REVIEW ARTICLE

Dietetic factors associated with prostate cancer. Protective effects of Mediterranean diet

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Abstract

Objective: To review diet risk factors (RF) implied, more or less evidence-based, in the etiopathology of prostate carcinoma (PC), especially those that characterize the traditional Mediterranean diet (MD).

Material and methods: Literature review of PC related diet RF in MedLine, CancerLit, Science Citation Index and Embase. Search profiles were “Dietetic Factors/Nutritional Factors/Mediterranean Diet/Primary Prevention”, and “Prostate Cancer”.

Results: Diet RF are associated with 35% of cancer mortality and 10–12% of PC mortality. The main diet RF, implied in the development of PC but with a protective effect, which are considered characteristic of MD are: high daily ingestion of vegetarian products (cereals, legumes, dried and fresh fruits, tubercles, vegetables, etc.); olive oil as main lipid source; low intake of animal saturated fat, processed red meat, milk and dairy products; regular consumption of small fish; and low alcohol intake (wine with meals). The MD contains many phytoactive compounds (lycopene, lupeol, quercetin, genistein, canosol, resveratrol, catechins, vitamins, etc.) with PC protective effects.

Conclusions: Diet RF have a role on prostatic carcinogenesis. Further epidemiologic studies with better designs are needed to clarify PC related diet RF. PC risk is reduced in people on MD compared with those on western diet. The common denominator of the preventive effect of the MD is based on the great quantity and quality of phytochemicals with antioxidant and antiinflammatory properties.

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Introduction

Prostate cancer (PC), despite diagnostic and therapeutic advances, causes a dramatic reduction in the potential years of life lost.\textsuperscript{1} Because of its high incidence, and in order to improve its primary prevention, we must increase our understanding of RF involved in its etiopathogeny.\textsuperscript{2,3}

The geographic and ethnic differences in its incidence and mortality, as well as the increases in the risk of the migrations from areas of low to high incidence, highlight the influence of the cultural RF.\textsuperscript{4,5} Among them, the dietary RF, which are associated with 35% of cancer deaths and 10–12% of PC ones.\textsuperscript{6} Western diets (high protein-energy intake) generate higher premature mortality than the MD and Eastern diets.\textsuperscript{6,7} Due to our Mediterranean area, we will analyze the major studies published until June 2011 on the association between the diet risk factors (DRF) and the PC within the characteristics of the MD (Table 1). We highlight the report Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective, whose results in the PC are described in Table 2.\textsuperscript{6}

Lifestyle and Mediterranean diet

The MD is based on the lifestyle and food consumption of the European coastal regions of the mid-twentieth century.\textsuperscript{6-8} Its inhabitants, healthy and long-lived, had low incidence of cardiovascular, metabolic, degenerative, and neoplastic diseases. The lifestyle in rural and agricultural societies, with daily physical activity, contrasts with the changes in recent decades due to industrializing globalization. In the diet we witness its manipulation and homogenization, generated by the technological innovations and economic interests of the Anglo-Saxon multinationals in the sector, whose prototype is the junk diet.\textsuperscript{9} Recovery and persistence of the MD needs all the social strata of the coastal countries and regions, and health professionals, including urologists. Next, we will describe the characteristics and specific components of the MD, analyzing its involvement in prostate carcinogenesis.

Characteristics of the Mediterranean diet

High and daily consumption of plant foods

There is evidence that its high intake reduces the risk of PC.\textsuperscript{4-7} The main bioactive nutrients involved are:

Table 1  Characteristics of the traditional Mediterranean diet.

<table>
<thead>
<tr>
<th>Main characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>High consumption of fruits and vegetables</td>
</tr>
<tr>
<td>High consumption of cereals and legumes</td>
</tr>
<tr>
<td>Use of olive oil as a usual lipid</td>
</tr>
<tr>
<td>Regular consumption of small-sized fish</td>
</tr>
<tr>
<td>Prevalence of the culinary processes:</td>
</tr>
<tr>
<td>Boil in water</td>
</tr>
<tr>
<td>Fry in olive oil bath</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional consumption of wine in moderate amounts with food</td>
</tr>
<tr>
<td>Low meat intake, predominantly poultry</td>
</tr>
<tr>
<td>Low-moderate intake, but regular, of dairy products, low intake of simple carbohydrates, and almost no intake of industrially prepared foods</td>
</tr>
</tbody>
</table>
Dietetic factors associated with prostate cancer

Table 2 Results of the report Food, Nutrition, Physical Activity, and the Prevention of Cancer: a global perspective in prostate cancer.

<table>
<thead>
<tr>
<th>Dietary components</th>
<th>Influence on prostate cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legumes</td>
<td></td>
</tr>
<tr>
<td>Foods with β-carotenes</td>
<td>Probably ↓ risk</td>
</tr>
<tr>
<td>Foods with lycopene</td>
<td>Probably ↓ risk</td>
</tr>
<tr>
<td>Foods with selenium</td>
<td>Probably ↓ risk</td>
</tr>
<tr>
<td>Foods with vitamin E</td>
<td>Suggest limited evidence ↓ risk</td>
</tr>
<tr>
<td>Processed meats</td>
<td>Suggest limited evidence ↑ risk</td>
</tr>
<tr>
<td>Diets high in calcium</td>
<td>Probably ↑ risk</td>
</tr>
<tr>
<td>Milk and derivatives</td>
<td>Suggest limited evidence ↑ risk</td>
</tr>
<tr>
<td>Supplements of β-carotenes</td>
<td>Improbable substantial effect on the risk</td>
</tr>
<tr>
<td>Supplements of selenium</td>
<td>Probably ↓ risk</td>
</tr>
<tr>
<td>Supplements of α-tocopherol</td>
<td>Limited suggestions of ↓ risk</td>
</tr>
</tbody>
</table>

Source: World Cancer Research Fund – American Institute for Cancer Research.6

Carotenoids (lycopene, lupeol, β-carotenes)

Lycopene is the most abundant dietary carotenoid, with greater antioxidant potential and plasma concentration, predominant in hormone-dependent tissues and especially in the prostate (30% of the total body). Therefore, its involvement in PC has been greatly studied. Its thermostability and lipophilicity allow for greater bioabsorptions after cooking in oil at more than 100°C, being mainly provided by the tomato and its derivatives. Although the intake of raw tomato and fresh juice, watermelon, pink grapefruit, papaya, red apricot, and pink guava have significant concentrations, they are of low bio-intake.4,18-20,24

In vitro and in vivo has antioxidant and apopogenic properties, reducing prostatic epithelial growth in androgen-independent tumors and reducing insulin growth factors.4,5,18-22

In cohorts, the high intake is associated with reductions (30–50%) of PC risk.4 A meta-analysis found that for every 10 mg/l of the increase in plasma, the risk of PC decreased by 4%.6 A recent study of 137,001 men in the European Prospective Investigation into Cancer and Nutrition found no association between serum levels and localized tumors, but elevated levels had reductions of 60% for metastatic ones.18

The Health Professional Follow-up Study documented that 2-4 servings of tomato sauce per week were associated with a 35% reduction of PC risk.19 In another work of 32 patients out of 66 diagnosed with biopsy, tomato sauce was administered (30 mg lycopene/day) for three weeks, and after prostatectomy, the tumors had 3.3 times more apoptosis than the 34 controls.20

In case–controls, the results are different, although most of them document non-significant reductions.5,13

In summary, the available data suggest that the high consumption of tomatoes and derivatives is probably associated with reduced risk and progression of PC.

Lupeol (olives, strawberries, raspberries, grapes, figs, mango, and many vegetables) is an anti-inflammatory, antimitogenic and proapoptotic terpene in hormone-dependent PC. It also has antiproliferative effects associated with increased cell cycle arrest at the G2-M phase.21,22

In plant foods (carrots, squashes, spinach, chards, sweet potatoes, and cabbages), there are other antioxidant β-carotenes, but epidemiological studies, based on dietary intakes, serum determinations, and supplementation have been inconclusive.4,17,25

Flavonoids or phytoestrogens (genistein, quercetin, fisetin)

Genistein (lentils, peas, beans, broad beans, soybeans, etc.) is the predominant isoflavone in human nutrition. It inhibits prostate carcinogenesis by estrogen metabolizing enzymes, such as 5α-reductase and aromatase, and it induces apoptosis by mitotic block in phase G1. It reduces the PSA expression and modulates various cell cycle genes. Finally, it inhibits the angiogenesis associated with PC progression.5,21

Quercetin (onion, garlic, pomegranate, broccoli, apple, grape, etc.) is the main representative of the flavonol family and it expresses the highest antioxidant capacity of phytoestrogens. The pomegranate also contains anthocyanins, ellagitannins, tannins, kaempferol and luteolytic glycosides, growth inhibitors, and prostate tumor proliferation, inducing apoptosis and decreasing the serum levels of the PSA in both hormone-dependent and independent malignancy.7,22

Fisetin (strawberries, blackberries, apples, persimmons, grapes, alliaceae, and cucumbers) is a bioactive flavone that in vitro shows antioxidant, anti-inflammatory, and antiangiogenic effects in the PC.21,22

Polyphenols (carnosol, curcumin, resveratrol, epigallocatechin-3-gallate)

Carnosol (rosemary, mint, thyme, oregano, sajolida, peppermint, pennyroyal, etc.) and derivatives (carnosic acid, rosmanol, rosmarinic acid, etc.) have antioxidant, anti-inflammatory (nitric acid pathways, leukotrienes, and COX-2), and pro-apoptotic (phase G2) effects in prostate carcinogenesis. Rosemary contains the highest concentrations, conditioning more than 90% of its antioxidant activity. A unique feature of the carnosol is its anti-prostate tumor ability, as a dual antagonist of α-androgenic and estrogenic receptors, without agonist effects.23

Curcumin (Indian saffron yellow pigment) has anti-inflammatory, antioxidant, immunomodulatory, proapoptotic, and anti-androgen actions across multiple genes and levels of the cell cycle in PC.21

Resveratrol (grape skin and juices, red wine, raisins, peanuts, blackberries, strawberries, etc.) develops antioxidant, anti-inflammatory, phytoestrogenic, and antitumor activities in hormone-dependent cancers (in PC it induces apoptosis by cell cycle arrest via inhibition of tyrosine kinase). Resveratrol has received special attention by the moderate consumption of red wine at meals, typical of the MD. In this regard, we will say that resveratrol and phenolic compounds in red wine can be achieved far through the consumption of grapes, especially black raisins, and grape juice.4,14,21,23

Epigallocatechin-3-gallate and other catechins (green tea), in vitro and in vivo, induce apoptosis and inhibit growth of the PC. They also impede local invasion and metastasis.
formation through the gene modulation of the group of metalloproteinase matrix and of the factors of vascular endothelial growth.5,22,26

Phytosterols
Phytosterols are bioactive phytochemicals (nuts, especially walnuts, almonds, and hazelnuts), antioxidant, and pro-apoptotics in prostate tumor cultures. Structurally similar to cholesterol, intake with fat and dairy products decreases cholesterol absorption. β-Sitosterol is the most abundant component and in vivo inhibits prostate carcinogenesis.14,15,21

Organosulfur compounds
The alliaceae family (onions, garlic, scallions, etc.) provide bioactive compounds with anticancer capacity in experimental animals and in human tumor cultures. The intake higher than three servings per week is associated in some studies with reductions of 41% of PC, as well as aggressive varieties.15 The main organosulfur compound of garlic, s-allylcysteine, is a volatile oil which is converted enzymatically into allicin and allinase. In PC, pro-apoptotic effects are presented, chemical carcinogens detoxified and the cell cycle is regulated by decreasing the secretion of the PSA.21,22 Among the few epidemiological studies performed, the only cohort study shows nonsignificant reduction in the risk of PC. In four cases, two controls documented significant reductions, including OR < 0.5 (CI 95%: 0.3–0.76) with intake > 10 g/day compared to ≤ 2 g/day.

In four case–controls, two document significant reductions, even with OR > 0.5 (CI 95%: 0.3–0.76), with intake ≥ 10 g/day versus ≤ 2.2 g/day.17 The brassica or cruciferous family (cabbage, watercress, wallflower, mustard, radish, turnip, cauliflower, broccoli, rape, etc.) provide phytochemicals such as sulforaphane and indole-3-carbinol. They have anti-angiogenic, anti-inflammatory, and carcinogen detoxifying properties.22 Sulforane also has pro-apoptotic effects in in vitro and in vivo prostate cancer cells. Indole-3-carbinol, in animal models of PC, has antiproliferative and antimetastatic properties.15,21 The few epidemiological studies examining the relation between the consumption and the risk of PC provide limited evidence.15,17,25,27

Complex carbohydrates
Complex carbohydrates are the main energy sources in the MD (cereals, tubers, and legumes). High consumption increases the intake of vegetable fiber involved in the neoplastic risk by reducing the glycemic load, improving insulin sensitivity and decreasing the concentrations of IGF-1. There is a moderate association between the consumption of fiber, especially cellulose and non-cellulosic polysaccharides, and the reduction of PC. Industrial refining transforms them into simple carbohydrates, causing high glycemic loads with lipogenesis and obesity, favoring prostate carcinogenesis due to the greater bioavailability of circulating estrogens and the IGF-1.4,6,15

Folates
Folates (cereals, legumes, fruits, and vegetables) have antitumor effects based on the actions on methylation and nucleotide synthesis and their influence on gene polymorphisms mediated by methylenetetrahydrofolate reductase. High dietary intakes significantly reduce the majority of cancers, including PC.5,6,14

Vitamins
Vitamin E (vegetable oils, hazelnuts, green vegetables, cereal grains, wheat germ, sweet potatoes, carrots, tomatoes, etc.): main liposoluble antioxidant of the human organism with additional anti-prostate tumor effects (anti-apoptotic, anti-angiogenic, reduced expression of the PSA and the androgen receptor mRNA and protein kinase C). However, the epidemiological studies are inconsistent.3,7,15,26 In short, there is limited evidence that the high intake of foods rich in vitamin E reduces the risk of PC, whereas other dietary supplements decrease it among smokers.

Vitamin C (green leafy vegetables, citrus fruits, peppers, tomatoes, squashes, potatoes, strawberries, melons, etc.): most abundant water-soluble antioxidant in the human organism and the only one able to regenerate when oxidized, detoxifying the carcinogens and protecting the DNA. The integrity of intra-and intercellular matrices increases, impeding tumor growth and local invasion. The epidemiological studies on the consumption of foods rich in vitamin C, plasma levels, and additional supplement use, and risk of PC are inconclusive.4,13,15,26

Selenium
The food content is related to its geological concentration, bioaccumulating in plants (cereals, legumes, and tubers) and animals (eggs, meat, fish, and seafood). Ecological studies show lower mortality of PC in countries and regions with soils rich in selenium (Se). In vitro and in vivo favors the synthesis of selenoproteins, with antioxidant, anti-inflammatory, and regulating androgen metabolism and normal prostate, and tumor growth effects.5,15

A meta-analysis of 16 epidemiological studies (11 cohorts and 5 case–controls) documents PC risk reductions of 28% in cohorts and 16% in case–controls when comparing high vs. low consumption.27 The supplementation with Se and the risk of PC has been analyzed in a randomized study in two cohorts. The first one found that administration of 200 µg daily reduced the risk of PC by 50%.28 In cohorts, no significant decreases in risk were found.5,15 In short, there is limited but consistent evidence that foods with Se and dietary supplements are likely to reduce the risk of PC.

Consumption of olive oil as usual lipid
It is the major lipid (95% of the total) in the traditional MD.7,8,13 Of the three varieties, refined, virgin, and extra-virgin, the last two are consumed naturally in salads and boiled vegetables, increasing its palatability and intake. It withstands high temperatures (cooking and frying in oil bath) without pyrolysis which deteriorates other vegetable oils and animal fats, enabling its reuse.29
The probable benefit in reducing the PC is based on direct and indirect effects. The direct ones are due to its components: oleic acid, low content of saturated lipids, high concentration of vitamin E, squalene, and phenolic compounds (simple phenols, secoiridoids, and lignans); in vitro oleic acid regulates oncogenes related to carcinogenesis; vitamin E, squalene, and phenols develop important antioxidant and antiinflammatory properties. The indirect effects of regular and high consumption of olive oil are based on: (a) increased intake of plant foods because of their greater palatability and (b) reduced requirements for saturated animal fats.14,16,29

**Low consumption of saturated animal fat, meat (red, smoked, and seasoned), milk, and dairy products**

Saturated animal fat has been considered a RF for PC in ecological and case–control analyses.26 International studies of animal fat consumption per capita is positively associated with the incidence and mortality of PC.4,5,7 The case–controls document associations between PC and high intakes of total fat or fatty foods (red meat and dairy derivatives). They also find a relation between fat intake and advanced disease with OR = 1.6–2.9, comparing the categories of highest and lowest intake. In contrast, the cohort data are inconsistent.30

A recent case–control population-based study in patients ≤60 years found a statistically significant risk comparing high and low intake of: total fat with OR = 2.53 (CI 95%: 1.72–3.74), saturated fat with OR = 2.49 (CI 95%: 1.69–3.66), monounsaturated fat with OR = 2.69 (CI 95%: 1.82–3.96), and polyunsaturated fat with OR = 2.34 (CI 95%: 1.59–3.46), after adjusting for all confounding variables. The authors comment that if the association were causal, approximately 40% of PC ≤60 years would be attributed to lipid consumption.31

The biological mechanisms involved are the following: (a) high energy intake increases the basal metabolism, increases the insulin growth factors, and promotes tumor proliferation, (b) lipid metabolism generates free radicals with oxidizing properties on nucleic acids, and leukotrienes and inflammatory prostaglandins that stimulate proliferation and tumor growth and (c) promotes prostate carcinogenesis via androgen, increasing levels of dihydrotestosterone in prostatic epithelial cells. Other nutrients contained in fatty foods, such as red and processed meat, milk, and derivatives could also play a role.4,5,7

Red and processed meat (smoked and salted) provides saturated fat, animal protein, iron, and contains additives or contaminants such as nitrates, nitrates, and byproducts of cooking at high temperatures and of smoked (polycyclic aromatic hydrocarbons and heterocyclic amines). Ecological studies directly associate the high intake of these varieties of meat with PC mortality. In cohort studies, most have associated high dietary intakes of the total meat with risk of PC, while others have not. Cooking at elevated temperature causes the formation of mutagenic heterocyclic amines, after animal amino acids reacting with muscle creatine. The traditional MD consumes little meat intake of poultry, fed with natural nutrients (cereals, vegetables, insects, worms, etc.)4,5,12,24

Milk and dairy products contribute to the increase of saturated animal fats in Western modern diets, providing high calcium content. Countries with high consumptions have higher incidence and mortality of PC. In most case–controls, the high intake has more risk of PC, after adjusting for the total saturated animal fat. In cohorts, the results are less conclusive.5,15,32–34 A meta-analysis of 12 publications showed that men with high dairy intake (RR = 1.11; CI 95%: 1.00–1.22) and calcium (RR = 1.39; CI 95%: 1.09–1.77) had higher risks, statistically significant, of PC than men with low intake, as well as in aggressive cases (RR = 1.33; CI 95%: 1.00–1.78) and (RR = 1.46; CI 95%: 0.65–3.25), respectively.31

Possibly, the association between milk and dairy products and increased risk of PC may be due to other nutrients in these foods. The high intake leads to elevated serum calcium levels, and their tissue concentrations, with the consequent reduction of 1,25-dihydroxyvitamin D, steroid hormone that increases the intestinal absorption of calcium and also regulates and controls cellular differentiation and proliferation of prostatic epithelial cells. The high and usual intake of foods rich in calcium can decrease the serum and tissue levels of 1,25-dihydroxyvitamin D, with increased risk of PC. The case–control and cohort studies document positive associations between high intake of calcium and risk of PC, being higher with oral supplements and advanced PC.4,5,33,34

**Regular consumption of fish (small and medium size)**

The MD is characterized by a regular intake of white fish from small to medium size, caught in fresh water and marine coastal areas. Although it contains animal fat, it provides ω-3 polyunsaturated fatty acids, such as α-linolenic, eicosapentaenoic, and docosahexaenoic acid. The latter generates anti-inflammatory effects (via COX-2 and prostaglandin E3), antioxidants, and favorably modulates the enzymatic, molecular, and genetic parameters involved in prostate carcinogenesis.34

Numerous epidemiological studies have evaluated the role of ω-3 in PC. Although most suggest risk reductions associated with its high intake, others are contradictory. A review of 8 prospective and 9 case–control studies found no risk reduction when comparing high consumptions of ω-3 provided by the fish, compared with the low intake.35 Likewise, in a recent systematic review, it did not show its beneficial effects either.36 It should be noted that there is evidence that the effects of frequent fish intake can be modified by the genetic polymorphisms involved in fatty acid metabolism and inflammatory processes.4,5

With regard to ω-3 supplementation in patients with PC compared to historical controls, it does not produce statistically significant reductions in the levels of PSA, but does in the other markers of tumor activity (total testosterone indexes and free plasma androgens). Significant reductions have also been documented in neoplastic proliferative indexes compared to controls.37 In summary, we can say that there is limited evidence that a high intake of
Ω-3 reduces the risk of PC and may benefit patients with PC.5,34 Linoleic acid is the main precursor of the Ω-6 acid, arachidonic acid, and proinflammatory prostaglandins family. Epidemiological studies have found significant associations between intake, serum levels, tissue concentrations, and increased risk of PC. Arachidonic acid is converted into prostaglandin E-2, pro-inflammatory cytokine which increases the proliferation of prostate cancer cells and increases the risk of advanced PC, possibly by gene activation of kinase pathway. High intake of Ω-6 is associated with increased risk of PC.4,5,15
The traditional MD has a ratio Ω-6/Ω-3 of 2/1, which contrasts with the 10/1 of the diets of Central and Western Europe, and with 20/1 in the U.S. For these reasons, the MD provides a better lipid profile that promotes the prevention of PC.14,15

Regular consumption of wine with meals

Regular and moderate consumption (≤2 drinks/day) of wine, especially red wine at meals, contains bioactive phenolic compounds (resveratrol, quercetin, and catechin), with anti-inflammatory and antineoplastic properties. But ethanol, by metabolizing, generates acetaldehyde (carcinogenic), increases free radicals and decreases the immune function regenerating of DNA. A recent meta-analysis finds statistically significant increases, between 5 and 21% of PC risk associated with alcohol consumption.38,39

Final remarks

The contradictory results and the lack of statistical consistency in most epidemiological studies between dietary RF and PC are partially based on: (a) the great complexity and current unfamiliarity with the molecular mechanisms between diet and cancer; (b) the constitutional and environmental multifactoriality of PC; (c) the weaknesses of specific epidemiological studies (Table 3)4,40; (d) the very slow process of prostate carcinogenesis and (e) the influence of traditional and cultural Mediterranean lifestyles beyond the strict MD.

The benefit of the MD in reducing PC requires some comments. The main common denominator is the immense variety of plant nutrients with anti-inflammatory properties and the huge antioxidant potential, which maintains and repairs the DNA and RNA. Most of the studies aimed at analyzing and isolating a specific food or bioactive component are doomed to fail or get results with little or no statistical consistency. The natural or synthetic use of each nutrient in chemoprevention, at best, will prevent the synergic effects that certainly produce the natural or culinary intake of the other bioactive compounds known and unknown at present. The beneficial effects should be obtained when greater adherence to the characteristics of the MD is globally analyzed. Finally, we would like to involve urologists in the recovery of the traditional MD and the other cultural factors typical of the traditional Mediterranean area (physical activity, reduction of domestic and industrial pollutants, and increase of stays in rural settings with less air pollution than in urban ones).

Table 3 Major deficiencies of epidemiological studies on associations between diet and prostate cancer.

| 1. | Accurately determine other constitutional and environmental RF related to PC. |
| 2. | Wide variety in the design and quality of the studies |
| 3. | Short duration of the cohort studies, taking into account the slow process of prostate carcinogenesis |
| 4. | Different diagnostic techniques or methods in PC |
| 5. | Questionable reliability of dietary surveys |
| 6. | Difficulties in verifying/contrasting intake, serum, tissue biomarkers, and their prolonged monitoring |
| 7. | Group or classify patients according to age, subclinical stages, clinical symptoms, and advanced or metastatic stages |
| 8. | Likelihood that dietary RF influence differently at each stage of prostate carcinogenesis (initiation, promotion, conversion, and progression). |

Source: Platz et al.,4 Mucci et al.,5 World Cancer Research Fund – American Institute for Cancer Research Report4,40 and International Agency for Research on Cancer.40

Conflict of interest

The authors declare that they have no conflict of interest.

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