

Etiology of prostate cancer (C61) in Central and South America

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Although the etiology of prostate cancer remains poorly understood, genetic, environmental, and behavioural factors have been associated with an increased risk of prostate cancer. These are briefly described in this section, with a special focus on modifiable factors such as obesity, physical inactivity, and dietary factors [1] to identify opportunities for prevention and research in the Central and South American region.

Family history and genetic susceptibility

A family history of prostate cancer has consistently been associated with an increased risk of prostate cancer that varies according to the degree of the relationship, the number of relatives affected, and the age at diagnosis [2–5]. Between 10% and 15% of men of African descent who have prostate cancer have been estimated to have one or more relatives with the disease [6]. In a recent meta-analysis of 33 studies (25 case–control and 8 cohort) conducted in Europe and North America, Kiciński et al. [3] showed that the risk of prostate cancer increased by 2.5-fold among those who had a first (father/brother) degree relative with the disease (pooled rate ratio [RR], 2.48; 95% confidence interval [CI], 2.25–2.74 vs no relative in 26 studies) and was higher among those whose first degree relatives were diagnosed before the age of 65 years (RR, 2.87; 95% CI, 2.21–3.74 vs those diagnosed at age \geq 65 years in 5 studies). Evaluations of the type of relative revealed that having a brother with prostate cancer increased the risk by 3.14-fold while having a father with prostate cancer increased the risk by 2.35-fold. Men who had two or more first-degree relatives with prostate cancer had 4.39 (95% CI, 2.61–7.39) times the risk of prostate cancer compared with those with none.

Kral et al. [7] reviewed the genetic determinants of prostate cancer and summarized the function of several candidate genes for the development of this malignancy. The *RNaseL/hereditary prostate cancer 1 (HPC1)* gene (located in 1q25.3) is associated with prostate cancer in younger men (< 65 years), and those who have a more aggressive disease (based on the Gleason score), advanced cancer at time of diagnosis, and a family history of prostate cancer (strongest associations in those with > 5 affected relatives). The *HPCX* gene (located in Xq27–28) is also related to a family history of prostate cancer and the risk is higher in men with an affected brother than in those with an affected father. The *HPC20* gene (located in 20q13) is associated with an older age at diagnosis. The *breast cancer 1* (located in 17q21) and 2 (located in 13q12–13) genes have been associated with prostate cancer in younger men and with functions in DNA repair, respectively. The *macrophage scavenger receptor 1* gene (located in 8p22–23) is responsible for the initiation of inflammation and affects the induction and course of infection; however, no clear

correlation has been found between this gene and the hereditary risk of prostate cancer. Although the *bacterial RNase Z 2* gene (located in 17p11) has been associated with an increased risk of prostate cancer, its function has yet to be determined. A growing body of evidence also suggests a possible association between other gene mutations (*Kruppel-like factor 6*, *phosphatase and tensin homologue*, *mitotic arrest deficient-like 1*, and *glutathione S-transferase mu 1* among others) and the development and progression of prostate cancer [7, 8]. However, most prostate cancers are sporadic (85% of all cases) and only 15% are familial or hereditary [7], indicating that other factors must be involved in the carcinogenesis process in the prostate.

African descent

Several reports indicate that African descendants have a higher incidence of prostate cancer than other groups, although the reasons for this are still unclear [6, 9]. For instance, African American men on average have a 60% higher incidence rate of prostate cancer and 2.4-fold higher mortality rates compared with white men (as cited in [9]). However, geographical variations in the incidence of prostate cancer have been observed within African populations, with rates in southern Africa being twice as high as the highest rates in western Africa and 7 times higher than the lowest rate in northern Africa. These differences within African countries are probably due to opportunistic screening and life expectancy rather than true differences in the occurrence of the disease [6]. The burden of prostate cancer among men in Ghana and Nigeria and African descendants in the Caribbean Islands (Trinidad and Tobago and Jamaica) and the United Kingdom is similar to or worse than that among African Americans in the USA [6, 9].

Only a few studies investigating racial differences in risk have been conducted in the Central and South American region and the results are conflicting. In Guyana between 2000 and 2006, the prevalence of prostate cancer was remarkably higher in African descendants (65%) than in any other group (19% in Indo-Guyanese, 2% in Amerindians, and 14% in other/non-specified) [10]. In a study in Brazil that used cancer registry data from São Paulo from 1969 to 1974, Bouchardy et al. [11] showed that mulatto men and men of African descent had a 40% and 80% higher risk of prostate cancer than white men, respectively. Similarly, in a study conducted in Ipirá, Bahia (Brazil), of prostate cancer screening volunteers aged 40–79 years using prostate-specific antigen (PSA), Paschoalin et al. [12] found that the prevalence of biopsy-confirmed prostate cancer cases ($n = 121$) was higher in mulatto men and men of African descent than in white men (6.7%, 8.5%, and 0.6%, respectively; $P = 0.006$). In contrast, in a study of prostate cancer during a screening campaign among 1432 men at a public hospital in São Paulo in 1996–97, Glina et al. [13] observed a similar prevalence of prostate cancer among men of African descent and white men ($P > 0.05$); white men ($n = 1140$) had the largest number of biopsies and number of tumours (212 and 17, respectively) while men of African ($n = 202$) and Asian ($n = 43$) descent had the smallest numbers (33 and 2, and 5 and 0, respectively). In a study conducted at the hospital of the Federal University of Bahia, Barros [14] showed that, based on PSA levels, the prevalence of prostate cancer in men aged 40–79 years in 1999–2001 was similar among mulatto men (18.1 ng/dL), men of African descent (19.3 ng/dL), and white men (22.0 ng/dL) ($P = 0.65$) and that

of prostate adenocarcinoma was comparable across the three groups (53.3% for mulatto men, 64.9% for men of African descent, and 53.3% for white men; $P = 0.36$).

Although some of these findings indicate an important role of genetic factors, the variability across populations of African descendants also suggests that environmental and lifestyle factors play a role in the risk of prostate cancer [9, 15]. The study of race and cancer risk in most countries of the Central and South American region is very challenging, not only because cancer registries do not systematically record race/ethnicity, but also because of the racial heterogeneity of the population [16, 17]. In the region, race is measure based on the perception of skin colour (phenotype) and not ancestry (origin) of the subjects; moreover, racial categories based on skin colour are influenced by socioeconomic position [16]. Therefore, research and intervention efforts in the region should be focused on understanding differences in treatment, stage at diagnosis, and early detection by socioeconomic status.

Increased body weight

A growing body of epidemiological evidence suggests a positive link between obesity and the incidence of and mortality from prostate cancer, particularly in aggressive cases [18–20]. Obesity may promote the development and progression of prostate cancer by several mechanisms, including increased levels of insulin-like growth factor 1, sex hormones, and adipokines [18]. Obesity is also associated with inflammation that maybe involved in the development of prostate cancer [19].

Several meta-analyses have shown that obesity increases the risk of developing prostate by 1% (per 1-kg/m² increase in body mass index [BMI]) to 5% (per 5-kg/m² increase in BMI) [21–23]. In a meta-analysis of 56 studies (31 cohort and 25 case–control), MacInnis and English [22] showed that obesity was associated with an increased risk of advanced disease (RR, 1.12; 95% CI, 1.01–1.23 per 5 kg/m² increment in BMI) but not with localized disease (RR, 0.96; 95% CI, 0.89–1.03 per 5 kg/m² increment in BMI). One meta-analysis revealed important differences between obesity and the risk of prostate cancer by study location; in studies in Australia and Europe, obesity was associated with a 4% (95% CI, 1–7%) increase in prostate cancer but not North American and Asian-Pacific studies (RR, 1.0; 95% CI, 0.96–1.03 for North American studies; RR, 1.15; 95% CI, 0.96–1.39 for Asian-Pacific studies per 5 kg/m² increment in BMI) [23]. These geographical variations may indicate differences in prostate cancer screening using PSA [18]. Moreover, it has been suggested that prostate cancer cases in obese men maybe missed due to lower biopsy rates, reducing the early detection of cancer. For instance, PSA values are lower in overweight (BMI, 25–30 kg/m²), obese (BMI, 30–35 kg/m²), and morbidly obese (BMI > 35 kg/m²) men compared with those with a BMI of less than 25 kg/m², the performance of a comprehensive digital rectal examination maybe more difficult, and the probability of finding cancer at biopsy maybe reduced because of their enlarged prostates [18].

Obesity has also been linked with an increased risk of prostate cancer mortality [20]. The mechanisms by which obesity may influence the progression of prostate cancer are not completely understood, but it has been associated with changes in several hormone levels (i.e. testosterone, estrogen, insulin, and leptin) and growth factors

(i.e. insulin-like growth factor 1) which have also been related to prostate cancer in some studies [24]. In a meta-analysis of six population-based cohort studies that included over 1.2 million cancer-free men and 6817 prostate cancer cases, Cao et al. [20] found that obesity increased the risk of prostate cancer death by 15% (95% CI, 6–25% for a 5 kg/m² increase in BMI). In a subanalysis, obesity was also associated with a 20% increase in prostate cancer mortality and 21% of biochemical recurrences (an increase in PSA levels in men treated for localized prostate cancer) for a 5 kg/m² increase in BMI (in 6 post-diagnosis survival studies and 16 follow-up studies after primary treatment, respectively). These associations may be due to the lack of PSA testing, delayed diagnosis, and advanced disease at diagnosis in obese men.

Dietary factors

The worldwide variation in the incidence of prostate cancer coincides with variations in dietary patterns [25]. Some ecological studies have correlated a diet typical of industrialized countries (a high consumption of saturated and trans fats, fatty meats, and dairy products) with prostate cancer (as cited in [26]). In industrialized countries, the incidence of prostate cancer is the highest in the world and the diet is high in animal fat (30–40% calories from fat), whereas, in Asian countries, the incidence of prostate cancer is low and the diet is rich in soya proteins and low in animal fats [25].

The World Cancer Research Fund/American Institute for Cancer Research [27] reviewed the evidence regarding the relationship between several foods and nutrients and the risk of cancer and found that diets high in calcium (i.e. > 1.5 g per day) increased the risk of prostate cancer by 27% (95% CI, 9–48% per g per day) (meta-analysis of 8 cohort studies with moderate heterogeneity) and that of advanced and aggressive prostate cancer by 32% (95% CI, 5–64% per g per day) (meta-analysis of 4 cohort studies with moderate heterogeneity). However, a meta-analysis of observational studies indicated that consumption of dairy products was not associated with an increased risk of prostate cancer [28].

The association between meat (red or processed) consumption and the risk of prostate cancer has been studied extensively [29]. In the most recent evaluation of meat consumption conducted by the International Agency for Research on Cancer indicated that red meat consumption increases the risk of prostate cancer [30]. In a systematic review in 2011 of dietary patterns and the risk of prostate cancer in South America, Niclis et al. [26] showed that high meat consumption (total, red, and processed) increased the risk of prostate cancer in men in Uruguay (odds ratio [OR] for high vs low consumption, 1.5–2.0; $P \leq 0.05$; 5 case–control studies).

The ingestion of large quantities of dietary fat (total, saturated, monounsaturated, and polyunsaturated) has been inconsistently associated with the risk of prostate cancer in two case–control studies conducted in Uruguay and one conducted in Argentina [26]. In contrast, high levels of dietary cholesterol compared with low consumption increased the risk of prostate cancer in a case–control study in Uruguay (OR, 1.61; 95% CI, 1.09–2.37 for 335–443 mg; OR, 2.30; 95% CI, 1.57–3.39 for 444–572 mg; OR, 2.10; 95% CI, 1.43–3.09 for ≥ 573 mg vs ≤ 334 mg of cholesterol; P for trend < 0.001) [31].

Studies of dietary patterns and the risk of prostate cancer conducted in Argentina, Australia, Canada, Uruguay, and the USA have revealed inconsistent associations [26, 32–34]. In South America, a case–control study conducted in Uruguay showed that men who had a traditional dietary pattern (lamb, dairy foods, cooked vegetables, and all tubers) and a dietary pattern typical of industrialized countries (beef, processed meat, boiled eggs, fried eggs, and total grains) had an approximately 2-fold increased risk of prostate cancer when the highest (quartile) and lowest (quartile) consumption of the respective dietary patterns were compared (OR, 1.85; 95% CI, 1.16–2.94 for traditional; OR, 2.35; 95% CI, 1.44–3.85 for industrialized) [33]. A case–control study conducted in Argentina indicated that men who had a Cono Sur dietary pattern (red meats, starchy vegetables, and wine), a sugary drink dietary pattern (soda and juices) and a typical measured pattern (lean red meats and infusions) had a higher risk of prostate cancer (OR, 1.91; 95% CI, 1.73–2.11 for Cono Sur; OR, 1.66; 95% CI, 1.09–2.55 for sugary drink; OR, 1.09; 95% CI, 1.05–1.14 for typical measured for highest vs lowest tertile) [34]. In the case–control studies in both Argentina and Uruguay, a prudent dietary pattern (raw vegetables, citrus fruit, other fruit, and tea and fruit, non-starchy vegetables, and dairy, respectively) was not associated with an increased risk of prostate cancer [33, 34].

Protective effects against prostate cancer have been found for foods that contain lycopene (found mainly in tomatoes and tomato products, and some fruit, such as grapefruit, watermelon, guava, and apricot) and selenium (found in animal foods, fish, brazil nuts, whole grains, wheat germ and sunflower seeds, and supplements at doses no higher than 200 µg per day, above which it is toxic) [27]. A recent meta-analysis of 12 observational studies (9 nested case–control studies and 3 case–control studies) showed that selenium in plasma or toenails was protective against prostate cancer (RR, 0.85 for 135 ng/mL and RR, 0.75 for 170 ng/mL plasma selenium levels in the meta-analysis of 9 studies; RR, 0.29 for 0.85–0.94 µg/g total concentration of selenium in toenails in the meta-analysis of 3 studies). This meta-analysis also revealed that selenium in plasma was protective against advanced prostate cancer (RR, 0.60 for 135 ng/mL and RR, 0.50 for 170 ng/mL plasma selenium levels in 6 studies) [35]. Furthermore, vegetarian diets might reduce the risk of prostate cancer, probably because of the increased consumption of plant-based foods (including a variety of potential cancer-preventive substances) and not the exclusion of meat (as cited in [27]). From the current evidence, no conclusions can be drawn on any possible relationship between dietary patterns and the risk of prostate cancer.

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