained wide acceptance among the urological community. In 1904 he performed the first radical prostatectomy for prostate cancer in the John Hopkins Hospital. He was recognized not only as an extraordinary and innovative surgeon but also as a world authority on the treatment of prostate cancer.

At the turn of the twentieth century, one of the treatments developed for not only prostate cancer but cancer in general was that of radiation therapy. Radium implants were used in the early twentieth century to treat prostate cancer, and this is the first form of radiation treatment used in prostate cancer history.

External beam radiation became more popular as stronger radiation sources became available in the middle of the twentieth century. Brachytherapy with implanted seeds was first described in 1965.

Another important development in the world of prostate cancer history came from the Canadian physician and physiologist *Charles Brenton Huggins* (*1901–1997*). In 1941, he published studies in which he used oestrogen to oppose testosterone production in men with metastatic prostate cancer. Huggins was awarded the Nobel Prize in physiology and medicine for this discovery of the effects of "chemical castration" in 1966. This led to the development of other hormone treatments for prostate cancer and other hormone-treatable cancers. Two of the most common hormone treatments used today are leuprolide and goserelin; these developments began in the late 1970s with the discovery of the neurohormone GnRH by both a Polish-born American endocrinologist *Andrzej Viktor Schally* (*1926–*) and a French-born American biologist *Roger Guillemin* (*1924–*), who won the Nobel Prize in medicine for their work in 1977. Today hormone therapy remains the mainstay for systemic treatment of advanced prostate cancer. New discoveries on the resistance mechanisms to castration have led to the discovery of newer drugs such as abiraterone, a steroid synthesis inhibitor, and MDV3100, a new antiandrogen.

At the same time, the various methods of radiation therapy and chemotherapy also continued to develop.

Systemic chemotherapy for prostate cancer was first studied in the 1970s. The initial regimen of cyclophosphamide and 5-fluorouracil was quickly joined by multiple other regimens of systemic chemotherapy drugs.

Unlike many other forms of cancer, prostate cancer does not respond well to chemotherapy alone. Chemotherapy is, however, used in conjunction with hormone therapy and other medications. In 1996, the FDA approved mitoxantrone on the basis of its palliative effect becoming the first chemotherapeutic drug used in combination with steroids to fight hormone refractory prostate cancer. In 2004, the FDA approved docetaxel (Taxotere) along with prednisone steroids for prostate cancer that did not respond to hormone therapy anymore.

Recently new hormonal and chemotherapeutic agents have been approved for the management of castration-resistant prostate cancer (CRPC) including abiraterone and cabazitaxel. It has also been shown that vaccine therapy for prostate cancer is feasible, leading to the introduction of sipuleucel-T.

In the surgical field, radical retropubic prostatectomy (RRP) was developed for the first time in 1983 by Patrick Walsh. This surgical approach allowed removal of the prostate with preservation of both continence and erectile function, thanks to the preservation of neurovascular bundles.

Over the last decade, open surgery for the prostate is gradually being substituted with laparoscopic and robotic surgery.

New technologies are continually developing for the treatment of prostate cancer, with the promise to offer patients minimally invasive therapies in which cancer is eradicated (e.g. focal therapy), while normal physiological functions are maintained after treatment.

2.2 Epidemiology of Prostate Cancer

2.2.1 Incidence and Mortality

Cancer of the prostate (PCa) is now recognized as one of the most important medical problems facing the male population, being the most frequently diagnosed cancer in men. Furthermore, PCa is currently the second most common cause of cancer death in men (Jemal et al. 2011).

In Europe, PCa is the most common solid neoplasm, with an incidence of 370,733 cases, 21.8 % of the total (12 % of all male cancers), according to data of the *International Agency for Research on Cancer* (Ferlay et al. 2010; Bray et al. 2010) (Figs. 2.1 and 2.2).

In the United States (US), an estimated 240,890 new cases of prostate cancer will occur during 2011 (Fig. 2.2). For reasons that remain unclear, incidence rates are significantly higher in African-Americans than in whites (Fig. 2.3).

Incidence rates for prostate cancer changed substantially between the mid-1980s and mid-1990s, in large part reflecting changes in prostate cancer screening with the prostate-specific antigen (PSA) blood test. Since 1998, incidence rates have remained relatively stable (Jemal et al. 2011).

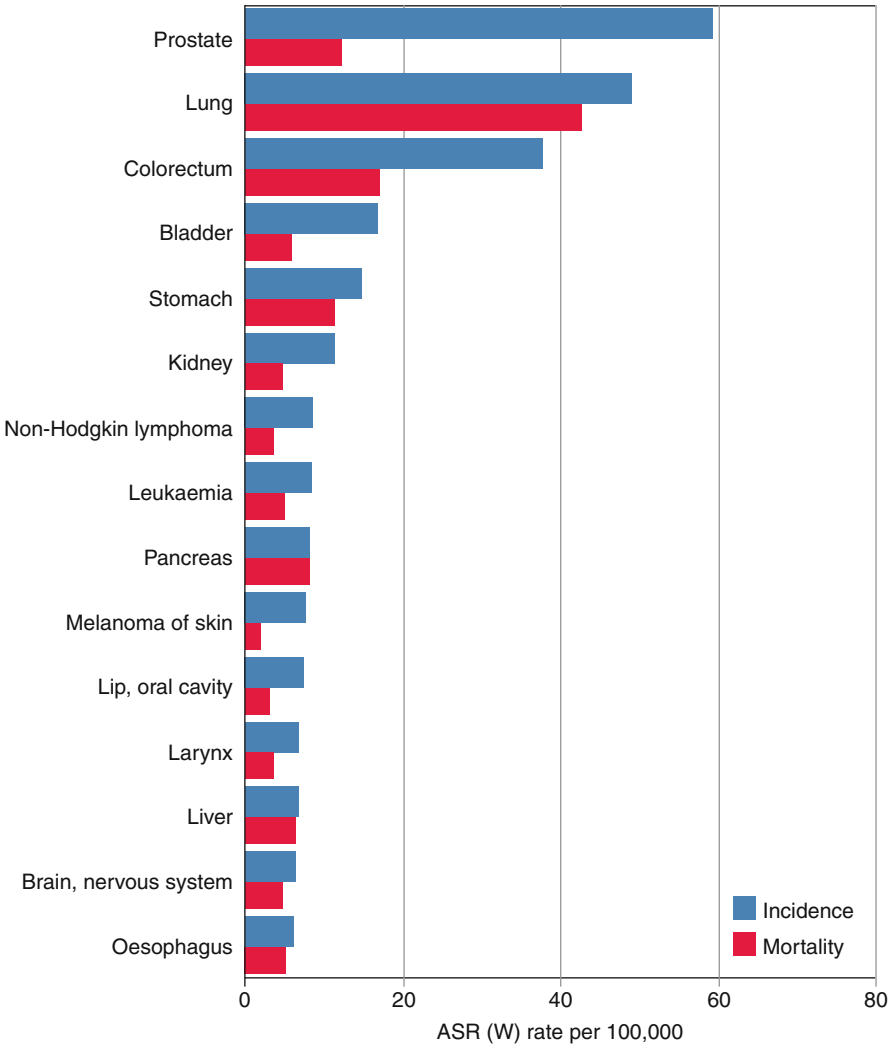


Fig. 2.1 Incidence and mortality for major cancer types

Prostate cancer affects elderly men more often than young men. It is therefore a bigger health concern in developed countries with their greater proportion of elderly men. Thus, in developed countries about 15 % of male cancers are PCa compared to 4 % of in underdeveloped countries (Quinn and Babb 2002).

There are large regional differences in incidence rates of PCa, which vary by more than 25-fold worldwide; the highest rates are in Australia/New Zealand (104.2 per 100,000), Western and Northern Europe, and Northern America, partly due to the practice of prostate-specific antigen (PSA) testing and subsequent biopsy, having become widespread in those regions. Incidence rates are relatively high in

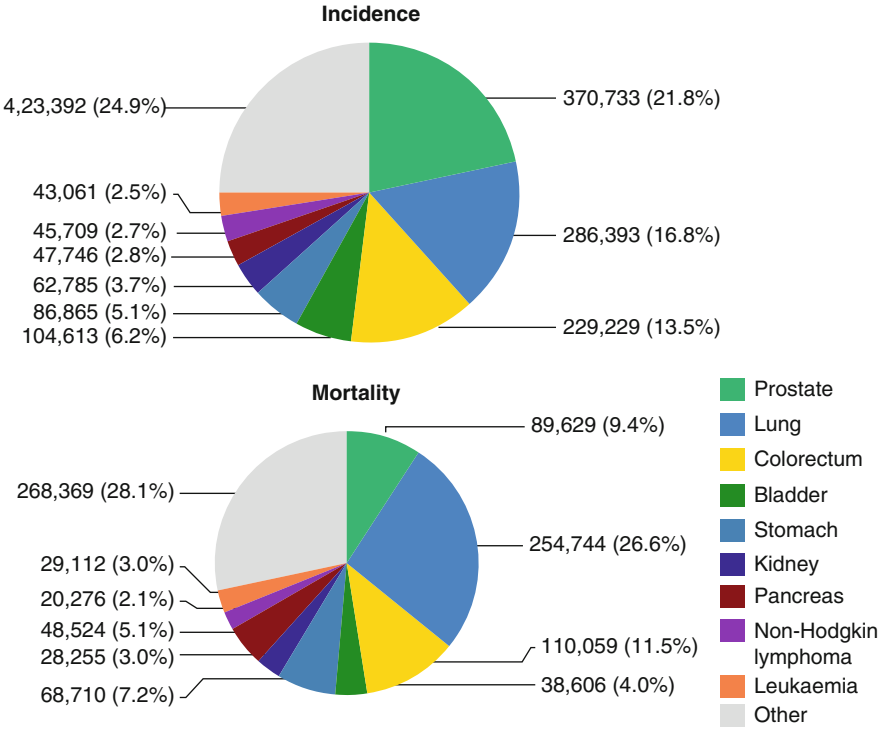


Fig. 2.2 Incidence and mortality for different types of cancer

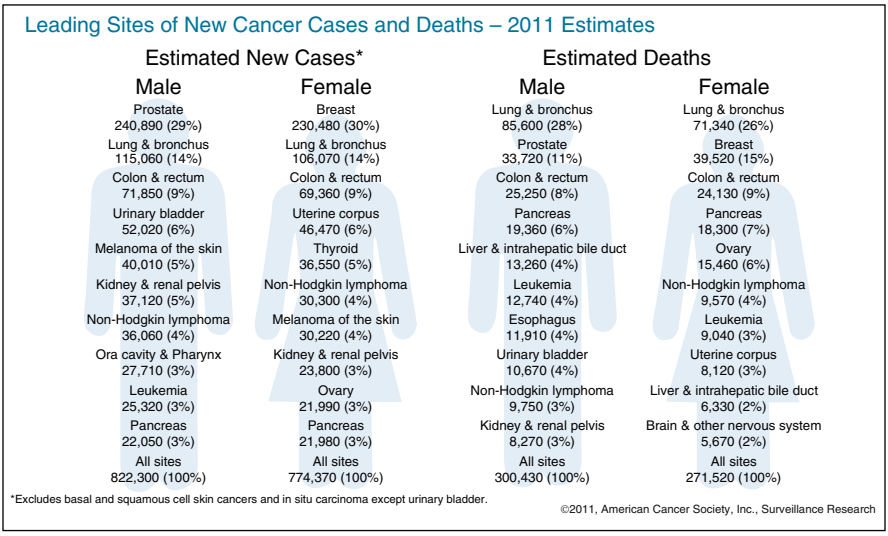


Fig. 2.3 Leading sites of new cancer cases and deaths per gender

Cancer Incidence and Mortality Rates* by Site, Race and Ethnicity, US, 2000–2004

Incidence	White	African American	Asian American and Pacific Islander	American Indian and Alaska Native†	Hispanic/ Latino‡§
All sites					
Males	556.7	663.7	359.9	321.2	421.3
Females	423.9	396.9	285.8	282.4	314.2
Breast (female)	132.5	118.3	89.0	69.8	89.3
Colon & rectum					
Males	60.4	72.6	49.7	42.1	47.5
Females	44.0	55.0	35.3	39.6	32.9
Kidney & renal pelvis					
Males	18.3	20.4	8.9	18.5	16.5
Females	9.1	9.7	4.3	11.5	9.1
Liver & bile duct					
Males	7.9	12.7	21.3	14.8	14.4
Females	2.9	3.8	7.9	5.5	5.7
Lung & bronchus					
Males	81.0	110.6	55.1	53.7	44.7
Females	54.6	53.7	27.1	36.7	25.2
Prostate	161.4	255.5	96.5	68.2	140.8
Stomach					
Males	10.2	17.5	18.9	16.3	16.0
Females	4.7	9.1	10.8	7.9	9.6
Uterine cervix	8.5	11.4	8.0	6.6	13.8

Mortality	White	African American	Asian American and Pacific Islander	American Indian and Alaska Native†	Hispanic/ Latino‡§
All sites					
Males	234.7	321.8	141.7	187.9	162.2
Females	161.4	189.3	96.7	141.2	106.7
Breast (female)	25.0	33.8	12.6	16.1	16.1
Colon & rectum					
Males	22.9	32.7	15.0	20.6	17.0
Females	15.9	22.9	10.3	14.3	11.1
Kidney & renal pelvis					
Males	6.2	6.1	2.4	9.3	5.4
Females	2.8	2.8	1.1	4.3	2.3
Liver & bile duct					
Males	6.5	10.0	15.5	10.7	10.8
Females	2.8	3.9	6.7	6.4	5.0
Lung & bronchus					
Males	72.6	95.8	38.3	49.6	36.0
Females	42.1	39.8	18.5	32.7	14.6
Prostate	25.6	62.3	11.3	21.5	21.2
Stomach					
Males	5.2	11.9	10.5	9.6	9.1
Females	2.6	5.8	6.2	5.5	5.1
Uterine cervix	2.3	4.9	2.4	4.0	3.3

*Per 100,000, age adjusted to the 2000 US standard population. †Data based on Contract Health Service Delivery Areas (CHSDA), 624 counties Comprising 54% of the US American Indian/Alaska Native population: for more information, please see: Espey DK, Wu XC, Swan J, et al. Annual report to the nation on the status of cancer, 1975–2004, featuring cancer in American Indians and Alaska Natives. ‡Persons of Hispanic/Latino origin may be of any race. §Data unavailable from the Alaska Native Registry and Kentucky. ¶Data unavailable form Minnesota, New Hampshire, and North Dakota.

Source: Ries LAG, Melbert D. Krapcho M. et al (eds.). *SEER Cancer Statistics Review, 1975–2004*, National Cancer Institute, Bethesda, MD, www.seer.cancer.gow/csr/1975_2004/, 2007.

American Cancer Society, Surveillance Research, 2008

Fig. 2.4 Cancer incidence and mortality rates by site, race and ethnicity

certain developing regions such as the Caribbean, South America, and sub-Saharan Africa. The lowest age-standardized incidence rate is estimated in South Central Asia (4.1 per 100,000) (Figs. 2.4 and 2.5).

Incidence has been uniformly increasing in most of the European countries, although in a few of them (Sweden, Finland, and the Netherlands), incidence has begun to fall during the last 3–4 years. Incidence rates were highest in Ireland,

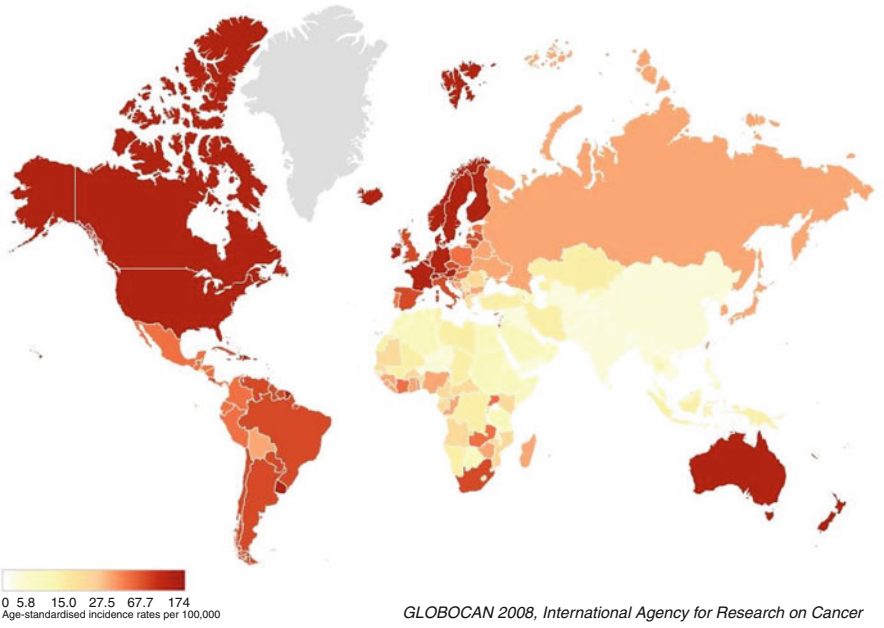


Fig. 2.5 Global differences in the incidence of prostate cancer

France, Belgium, and Northern European countries (Norway, Sweden, Iceland, and Finland). Rates were lower in a range of Central, Eastern, and Southern European countries, including Turkey, Greece, Romania, and Bulgaria. At least part of the fivefold difference between countries with the highest and lowest incidence rates is due to under-registration of prostate cancer in some countries as well as the use of sensitive diagnostic tests for early detection in others (Ferlay et al.2010) (Fig. 2.6).

Prostate cancer is currently the second most common cause of cancer death in men (Jemal et al. 2011). Because PSA testing has a much greater effect on incidence than on mortality, there is less variation in mortality rates worldwide (tenfold) than is observed for incidence (25-fold), and the number of deaths from prostate cancer is almost the same in developed and developing regions. Mortality rates are generally high in predominantly black populations (Caribbean, 26.3 per 100,000 and sub-Saharan Africa, 18–19 per 100,000), very low in Asia (e.g. 2.5 per 100,000 in Eastern Asia), and intermediate in Europe and Oceania (Jemal et al. 2011) (Fig. 2.7).

Mortality rates increased slowly for most countries between 1985 and 1995 (Quinn and Babb 2002). The CONCORD study (Coleman et al. 2008), a worldwide population-based analysis of cancer survival in five continents, analysed international differences in survival for breast, colorectal, and prostate cancer. Using data from cancer registries, age-standardized 5-year survival rates were found to vary greatly, ranging from 80 % or higher in the United States (92 %), Australia, and Canada to less than 40 % in Denmark, Poland, and Algeria (Coleman et al. 2008).

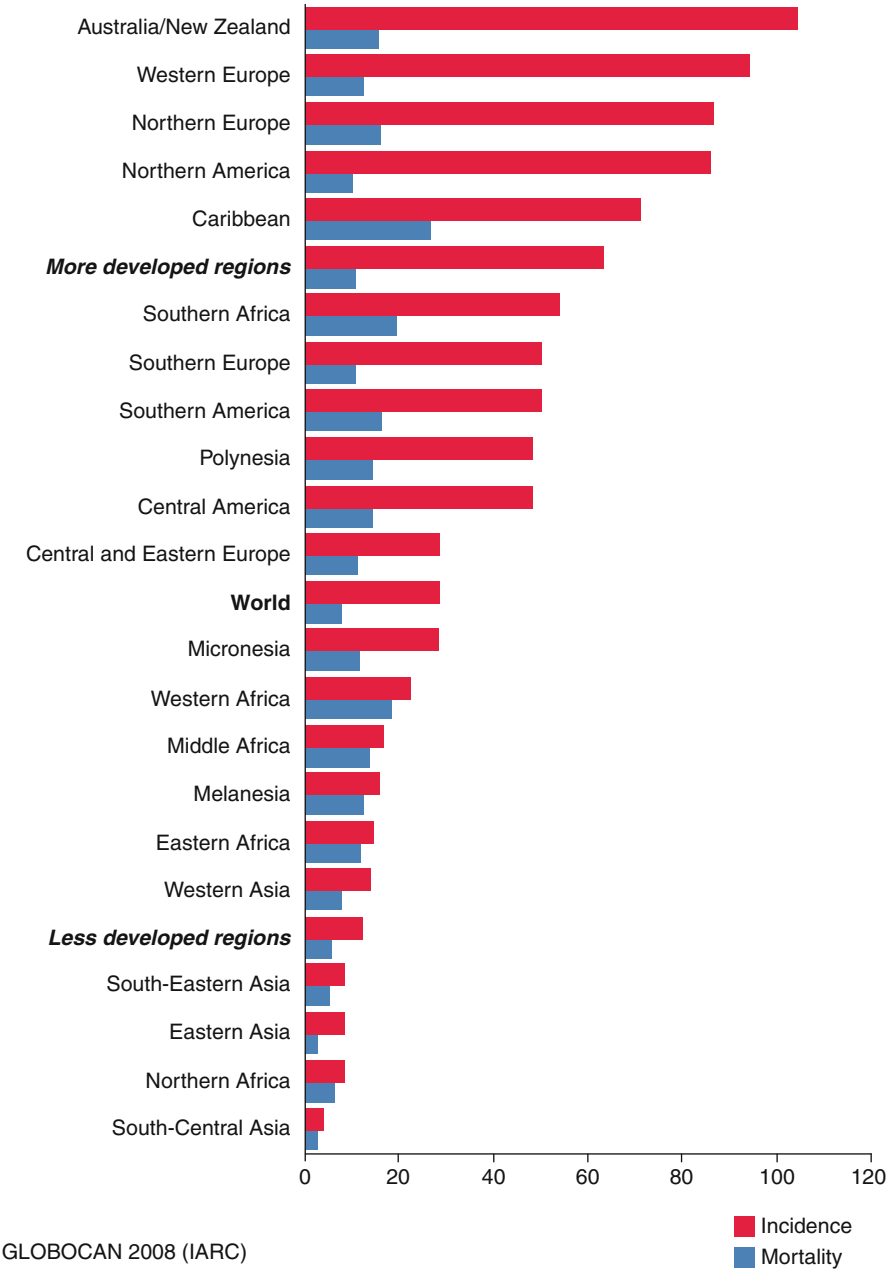
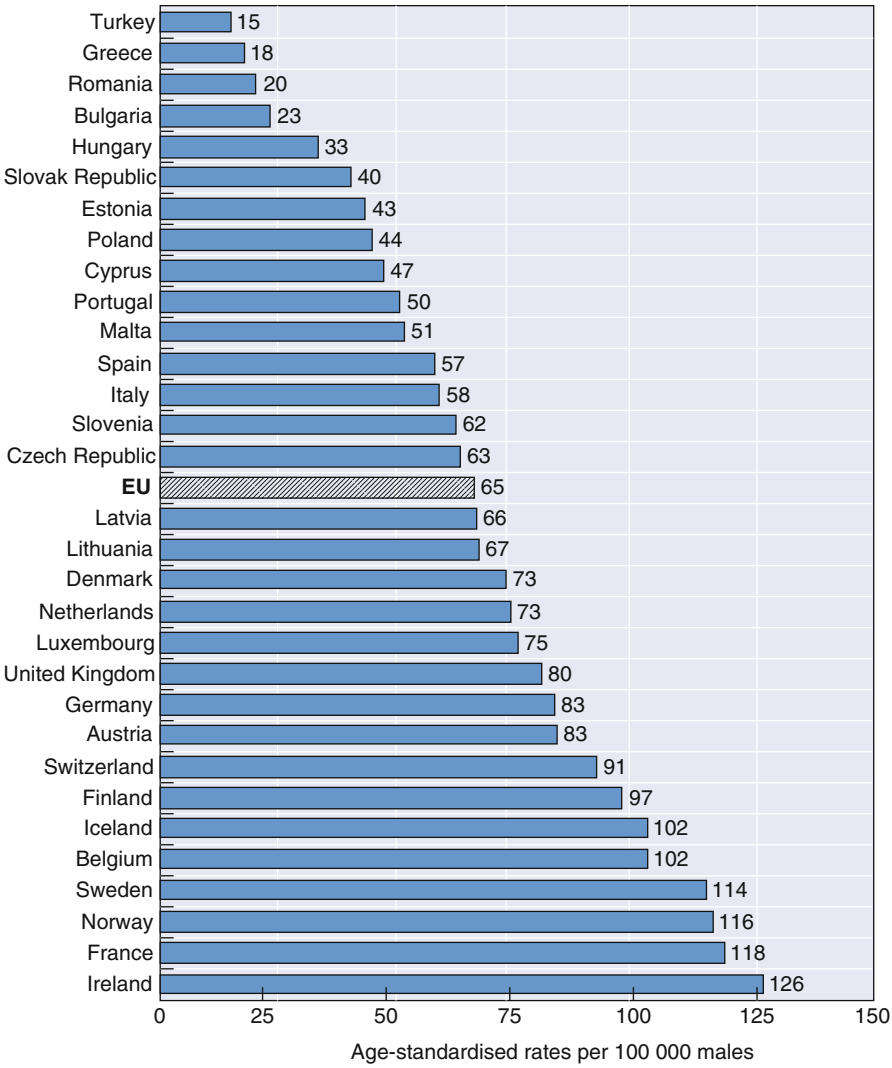


Fig. 2.6 Regional differences in the incidence and mortality of prostate cancer

Possible explanations for the worldwide and ethnic variations in prostate cancer incidence and mortality could be due to the access and quality of health care, the accuracy of cancer registries, and the PSA screening performance.



Source: OECD Health Data 2010; Ferlay et al. (2010).
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Fig. 2.7 Differences in the incidence of prostate cancer among European countries

In the USA, with an estimated 33,720 deaths in 2011, prostate cancer is the second leading cause of cancer death in men (Fig. 2.8). Prostate cancer death rates have been decreasing since the mid-1990s in both African-Americans and whites. Although death rates have decreased more rapidly among African-American than white men, rates in African-Americans remain more than twice as high as those in whites (Jemal et al. 2011) (Fig. 2.3).

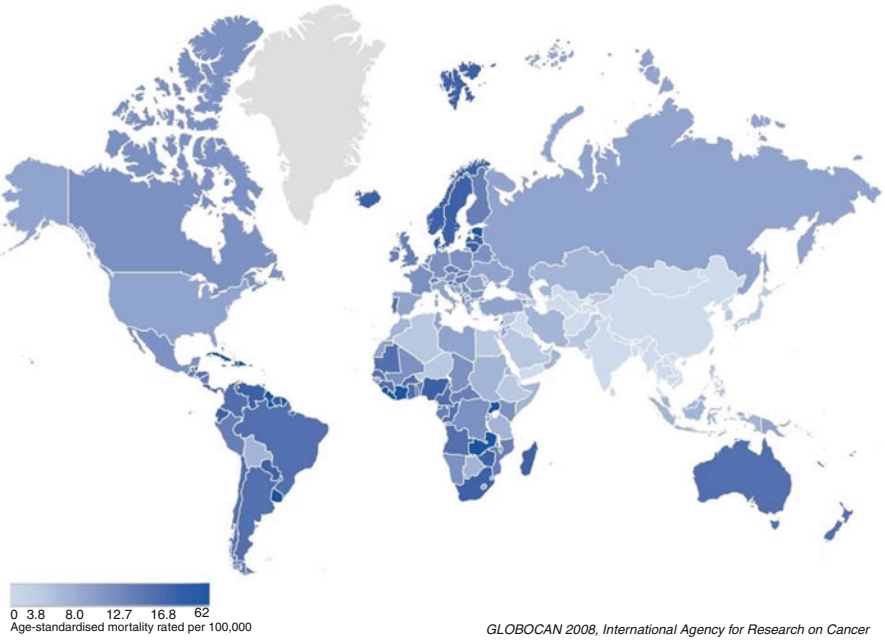

Fig. 2.8 Global differences in the mortality of prostate cancer

In Europe, the highest prostate cancer mortality rates were observed in the Baltic region (Estonia, Latvia, and Lithuania) and in the Nordic countries (Denmark, Norway, and Sweden). Mortality rates have been decreasing in many European countries, predominantly since the mid-1990s, and mostly in higher-resource countries in Western Europe (e.g. Great Britain, France, Germany, and the Netherlands) and the Nordic countries (e.g. Finland and Norway). Mortality increased in several Eastern European countries (including several former Soviet countries) in stark contrast to the decline observed in Hungary and the Czech Republic. Thus, a substantial heterogeneity can be seen across populations. While it is likely that there are geographical and temporal variations in the quality of reporting of the underlying cause of death in Europe, regional patterns emerge, with downward turns in several Western, Northern, and, lately, Eastern European countries.

There appears however little relation between the increasing incidence and decreasing mortality in the recent past, consistent with an effect of over-diagnosis or detection of indolent tumours via PSA testing. In contrast, uniformly increasing mortality trends persist in a number of Central and Eastern European countries, other than the Czech Republic and Hungary. It remains unclear as to what extent such trends reflect true changes in risk or are a result of increasing detection of latent disease (Bray et al. 2010) (Fig. 2.9).

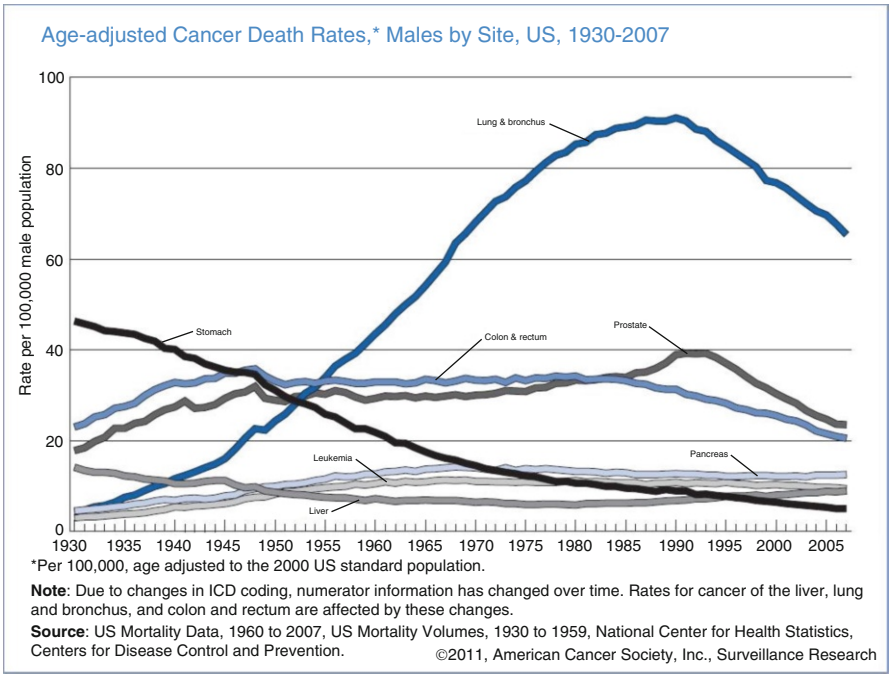

Fig. 2.9 Age-adjusted cancer death rates by site

2.2.2 Effect of PSA-Based Screening on Mortality

The benefit of PSA-based screening on overall mortality remains one of the hottest and most intensively debated topics in modern urology.

Recently, the results of two large randomized trials assessing the effect of PSA screening on prostate cancer mortality were published (Djavan 2011).

The first examined results from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and reported on 76,693 men aged 55–74 years at 10 US centres receiving either annual screening or usual care (Strope and Andriole 2010). After 7 years of follow-up, no difference in prostate cancer mortality was detected between the groups, with an incidence of 2.0 deaths per 10,000 person-years (50 deaths) in the screening group and 1.7 deaths per 10,000 person-years (44 deaths) in the control group (rate ratio = 1.13; 95 % CI = 1.16–1.29). The data at 10 years were 67 % complete and consistent with these overall findings. The PLCO project team concluded that PCa-related mortality was very low and not significantly different between the two study groups.

The second trial, the European Randomized Study of Screening for Prostate Cancer (ERSPC), included 162,243 men between the ages of 55 and 69 years randomized to either PSA screening every 4 years or no screening (Schroder 2008). After a median follow-up of 9 years, screening reduced the rate of death from

prostate cancer by 20 % (rate ratio = 0.80; 95 % CI = 0.65–0.98). The cumulative incidence of PCa was 8.2 % in the screened group and 4.8 % in the control group. The absolute risk difference was 0.71 deaths per 1,000 men. However, they estimated that to prevent one prostate cancer death, one would need to screen 1,410 men (95 % CI = 1,142–1,721) and treat 48 additional cases of prostate cancer. The ERSPC investigators concluded that PSA-based screening reduced the rate of death from PCa by 20 % but was associated with a high risk of over-diagnosis.

Based on the results of these two large, randomized trials, most of the major urological societies concluded that at present widespread mass screening for PCa is not appropriate, primarily for two reasons: first, prostate cancer is an indolent disease with a very low cause-specific death rate and will only impact life expectancy in a minority of men; second, the morbidity of early detection (opportunistic screening) should be offered to a well-informed man, thus ensuring his compliance for PSA testing, DRE, and prostate biopsy.

Very recently the US Preventive Services Task Force has performed a review on the evidence for screening for prostate cancer and published a very negative recommendation: "Prostate-specific antigen-based screening results in small or no reduction in prostate cancer-specific mortality and is associated with harms related to subsequent evaluation and treatments, some of which may be unnecessary. Primary Funding Source: Agency for Healthcare Research and Quality" (Chou et al. 2011). This stressed the difficulty making recommendation for the individual and for the society.

2.3 Risk Factors

The factors that determine the risk of developing clinical PCa are not well known, although a few have been identified. There are three well-established risk factors for PCa: increasing age, ethnic origin, and heredity (Heidenreich et al. 2011). Nevertheless, several exogenous risk factors have been described that may be involved in the development of prostate cancer and include environmental factors, dietary intake, obesity and physical activity, smoking and alcohol consumption, vasectomy and sexual activity, and steroid hormones.

2.3.1 Age

Age is the strongest risk factor for prostate cancer. Prostate cancer is very rare before the age of 40, but the chance of having prostate cancer rises rapidly after age 50. The median age at diagnosis is 68 years, with 63 % diagnosed after the age of 65. At 85 years of age, the cumulative risk of clinically diagnosed prostate cancer ranges from 0.5 to 20 % worldwide, despite autopsy evidence of microscopic lesions in approximately 30 % of men in the fourth decade, 50 % of men in the sixth decade, and more than 75 % of men older than 85 years (Sakr 1999).

2.3.2 Race/Ethnicity

It has been accepted that there might be subtle biologic differences among populations, but disease-related differences observed between groups may be more likely due to environmental exposure, diet, lifestyle, and attitudes toward health care than of differences in genetic structure or function.

It is noteworthy that African-American men have the highest reported incidence of prostate cancer in the world, with a relative incidence of 1.6 compared with white men in the United States (Crawford 2003). Although African-Americans have experienced a greater decline in mortality than white men since the early 1990s, their death rates remain more than 2.4 times higher than whites.

On the other hand, prostate cancer occurs less often in Asian-American and Hispanic/Latino men than in non-Hispanic whites. The reasons for these racial and ethnic differences remain unclear (Fig. 2.3).

2.3.3 Heredity, Familial Aggregation, and Genetic Background

Prostate cancer seems to occur in some families, which suggests that in some cases there may be an inherited or genetic factor. The risk of developing prostate cancer is at least doubled when a first-line relative has PCa. If two or more first-line relatives are affected, the risk increases 5- to 11-fold (Kalish et al. 2000). A small subpopulation of individuals with PCa (about 9 %) has true hereditary PCa. This is defined as three or more affected relatives or at least two relatives who have developed early onset disease (55 years of age or younger), usually 6–7 years prior to spontaneous cases (Carter et al. 1992).

Scientists have found several inherited genes that seem to increase prostate cancer risk, but they probably account for only a small number of cases overall. Genetic testing for most of these genes is not yet available. Recently, some common gene variations have been linked to the risk of prostate cancer. Studies to confirm these results are needed to see if testing for the gene variants will be useful in predicting prostate cancer risk.

Some inherited genes raise the risk for more than one type of cancer. For example, inherited mutations of the *BRCA1* (17q21) and *BRCA2* (13q12) genes are the reason that breast and ovarian cancers are much more common in some families. Mutations in these genes may also increase prostate cancer risk in some men, with a cumulative risk of 30 % by 80 years of age, but they account for a very small percentage of prostate cancer cases (Gallagher et al. 2010).

Linkage studies have identified a number of candidate prostate cancer susceptibility genes, including *RNaseL* (hereditary prostate cancer-1 [*HPC1*] region, 1q23-25), *ELAC2* (*HPC2* region, 17p), and *MSR1* (8p22–23). Many other genetic loci and prostate cancer susceptibility genes have been more recently identified, and the list is continually growing (Simard et al. 2002).

To date, only limited information about the prostate cancer genetic background has been discovered. With the continued improvement in genetic technology, it is likely that the number of known susceptibility genes will increase.

2.4 Environmental Factors

It has been accepted that the environment also plays an important role in modulating prostate cancer risk around the world. As it was described before, the incidence of clinical PCa differs widely between different geographical areas, being high in the USA and Northern Europe and low in Southeast Asia (Quinn and Babb 2002). However, if Japanese men move from Japan to Hawaii, their risk of PCa increases; if they move to California, their risk increases even more, approaching that of American men. Japanese and Chinese men in the United States have a higher risk of developing and dying from prostate cancer than do their relatives in Japan and China (Hsing et al. 2000). It is important to note, however, that Asian-Americans have a lower prostate cancer incidence than white or African-American men, indicating that genetics still plays a role in determining prostate cancer predisposition.

2.4.1 Dietary Intake

It has been shown that prostate cancer incidence and mortality rates around the world correlate highly with the average level of fat consumption, especially for polyunsaturated fats (Bostwick et al. 2004). The Western diet, together with other lifestyle factors such as physical activity levels, may be a significant risk factor in the development of prostate cancer. The Western diet tends to be high in animal products and processed, refined foods, resulting in a high intake of saturated fats, processed polyunsaturated fats (such as the *trans* fats), and refined carbohydrates. In addition, the Western diet, usually high in meats, is often low in fresh vegetables, fruit, pulses, and whole grains, resulting in a low intake of fibre and phytonutrients that may protect against prostate cancer. Overall, the Western diet is often calorie dense but lacking in certain essential nutrients. Furthermore, meats and dairy products contain other constituents such as zinc (Zn) and calcium (Ca) that may affect prostate cancer risk. Some studies have suggested that men who consume a lot of calcium (through food or supplements) may have a higher risk of developing advanced prostate cancer. Most studies have not found such a link with the levels of calcium found in the average diet, and it is important to note that calcium is known to have other important health benefits (Butler et al. 2010). By contrast, in Far Eastern countries, e.g. Japan and China, where the incidence of prostate cancer is lower, the traditional diet is mainly plant-based and minimally processed or refined. Relatively small amounts of animal products accompany vegetables, fruit, and other plant foods, and overall the diet is lower in calories than the Western diet but is likely to contain greater amounts of certain essential nutrients. Particular foods that feature more heavily in a traditional Far Eastern diet may have an impact on prostate cancer risk including green tea, soy, and cruciferous vegetables (Bostwick et al. 2004).

2.4.2 Obesity and Physical Activity

Obesity has been suggested to be a risk factor for prostate cancer because of its common occurrence in middle-aged men and clear links to colon and breast cancer risk (Hsing et al. 2007). White fat in mammals serves not only as an important energy reservoir but also as an endocrine organ, with secretion of cytokines and agents with cytokine-like activity (tumour necrosis factor [TNF]-α, interleukin [IL]-1β, IL-6, IL-8, IL-10, transforming growth factor [TGF]-β), as well as their soluble receptors (Baillargeon and Rose 2006). Treatment of obesity through reduction in fat intake and increased exercise has been shown to reduce oxidative stress, suggesting that lifestyle modification could be important in reducing the risk of prostate cancer (Wright et al. 2007). Some studies have found that high levels of physical activity, particularly in older men, may lower the risk of advanced prostate cancer. More research in this area is needed (Nilsen et al. 2006).

Recently, large prospective studies, examining the association between obesity and prostate cancer risk by stage and/or grade at diagnosis, suggested that obesity was associated with a lower risk of low-grade disease but a greater risk of high-grade disease (Wright et al. 2007; Gong et al. 2006; Rodriguez et al. 2007). This could be related to detection bias given that the lower serum PSA usually associated to obese patients could lead to fewer prostate biopsies. An association has also been observed in obesity with higher serum estradiol, insulin, free IGF-1, and leptin levels and lower free testosterone and adiponectin levels, which have also been associated with more aggressive prostate cancer (Hsing et al. 2007).

2.4.3 Smoking

It has been suggested that smoking may increase the risk of death from prostate cancer (Daniell 2010). Nevertheless, a clear dose–response relationship has not been demonstrated and will need to be confirmed by further investigations.

2.4.4 Alcohol Consumption

Although initial studies suggested an association between alcohol intake and prostate cancer risk, to date, it has not been possible to determine an association between total alcohol intake and the incidence of prostate cancer, suggesting that alcohol does not contribute appreciably to the aetiology of this disease. The only noticeable exception goes to red wine: a population-based case–control study conducted in King County, WA (USA), pointed out that each additional glass of red wine consumed per week showed a statistically significant 6 % decrease in relative risk (OR = 0.94; 95 % CI = 0.90–0.98) and there was evidence for a decline in risk estimates across increasing categories of red wine intake (trend $P = 0.02$). No clear associations were seen for consumption of beer or liquor (Schoonen et al. 2005).

2.4.5 Vasectomy and Sexual Activity

Some earlier studies had suggested that men who underwent vasectomy, especially at an early age, had a higher risk for prostate cancer (Giovannucci et al. 1993). But most recent studies have not been able to find a strong association between vasectomy and prostate cancer (Dennis et al. 2002a; Cox et al. 2002). The biologic mechanism by which vasectomy might predispose to cancer is unknown, although presence of antisperm antibodies, decreased seminal androgen concentrations, or secretory activity have been proposed.

Studies have also suggested a protective association between prostate cancer and frequency of ejaculation; the existence of a protective effect existed for men in their 20s and 40s, when a reported frequency greater than or equal to 21 ejaculations per month was found (Giles et al. 2004; Leitzmann et al. 2004). The biologic basis for this effect is not known.

2.4.6 Infection and Prostate Cancer

It has been suggested that the association between sexual activity and the exposure to sexually transmitted infections (HPV, gonorrhoea, or Chlamydia), possibly by leading to prostatic inflammation, may increase the risk of developing prostate cancer (Nelson et al. 2004).

Two meta-analyses examining 34 case–control studies reported statistically significant associations of prostate cancer with a history of sexually transmitted infection (RR = 1.4) or prostatitis (OR = 1.57) (Dennis et al. 2002b). Supportive evidence is provided by studies demonstrating positive associations of antibodies against syphilis, human papillomavirus (HPV), and human herpesvirus-8 (HHV-8) with prostate cancer (De Marzo et al. 2007). However, recent studies assessing the association between infection and prostate cancer have shown mixed results (Sutcliffe et al. 2006; Sarma et al. 2006). To date, no firm conclusions have been reached and further investigations are needed.

2.4.7 Steroid Hormones

Androgens play an important role in prostate carcinogenesis, as supported by the historical observation that the majority of prostate cancers initially respond to androgen-deprivation therapy and more recently by results of the Prostate Cancer Prevention Trial, which indicated that inhibition of the conversion of testosterone to the more potent dihydrotestosterone by finasteride reduces the incidence of prostate cancer by approximately 25 % (Thompson et al. 2007). High serum androgen levels have long been hypothesized to be a risk factor for prostate cancer. However, studies examining this association have been inconsistent, with some studies finding an association between specific hormones and prostate cancer risk.

Estrogens have been postulated to play a role in prostate cancer initiation and progression. Historically, estrogens have been considered protective against prostate cancer and have been used as a treatment for advanced disease. However, there is increasing evidence that estrogens may act as procarcinogens in the prostate (Dorgan et al. 1998). However, the association between serum oestrogen levels and prostate cancer risk is still inconsistent.

Leptins, peptide hormones produced by adipocytes which contribute to body weight and fat deposits, may be associated with development of prostate cancer by stimulation of androgen-independent prostate cancer cell lines (Ribeiro et al. 2004).

An association has been suggested between vitamin D and the risk of the development of prostate cancer. Lower serum vitamin D levels could be related to higher risk of prostate cancer (Giovannucci 1998). On the other hand, prostate cancer cells express the vitamin D receptor, and several studies have demonstrated an antiproliferative effect of vitamin D on prostate cancer cell lines (Chen and Holick 2003). All these findings need further investigations.

2.5 Prevention of Prostate Cancer

It has been accepted that carcinogenesis occurs slowly during a prolonged interval, from precursor lesions to the development of malignant cells. Theoretically, this provides the opportunity to intervene before malignancy is established, through lifestyle changes (dietary alterations, smoking cessation, exercise) or by chemoprevention, defined as the use of natural or synthetic agents that reverse, inhibit, or prevent the development of cancer (Boyle and Severi 1999). Effective chemoprevention requires the use of non-toxic agents that inhibit specific molecular steps in the carcinogenic pathway (Boyle and Severi 1999). As PCa is extremely common and generally slow to progress, it is regarded as an ideal candidate for chemoprevention. At present, the 5-alpha-reductase inhibitors finasteride and dutasteride have been identified as preventive agents. Today, chemopreventive agents may be appropriate for high-risk patients like those with high-grade prostatic intraepithelial neoplasia (PIN) and other high-risk groups such as patients with elevated prostate-specific antigen (PSA) and negative biopsy, rapid PSA velocity, and a family history of PCa. Although larger randomized controlled studies are needed and epidemiologic evidence should be placed in a clinical context, physicians must be aware of these preventive opportunities in PCa care (Van and Tombal 2011).

Numerous observations in the epidemiologic literature during the last years suggest associations between various dietary, lifestyle, genetic, and nontraditional factors and the risk for developing prostate cancer. Several randomized studies for prevention of PCa with pharmaceutical agents, dietary modifications, and supplements have been published. Some of the most promising dietary nutrients and supplements as well as the most important clinical studies on their effect on PCa are summarized in this review.

2.5.1 Prostate Cancer Prevention Trial

The most significant event in chemoprevention of prostate cancer occurred with the publication of the results of the Prostate Cancer Prevention Trial (PCPT) (Thompson et al. 2003a). This study, carried out in 1993, was the first large-scale population-based trial to test a chemopreventive strategy in men at risk for prostate cancer. The PCPT study was designed on the theoretical basis that androgens are required for the development of prostate cancer and men with a congenital deficiency of type 2 5α-reductase are unaffected by benign prostatic hyperplasia (BPH) and prostate cancer. Hypothetically, treatment with finasteride would lower intraprostatic DHT levels and thereby prevent prostate cancer. In this study, 18,882 men older than or equal to 55 years of age with a normal digital rectal examination (DRE) and a prostate-specific antigen (PSA) level of less than or equal to 3.0 ng/mL were randomly assigned to treatment with finasteride (5 mg/day) or a placebo for 7 years. Prostate biopsy was recommended if the annual PSA level, adjusted for the effect of finasteride, exceeded 4.0 ng/mL or if the DRE was abnormal. The primary endpoint was the prevalence of prostate cancer during the 7 years of the study, as diagnosed by either for-cause biopsies (abnormal DRE or PSA) or end-of-study biopsy. The results of the study were satisfactory, and the trial was stopped approximately 15 months early because the primary endpoint of a 25 % risk reduction on the finasteride arm was reached, and sensitivity analyses suggested that additional follow-up would not change that outcome.

The prevalence of prostate cancer was reduced by 24.8 % (hazard ratio [HR] = 0.75; 95 % CI = 18.6–30.6) from 24.4 to 18.4 % in those participants randomized to finasteride compared with placebo. The prevalence of Gleason grade 7–10 tumours was higher in the finasteride group than the placebo group (6.4 % vs. 5.1 %; HR = 1.27; 95 % CI = 1.07–1.50). The risk reduction associated with finasteride among risk groups was of the same general magnitude, but sexual side effects were more common with finasteride, whereas urinary symptoms were more common within the placebo group.

Deciding whether or not the advantages of taking finasteride outweigh the potential disadvantages is not a simple task. Several studies analysed the cost-effectiveness relation for chemoprevention with finasteride, but none suggested that it may be cost-effective in high-risk populations (Klein 2005; Unger et al. 2004; Zeliadt et al. 2005).

In addition to the prevention of prostate cancer, 5α-reductase inhibitors (5ARIs) have other benefits that need to be considered. Finasteride improves the sensitivity of PSA and DRE in prostate cancer screening (Thompson et al. 2006), decreases the risk of high-grade prostatic intraepithelial neoplasia (HR = 0.79; 95 % CI = 0.70–0.89), and may be effective in the treatment and possible prevention of chronic nonbacterial prostatitis (Thompson et al. 2007). Furthermore, benign prostatic hyperplasia (BPH) treatment trials in patients with moderate to severe lower urinary tract symptoms demonstrated reduction in symptom scores, reduction in the risk of acute urinary retention, and reduction in the risk of surgical intervention due to BPH progression (Wilt et al. 2008).

2.5.2 Other 5α-Reductase Inhibitors

A second large-scale trial of another 5ARI, dutasteride, was carried out in 2005. This agent inhibits both type 1 and type 2 forms of 5α-reductase, is anti-androgenic, promotes death of prostate cancer cell lines, and has been shown to reduce the risk of prostate cancer in men treated for lower urinary tract symptoms related to benign prostatic enlargement when compared with placebo (Andriole et al. 2004). The eligibility for the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial included men aged older than or equal to 50 and younger than or equal to 75 years who had PSA scores from 2.5 to 10 ng/mL, prostate volumes less than or equal to 80 cc, and one prior negative prostate biopsy within 6 months of enrolment, thus representing a group at high risk for cancer on subsequent biopsy (Andriole et al. 2004). The primary endpoint of REDUCE was the prevalence of cancer on study-mandated prostate biopsies performed at 2 and 4 years after entry. The trial recruited 8,231 men, of whom 6,726 (82.6 %) underwent at least one biopsy and 1,516 (22.5 %) were diagnosed with prostate cancer. Dutasteride reduced the risk of prostate cancer over 4 years by 23 % (857 in the placebo arm vs. 659 in the dutasteride arm, $P<0.0001$). Interestingly, no significant increase in Gleason sum 8–10 tumours was observed in the study (19 in the placebo arm vs. 29 in dutasteride arm, $P=0.15$). Preliminary analyses also suggested that dutasteride enhanced the utility of PSA as a diagnostic test for prostate cancer, demonstrated beneficial effects on BPH outcomes (relative risk reductions of 77 % for acute urinary retention and 73 % for BPH-related surgery), and was generally well tolerated (15 % drug-related adverse events in the placebo arm vs. 22 % in dutasteride arm). The fact that the results of REDUCE were congruent with those of the PCPT with respect to the magnitude of risk reduction, benefits for BPH endpoints, minimal toxicity, and no issues related to tumour grade suggests a class effect for 5 ARIs and that these agents should be used more liberally for prevention of prostate cancer (Musquera et al. 2008). In December 2010, the FDA's Oncologic Drugs Advisory Committee (ODAC) voted against recommending finasteride and dutasteride for the indication to reduce prostate cancer risk because in the view of the ODAC members, the risk for more aggressive tumours outweighed the potential for chemoprevention. Panelists and FDA reviewers shared three main concerns about the drugs: the risk of exposing currently healthy people to an increased risk for high-grade tumours, the fact that risk reduction was only in low-grade tumours, and the doubt that the supporting clinical studies are generalizable to clinical practice in the American population.

2.5.3 Selenium and Vitamin E

Selenium is an essential trace element found in vegetables, grains, red meat, fish, poultry, and eggs. The concentration of selenium in the vegetables depends on how much of the mineral was in the soil where the plants grew. Selenium is distributed in body tissues and helps to make special proteins, called antioxidant enzymes,

which play a role in preventing cell damage. Epidemiologic evidence provides support for a cancer prevention effect.

The strongest evidence for a protective effect of selenium came from the Nutritional Prevention of Cancer Trial, a randomized study of oral selenized yeast in patients with nonmelanoma skin cancer, which showed a 65 % reduction in the prostate cancer incidence when compared with the placebo (Clark et al. 1998). In that trial, 1,312 participants took the equivalent of 200 mcg yeast per day versus the placebo, and with a mean follow-up of 4.5 years, the incidence of prostate cancer was reduced in the selenium arm by 65 % compared with the placebo. Of note, the effect was strongest for those with a PSA value less than 4 ng/mL and those with the lowest serum selenium levels at study entry (Duffield-Lillico et al. 2003).

Vitamin E is an essential lipid-soluble antioxidant found in plant oils such as soy, corn, and olive oil. Other sources include nuts, seeds, and green leafy vegetables. It protects cells from free radicals. Several forms of vitamin E have been identified. The most active form with the highest bioavailability in human tissues is alpha-tocopherol. The body is not capable of producing this substance, and it must be consumed in the diet or supplements for proper health. Alpha-tocopherol may influence the development of cancer through several mechanisms, including induction of cell cycle arrest, and through direct antiandrogen activity (Thompson et al. 2003b). The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (ATBC), a randomized, placebo-controlled trial of α-tocopherol (50 mg/day) and beta-carotene (20 mg/day) alone or in combination in male smokers, with a primary endpoint of lung cancer incidence and mortality, on secondary analysis found a statistically significant 32 % reduction in prostate cancer incidence and a 41 % lower mortality in those receiving α-tocopherol (Albanes 2000).

2.5.4 Selenium and Vitamin E Cancer Prevention Trial (SELECT)

The accumulated epidemiologic and biologic evidence that selenium and vitamin E might prevent prostate cancer led to the design of SELECT, the Selenium and Vitamin E Cancer Prevention Trial (Klein et al. 2001; Lippman et al. 2009). SELECT was a phase III, randomized, double-blind, placebo-controlled, population-based trial designed to test the efficacy of selenium and vitamin E alone and in combination in the prevention of prostate cancer. It was the largest cancer prevention trial ever performed. Eligibility criteria include age greater than or equal to 50 years for African-Americans, age older than or equal to 55 years for whites, a DRE not suspicious for cancer, serum PSA less than or equal to 4 ng/mL, and normal blood pressure. Randomization was equally distributed among the four study arms (selenium + placebo, vitamin E + placebo, selenium + vitamin E, and placebo + placebo). Although the study duration was planned for 12 years, as a result of a planned interim analysis in August 2008, an independent data and safety monitoring committee recommended discontinuation of the study because the data demonstrated no effect on the risk of prostate cancer by either agent alone or in combination and no chance of a beneficial effect of the hypothesized magnitude

with continued supplementation (Lippman et al. 2009). There were statistically nonsignificant increased risks of prostate cancer in the vitamin E group (HR = 1.13; 99 % CI = 0.95–1.35; $P = 0.06$) and type 2 diabetes mellitus in the selenium group (RR = 1.07; 95 % CI = 0.94–1.22; $P = 0.16$). However, neither of these findings was observed in the combination group.

More mature results were published recently, reflecting the final data collected by the study sites on their participants on July 5, 2011. The final report includes 54,464 additional person-years of follow-up and 521 additional cases of prostate cancer since the primary report. Compared with the placebo (referent group) in which 529 men developed prostate cancer, 620 men in the vitamin E group developed prostate cancer (hazard ratio [HR] = 1.17; 99 % CI = 1.004–1.36; $P = 0.008$), as did 575 in the selenium group (HR = 1.09; 99 % CI = 0.93–1.27; $P = 0.18$) and 555 in the selenium plus vitamin E group (HR = 1.05; 99 % CI = 0.89–1.22; $P = 0.46$). Compared with placebo, the absolute increase in risk of prostate cancer per 1,000 person-years was 1.6 for vitamin E, 0.8 for selenium, and 0.4 for the combination (Klein et al. 2011).

This study therefore indicates that supplementation with vitamin E significantly increased the risk of prostate cancer among healthy men.

There are many attempts to explain the negative results of SELECT. The high dose of vitamin E (400 IU/D of the alpha-tocopherol form) in SELECT may have been less effective than a lower dose such as the eightfold lower 50 IU/D of the ATBC study (Lippman et al. 2009).

In SELECT, 200 μg of L-selenomethionine was chosen, whereas in the NPC trial, 200 μg of high-Se yeast contained only 20 % of L-selenomethionine (Duffield-Lillico et al. 2003). Another drawback of SELECT is the absence of selection of patients since it is likely that personal predispositions may enhance or hinder the benefit of supplementation. For example, several studies have suggested that vitamin E is more protective against PCa in smokers, and in SELECT less than 60 % of men were current or former smokers, whereas in the ATBC study all men were smokers. As for Se, genetic susceptibilities exist that may confer different benefit to Se supplementation. Chan et al. have assessed manganese superoxide dismutase (SOD2) gene variants and plasma Se in 489 patients with localized/locally advanced PCa (Chan et al. 2009). SOD2 is an endogenous mitochondrial enzyme that metabolizes reactive oxygen species and superoxide anions to oxygen and hydrogen peroxide. Several polymorphisms of SOD2 have been identified, including a single nucleotide permutation that encodes either an alanine (A) or a valine (V). SOD2 genotype alone was not associated with disease aggressiveness, whereas higher versus lower Se levels were associated with a slightly increased likelihood of presenting with aggressive disease (RR = 1.35; 95 % CI = 0.99–1.84). There was evidence of an interaction between SOD2 and Se levels such that among men with the AA genotype, higher Se levels were associated with a reduced risk of presenting with aggressive disease (RR = 0.60; 95 % CI = 0.32–1.12), whereas among men with a V allele, higher Se levels were associated with an increased risk of aggressive disease (for VV or VA men, RR = 1.82; 95 % CI = 1.27–2.61; P for interaction <0.007).

But clearly one of the more consistent hypotheses is that the positive effects of Se in the NPC study and of vitamin E in the ATBC trial could have been due to chance in secondary analyses. Recent results from the Prostate Cancer Prevention Trial found no significant association between vitamin E and Se and the incidence of PCa (Kristal et al. 2010).

2.6 Other Agents

2.6.1 Isoflavones

Isoflavones, a subclass of the flavonoids, are plant-derived compounds with weak estrogenic activity and therefore classified as phyto-oestrogens. Phyto-oestrogens have been suggested to have a preventive effect against various cancers. Soy foods are a rich source of isoflavones. Isoflavone intake in Asian countries is approximately 50 mg daily, which is about ten times higher than intake in Western countries. Migration studies and lower prostate cancer rates in Asian men with higher soy intake also support the role of soy as an anticancer agent.

The main isoflavones found in most soy products are genistein, daidzein, and glycitein. It has been suggested that these may inhibit benign and malignant prostatic epithelial cell growth, downregulate androgen-regulated genes, and reduce tumour growth in animal models (Castle and Thrasher 2002; Kurahashi et al. 2007; Lee et al. 2003). Also a protective effect of isoflavones against PCa development has been demonstrated. Among these effects, isoflavones possess weak oestrogen activity, inhibit tyrosine protein kinases, block angiogenesis, and reduce serum testosterone levels. They also inhibit 5-alpha-reductase, an enzyme that metabolizes testosterone to dihydrotestosterone. Isoflavones are further metabolized in humans to many different intermediates, such as equol, perhaps the best-studied metabolite of daidzein. Equol is ten times more potent than daidzein in retarding PCa growth (Lampe 2010).

Although there exists overwhelming data from epidemiologic studies, case–control studies, and in vitro/vivo data that soy isoflavone may be a promising chemopreventive agent against PCa, there have been no published prospective randomized clinical studies with sufficient statistical power to assess whether isoflavone supplementation can reduce PCa development or delay PCa progression. Shortcomings of many studies published to date are small patient numbers, lack of randomization, short-term isoflavone administration, and possibly insufficient doses. Current ongoing clinical trials may help us understand the role of soy in the prevention of PCa.

2.6.2 Lycopene

Lycopene is a carotenoid without vitamin A activity that gives the red colour to tomatoes and tomato-derived products. It is also available in other red fruits and vegetables such as red carrots, watermelons, pink grapefruit, and papayas. Lycopene

is a highly unsaturated acyclic isomer of β-carotene, is the predominant carotenoid in human plasma, and possesses potent antioxidant activity. Lycopene has been shown to inhibit the growth of benign and malignant prostatic epithelial cells in vitro, having shown anticancer properties (Etminan et al. 2004). There is epidemiologic evidence that consumption of tomato products or lycopene is associated with a lower risk of prostate cancer (Giovannucci et al. 2002). A meta-analysis of observational studies reported a 23 % reduction in prostate cancer risk with high tomato and lycopene intake (Etminan et al. 2004). However, nested case–control studies prospectively examined the intake of several tomato-containing foods in men and found no correlation with the incidence of prostate cancer (Giovannucci 2002). To date, results of initial clinical trials have demonstrated potential beneficial activity of lycopene in prostate cancer; however, further investigations and phase III trials examining the role of lycopene in prostate cancer prevention are required.

2.6.3 Polyphenols

Polyphenols are the largest group of constituents found in tea. Green tea contains catechins, a category of water-soluble polyphenolic substances. The four principal catechins are (−)-epicatechin (EC), (−)-epicatechin-3-gallate (ECG), (−)-epigallocatechin (EGC), and (−)-epigallocatechin-3-gallate (EGCG) (Boehm et al. 2009). EGCG, found in the highest concentration in green tea, is the most studied and most active of all green tea catechins

(GTC) for the inhibition of oncogenesis and reduction of oxidative stress. Its mechanism of action has not yet been fully determined. Several epidemiologic studies have focused on the lower incidence of PCa in Asian populations where green tea is consumed regularly as compared with Western populations, suggesting that green tea is protective against PCa. To date, various small randomized trials have been conducted with mixed results (Boehm et al. 2009; Adhami et al. 2009; Jian et al. 2004; Kikuchi et al. 2006; Kurahashi et al. 2008). Confirmatory trials are needed to better assess the role of green tea consumption in prostate cancer prevention.

2.6.4 Resveratrol

Because tumours develop resistance to chemotherapeutic agents, the cancer research community continues to search for effective chemosensitizers. One promising possibility is to use dietary agents that sensitize tumours to the chemotherapeutics. Resveratrol (3,5,4′-trihydroxystilbene), a natural stilbenoid present in red wine, grapes, berries, peanuts, and dietary supplements as well as polyhydroxy analogues of resveratrol have potential cancer chemopreventive properties. It has sensitization/enhancing activities against tumour cells when used in combination with standard cancer chemotherapeutics (Hsieh et al. 2011). It has been suggested that resveratrol can sensitize tumour cells to chemotherapeutic agents. The tumours

shown to be sensitized by resveratrol include lung carcinoma, acute myeloid leukaemia, promyelocytic leukaemia, multiple myeloma, prostate cancer, oral epidermoid carcinoma, and pancreatic cancer. The chemotherapeutic agents include vincristine, adriamycin, paclitaxel, doxorubicin, cisplatin, gefitinib, 5-fluorouracil, velcade, and gemcitabine. The chemosensitization of tumour cells by resveratrol appears to be mediated through its ability to modulate multiple cell-signalling molecules, including drug transporters, cell survival proteins, cell proliferative proteins, and members of the NF-kappa B and STAT3 signalling pathways. Overall, studies suggest that resveratrol can be used to sensitize tumours to standard cancer chemotherapeutics.

Recent findings strongly suggest that a suppressor of cytokine signalling (SOCS-3), an antiapoptotic molecule that is upregulated in PCa, is one of the proteins that influence the ability of resveratrol and tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) to cause programmed cell death in PCa (Hsieh et al. 2011; Horndasch and Culig 2011). Future studies should concentrate on the determination of molecular mechanisms of chemosensitization and of resveratrol combinations by clinically relevant in vivo studies and demonstration of safety and effectiveness of combinations in humans.

2.6.5 Statins

Statins are widely used cholesterol-lowering drugs given for the treatment and prevention of atherosclerotic cardiovascular disease. They inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), the rate-limiting enzyme in cholesterol biosynthesis. Statins are hypothesized to play a role in the prevention of cancer by inhibiting inflammation, angiogenesis, cell proliferation, migration/adhesion, invasion, and/or preferentially promoting apoptosis in tumour cells (Moyad 2005). Observational studies of statin use demonstrate high heterogeneity with mixed results for prostate cancer risk.

Hypothetically, some of the mechanisms that increase the risk of cardiovascular disease (CVD) may also increase the risk or progression of prostate cancer. Numerous recent lifestyle interventions that reduce cholesterol have also been found to have a potential impact on reducing the risk of prostate cancer. Recent studies of statins and other heart healthy agents have found a secondary potential for exhibiting a reduced risk or progression of prostate cancer. Statin users have been shown to have lower serum PSA levels than non-users (Papadopoulos et al. 2011), suggesting an anticancer effect but potentially leading to fewer prostate biopsies and thus biasing results of epidemiologic and clinical studies. Statin users tend to be healthier and more medically compliant than non-users, making them more likely to undergo PSA screening and possibly resulting in earlier cancer detection. Further research is needed to help determine the role, if any, of statins in the prevention of prostate cancer.

Conclusion

The prostate carcinogenesis is a complex process. All constitutional, behavioural, molecular, and environmental factors continuously interact in different proportions in the organism during the years, and their effects become manifest through the diagnosis of prostate cancer. Several clinical trials and epidemiological studies have been carried out around the world in order to achieve a better understanding of the prostate carcinogenesis and its circumstances.

Prostate cancer is an attractive target for chemoprevention because of its ubiquity, treatment-related morbidity, long latency between premalignant lesions and clinically evident cancer, and defined molecular pathogenesis. High-risk patients should be the target of chemoprevention, as the risk of PCa may justify the cost and potential side effects of these agents. It also seems reasonable to believe that chemoprevention strategies are more effective in high-risk groups. Nevertheless, the identification of high-risk groups is at this moment not easy. Patients with isolated HGPIN on prostate biopsies constitute a unique and well-demarcated risk group for PCa. Prognostic, randomized data on chemopreventive strategies in HGPIN are scarce but seem promising. Other high-risk groups include those above 40 years of age, elevated PSA levels, rapid PSA velocity, sub-Saharan African ethnicity, a family history of PCa or with specific genes, or obese men with insulin resistance and those who would benefit from early diagnosis and treatment with at least 10–15 years of life expectancy.

Future research should focus on determining the target population for PCa chemoprevention. Large prospective randomized studies are required to define the benefits of chemopreventive agents for PCa. Some of these studies are ongoing and results are eagerly awaited. Combinations of chemopreventive agents for PCa should be carefully investigated.

References

Adhami VM, Siddiqui IA, Sarfaraz S, Khwaja SI, Hafeez BB, Ahmad N et al (2009) Effective prostate cancer chemopreventive intervention with green tea polyphenols in the TRAMP model depends on the stage of the disease. Clin Cancer Res 15(6):1947–1953

Albanes D (2000) Prostate cancer: epidemiology and prevention. Nestle Nutr Workshop Ser Clin Perform Programme 4:55–62

Andriole GL, Roehrborn C, Schulman C, Slawin KM, Somerville M, Rittmaster RS (2004) Effect of dutasteride on the detection of prostate cancer in men with benign prostatic hyperplasia. Urology 64(3):537–541

Androutsos G (2005) Carcinoma of the prostate. A historical account. J BUON 10(1):135–144

Baillargeon J, Rose DP (2006) Obesity, adipokines, and prostate cancer (review). Int J Oncol 28(3):737–745

Boehm K, Borrelli F, Ernst E, Habacher G, Hung SK, Milazzo S et al (2009) Green tea (Camellia sinensis) for the prevention of cancer. Cochrane Database Syst Rev 3:CD005004

Bostwick DG, Burke HB, Djakiew D, Euling S, Ho SM, Landolph J et al (2004) Human prostate cancer risk factors. Cancer 101(10 Suppl):2371–2490

Boyle P, Severi G (1999) Epidemiology of prostate cancer chemoprevention. Eur Urol 35(5–6): 370–376

Bray F, Lortet-Tieulent J, Ferlay J, Forman D, Auvinen A (2010) Prostate cancer incidence and mortality trends in 37 European countries: an overview. Eur J Cancer 46(17):3040–3052

Butler LM, Wong AS, Koh WP, Wang R, Yuan JM, Yu MC (2010) Calcium intake increases risk of prostate cancer among Singapore Chinese. Cancer Res 70(12):4941–4948

Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC (1992) Mendelian inheritance of familial prostate cancer. Proc Natl Acad Sci USA 89(8):3367–3371

Castle EP, Thrasher JB (2002) The role of soy phytoestrogens in prostate cancer. Urol Clin North Am 29(1):71–81, viii–ix

Chan JM, Oh WK, Xie W, Regan MM, Stampfer MJ, King IB et al (2009) Plasma selenium, manganese superoxide dismutase, and intermediate- or high-risk prostate cancer. J Clin Oncol 27(22):3577–3583

Chen TC, Holick MF (2003) Vitamin D and prostate cancer prevention and treatment. Trends Endocrinol Metab 14(9):423–430

Chou R, Croswell JM, Dana T, Bougatsos C, Blazina I, Fu R et al (2011) Screening for prostate cancer: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 155(11):762–771

Clark LC, Dalkin B, Krongrad A, Combs GF Jr, Turnbull BW, Slate EH et al (1998) Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. Br J Urol 81(5):730–734

Coleman MP, Quaresma M, Berrino F, Lutz JM, De AR, Capocaccia R et al (2008) Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol 9(8):730–756

Cox B, Sneyd MJ, Paul C, Delahunt B, Skegg DC (2002) Vasectomy and risk of prostate cancer. JAMA 287(23):3110–3115

Crawford ED (2003) Epidemiology of prostate cancer. Urology 62(6 Suppl 1):3–12

Daniell HW (2010) Smoking, obesity, and statin therapy in the prognosis of prostate cancer. J Clin Oncol 28(31):e643–e646

De Marzo AM, Platz EA, Sutcliffe S, Xu J, Gronberg H, Drake CG et al (2007) Inflammation in prostate carcinogenesis. Nat Rev Cancer 7(4):256–269

Dennis LK, Dawson DV, Resnick MI (2002a) Vasectomy and the risk of prostate cancer: a meta-analysis examining vasectomy status, age at vasectomy, and time since vasectomy. Prostate Cancer Prostatic Dis 5(3):193–203

Dennis LK, Lynch CF, Torner JC (2002b) Epidemiologic association between prostatitis and prostate cancer. Urology 60(1):78–83

Djavan B (2011) Screening for prostate cancer: practical analysis of the ERSPC [corrected] and PLCO trials. Eur Urol 59(3):365–369

Dorgan JF, Albanes D, Virtamo J, Heinonen OP, Chandler DW, Galmarini M et al (1998) Relationships of serum androgens and estrogens to prostate cancer risk: results from a prospective study in Finland. Cancer Epidemiol Biomarkers Prev 7(12):1069–1074

Duffield-Lillico AJ, Dalkin BL, Reid ME, Turnbull BW, Slate EH, Jacobs ET et al (2003) Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. BJU Int 91(7):608–612

Etminan M, Takkouche B, Caamano-Isorna F (2004) The role of tomato products and lycopene in the prevention of prostate cancer: a meta-analysis of observational studies. Cancer Epidemiol Biomarkers Prev 13(3):340–345

Ferlay J, Parkin DM, Steliarova-Foucher E (2010) Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer 46(4):765–781

Gallagher DJ, Gaudet MM, Pal P, Kirchhoff T, Balistreri L, Vora K et al (2010) Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. Clin Cancer Res 16(7):2115–2121

Giles GG, Severi G, English DR, Hopper JL (2004) Frequency of ejaculation and risk of prostate cancer. JAMA 292(3):329

Giovannucci E (1998) Dietary influences of 1,25(OH)2 vitamin D in relation to prostate cancer: a hypothesis. Cancer Causes Control 9(6):567–582
Giovannucci E (2002) A review of epidemiologic studies of tomatoes, lycopene, and prostate cancer. Exp Biol Med (Maywood) 227(10):852–859
Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC (1993) A prospective cohort study of vasectomy and prostate cancer in US men. JAMA 269(7):873–877
Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC (2002) A prospective study of tomato products, lycopene, and prostate cancer risk. J Natl Cancer Inst 94(5):391–398
Gong Z, Neuhouser ML, Goodman PJ, Albanes D, Chi C, Hsing AW et al (2006) Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial. Cancer Epidemiol Biomarkers Prev 15(10):1977–1983
Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V et al (2011) EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol 59(1):61–71
Horndasch M, Culig Z (2011) SOCS-3 antagonizes pro-apoptotic effects of TRAIL and resveratrol in prostate cancer cells. Prostate 71(12):1357–1366
Hsieh TC, Huang YC, Wu JM (2011) Control of prostate cell growth, DNA damage and repair and gene expression by resveratrol analogues, in vitro. Carcinogenesis 32(1):93–101
Hsing AW, Tsao L, Devesa SS (2000) International trends and patterns of prostate cancer incidence and mortality. Int J Cancer 85(1):60–67
Hsing AW, Sakoda LC, Chua S Jr (2007) Obesity, metabolic syndrome, and prostate cancer. Am J Clin Nutr 86(3):s843–s857
Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011) Global cancer statistics. CA Cancer J Clin 61(2):69–90
Jian L, Xie LP, Lee AH, Binns CW (2004) Protective effect of green tea against prostate cancer: a case–control study in southeast China. Int J Cancer 108(1):130–135
Josef MF, Karenberg A (2009) History of the term prostate. Prostate 69(2):208–213
Kalish LA, McDougal WS, McKinlay JB (2000) Family history and the risk of prostate cancer. Urology 56(5):803–806
Kikuchi N, Ohmori K, Shimazu T, Nakaya N, Kuriyama S, Nishino Y et al (2006) No association between green tea and prostate cancer risk in Japanese men: the Ohsaki Cohort Study. Br J Cancer 95(3):371–373
Klein EA (2005) Can prostate cancer be prevented? Nat Clin Pract Urol 2(1):24–31
Klein EA, Thompson IM, Lippman SM, Goodman PJ, Albanes D, Taylor PR et al (2001) SELECT: the next prostate cancer prevention trial. Selenium and Vitamin E Cancer Prevention Trial. J Urol 166(4):1311–1315
Klein EA, Thompson IM Jr, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ et al (2011) Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 306(14):1549–1556
Kristal AR, Arnold KB, Neuhouser ML, Goodman P, Platz EA, Albanes D et al (2010) Diet, supplement use, and prostate cancer risk: results from the prostate cancer prevention trial. Am J Epidemiol 172(5):566–577
Kurahashi N, Iwasaki M, Sasazuki S, Otani T, Inoue M, Tsugane S (2007) Soy product and isoflavone consumption in relation to prostate cancer in Japanese men. Cancer Epidemiol Biomarkers Prev 16(3):538–545
Kurahashi N, Sasazuki S, Iwasaki M, Inoue M, Tsugane S (2008) Green tea consumption and prostate cancer risk in Japanese men: a prospective study. Am J Epidemiol 167(1):71–77
Lampe JW (2010) Emerging research on equol and cancer. J Nutr 140(7):1369S–1372S
Lee MM, Gomez SL, Chang JS, Wey M, Wang RT, Hsing AW (2003) Soy and isoflavone consumption in relation to prostate cancer risk in China. Cancer Epidemiol Biomarkers Prev 12(7):665–668
Leitzmann MF, Platz EA, Stampfer MJ, Willett WC, Giovannucci E (2004) Ejaculation frequency and subsequent risk of prostate cancer. JAMA 291(13):1578–1586

Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG et al (2009) Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 301(1):39–51

Marx FJ, Karenberg A (2010) Uro-words making history: ureter and urethra. Prostate 70(9): 952–958

Moyad MA (2005) Heart healthy equals prostate healthy equals statins: the next cancer chemoprevention trial. Part I. Curr Opin Urol 15(1):1–6

Musquera M, Fleshner NE, Finelli A, Zlotta AR (2008) The REDUCE trial: chemoprevention in prostate cancer using a dual 5alpha-reductase inhibitor, dutasteride. Expert Rev Anticancer Ther 8(7):1073–1079

Nelson WG, De Marzo AM, DeWeese TL, Isaacs WB (2004) The role of inflammation in the pathogenesis of prostate cancer. J Urol 172(5 Pt 2):S6–S11

Nilsen TI, Romundstad PR, Vatten LJ (2006) Recreational physical activity and risk of prostate cancer: a prospective population-based study in Norway (the HUNT study). Int J Cancer 119(12):2943–2947

Papadopoulos G, Delakas D, Nakopoulou L, Kassimatis T (2011) Statins and prostate cancer: molecular and clinical aspects. Eur J Cancer 47(6):819–830

Quinn M, Babb P (2002) Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part I: international comparisons. BJU Int 90(2):162–173

Ribeiro R, Lopes C, Medeiros R (2004) Leptin and prostate: implications for cancer prevention – overview of genetics and molecular interactions. Eur J Cancer Prev 13(5):359–368

Rodriguez C, Freedland SJ, Deka A, Jacobs EJ, McCullough ML, Patel AV et al (2007) Body mass index, weight change, and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev 16(1):63–69

Sakr WA (1999) Prostatic intraepithelial neoplasia: a marker for high-risk groups and a potential target for chemoprevention. Eur Urol 35(5–6):474–478

Sarma AV, McLaughlin JC, Wallner LP, Dunn RL, Cooney KA, Schottenfeld D et al (2006) Sexual behavior, sexually transmitted diseases and prostatitis: the risk of prostate cancer in black men. J Urol 176(3):1108–1113

Schoonen WM, Salinas CA, Kiemeney LA, Stanford JL (2005) Alcohol consumption and risk of prostate cancer in middle-aged men. Int J Cancer 113(1):133–140

Schroder FH (2008) Screening for prostate cancer (PC) – an update on recent findings of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Urol Oncol 26(5):533–541

Simard J, Dumont M, Soucy P, Labrie F (2002) Perspective: prostate cancer susceptibility genes. Endocrinology 143(6):2029–2040

Strope SA, Andriole GL (2010) Prostate cancer screening: current status and future perspectives. Nat Rev Urol 7(9):487–493

Sutcliffe S, Giovannucci E, De Marzo AM, Leitzmann MF, Willett WC, Platz EA (2006) Gonorrhea, syphilis, clinical prostatitis, and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 15(11):2160–2166

Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG et al (2003a) The influence of finasteride on the development of prostate cancer. N Engl J Med 349(3):215–224

Thompson IM, Basler JA, Leach R, Troyer D, Klein E, Brawley O (2003b) Challenges and opportunities to the design and implementation of chemoprevention trials for prostate cancer. Urol Oncol 21(1):73–78

Thompson IM, Chi C, Ankerst DP, Goodman PJ, Tangen CM, Lippman SM et al (2006) Effect of finasteride on the sensitivity of PSA for detecting prostate cancer. J Natl Cancer Inst 98(16): 1128–1133

Thompson IM, Pauler AD, Chi C, Goodman PJ, Tangen CM, Lippman SM et al (2007) Prediction of prostate cancer for patients receiving finasteride: results from the Prostate Cancer Prevention Trial. J Clin Oncol 25(21):3076–3081

Unger JM, LeBlanc M, Thompson IM, Coltman CA Jr (2004) The person-years saved model and other methodologies for assessing the population impact of cancer-prevention strategies. Urol Oncol 22(4):362–368

Van PH, Tombal B (2011) Chemoprevention of prostate cancer with nutrients and supplements. Cancer Manag Res 3:91–100

Wilt TJ, MacDonald R, Hagerty K, Schellhammer P, Kramer BS (2008) Five-alpha-reductase inhibitors for prostate cancer prevention. Cochrane Database Syst Rev 2:CD007091

Wright ME, Chang SC, Schatzkin A, Albanes D, Kipnis V, Mouw T et al (2007) Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality. Cancer 109(4):675–684

Zeliadt SB, Etzioni RD, Penson DF, Thompson IM, Ramsey SD (2005) Lifetime implications and cost-effectiveness of using finasteride to prevent prostate cancer. Am J Med 118(8):850–857