The Risk Factors of Prostate Cancer and Its Prevention: A Literature Review

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ABSTRACT
This is a literature review study. Data was obtained from several literature reviews and journal resources that have correlation with the risk factors involved in PCa including age, ethnicity, family history, insulin-Like growth factor, sexually transmitted disease, obesity, smoking, alcohol consumption, vasectomy, and diet, and the prevention of PCa including soy, lycopene, green tea, supplementation, and exercise.

Numerous epidemiologic studies have linked PCa risk to various factors, i.e. age, ethnicity, family history, insulin like-growth factors, lifestyle, diet, environmental and occupational exposures. The results of epidemiological, In vivo, in vitro, and early clinical studies suggested that selected dietary products and supplementation may play a role in PCa prevention. More studies are still needed to explore and find the risk factors and preventive methods of PCa development. It is important for clinician to elaborate these informations for education to lower PCa risks and prevent PCa.

Keywords: prostate cancer, PCa, risk factor, prevention.
INTRODUCTION
Prostate cancer (PCa) which defined by National Cancer Institute (NCI) as cancer that forms in tissues of the prostate. The incidence of PCa is rising worldwide due to demographic factors, increasing of elderly population, and number of cases identified following prostate specific antigen (PSA) testing. American Cancer Society (ACS) estimated that in the year 2012 there were about 241,740 new cases of PCa and 28,170 men died from PCa. PCa occurs mainly in older men, nearly two thirds was diagnosed in men age 65 or older. The average range of age at the time of PCa diagnosis is between 60 until 70 years and about 1 men in 6 will be diagnosed with PCa during his lifetime.¹

In Indonesia PCa incidence currently 10.3 per 100,000 population, which has increased almost threefold in the last decade.² Data from WHO in Global Cancer Statistics (GLOBOCAN) cancer project 2008 have been shown that mortality rates are generally high in predominantly black populations (Caribbean, 26.3 per 100,000 and sub-Saharan Africa, ASRs 18-19 per 100,000), lower in Asia (ASR 2.5 per 100,000 in Eastern Asia), Europe and Oceania.²,³

African-American men have a higher incidence rate and at least twice mortality rate compared with men from other race/ethnic group caused by genetic susceptibility. Men with one family history of PCa are twice more likely to develop the disease, while those with two or more relatives are nearly four times as likely to get PCa. The risk is even higher if the affected family members were diagnosed before age of 65.²,⁴ The other possible risk factor including life style factors such as diet (animal fat, meat, milk and dairy products), supplementation intake (Vitamin D, Calcium), sunlight exposure, job related chemical exposure, smoking, obesity, alcohol consumption, level of physical activity, men with a history of vasectomy. It has also been suggested that socioeconomic factors, sexual activity and sexually transmitted infections may influence the probability of developing PCa or being diagnosed with PCa.²

The purpose of this review is to know and understand the risk factors and preventive measures in PCa. These risk factors need to be recognized and managed properly in order to choose the right treatment option, minimize adverse effects and loss of prevent quality of life. Clinicians need to determine whether patients are at high or low risk of PCa.

RISK FACTOR OF PROSTATE CANCER
Age
Older men are more likely to be diagnosed with high risk PCa and have lower overall survival. As a result, age often plays a role in treatment choice.⁵ This risk increases significantly after the age of 50 in white men who have no family history of the disease and after the age of 40 in black men and men who have a close relative with PCa. Table 1 shows the percentage of men who will have PCa over different time periods. Therefore, it is highly recommended for older men to get digital rectal examination (DRE) and prostate specific antigen (PSA) testing screening.⁵,⁶

<table>
<thead>
<tr>
<th>Current Age</th>
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Table 1. Percent of US. men who develop PCa over 10-, 20-, and 30-year intervals according to their current age, 2008–2010⁷

Study in Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) tried to investigate comprehensive risk of PCa.⁷ High-risk patients were identified by using the validated Cancer of the Prostate Risk Assessment (CAPRA) score. Competing risks regression was used to identify the independent impact of age on cancer survival among older men with high-risk disease. The results showed 26% of men of age 75 years old presented with high-risk disease (CAPRA score 6 to 10).³

Ethnicity
Recent studies suggest that ethnicity are essential risk factor of PCa.⁷ African American men, West African ancestry from the Caribbean
and South American men have a higher incidence and mortality of PCa than white men. The lowest incidence of PCa is typically found in Asian men, associated not only with genetic susceptibility but also with the diet, lifestyle and environmental factors.8-10

Data from the National Cancer Institute has shown that African American males PCa (54.2/100 000 vs 24.7/100 000) considerably higher than other ethnic races.4 Chromosome 8q24 variants have been reported to be associated with PCa risk and are more common in African American men. Some studies have also shown a higher rate of variations in cell apoptosis genes such as BCL2 and tumor suppression genes such as EphB2 in African American men.8,11

The evidence of relationship between genetic component to the high incidence and mortality rate in African American men came from epidemiologic studies with similar genetic backgrounds.8,9 The analysis implies that PCa in African American is biologically and genetically more aggressive compared with European American.8 Kyle et al have found that African American men without PCa significantly had higher PSA levels than white man in all age groups. Vijayakumar et al also found higher serum PSA levels in African American with newly diagnosed localized PCa than European American.9,10

**Family History**

Family history of PCa is well established risk factor for PCa risk in men.12 Zheng et al showed five single-nucleotide polymorphisms have been identified as having a significant association with PCa when present together with a family history of PCa.13

Health Professional Follow-Up Study, followed up 3,695 patients with PCa from 1986 to 2004 and found that there was a 2.3-fold increased risk of PCa with a family history of PCa in both a father and a brother (95% confidence interval (CI) = 1.76–3.12). Furthermore, that study reported a 2.16- and 1.95-fold increased PCa risk when the father or brother was diagnosed with PCa at <60 and 60 years of age, respectively. An increased risk of early onset PCa occurring at age <65 years was evident in men with a family history of PCa (OR = 2.25, 95% CI = 1.95 – 2.60). Three meta-analyses have confirmed the association between family history of PCa and risk of PCa in men. It has been proposed that there may be a hereditary component to PCa risk. This has been attributed to genes in 7 different loci. Although the role played by these genes in the development of PCa is unknown, it is estimated that they contribute to less than 5–10% of the disease risk.13,14

Linkage studies using genetic markers to search for chromosomal regions that show excessive sharing of inherited alleles in cancer affected families have been helpful in identifying important cancer susceptibility genes in other cancers. Advances in biogenetics have allowed identifying the numerous allelic low penetrance mutations denominated genetic polymorphisms, which are involved in the rest of familial forms of PCa. Some authors attribute up to 40% of all PCa to genetic factors. The highest risk is caused by the involvement of the hereditary factors as mentioned in Table 2, which increase the neoplastic transformation of prostate epithelial cells.13

**Insulin-Like Growth Factors**

Insulin-like growth factor (IGF-I), a polypeptide with mitotic and antiapoptotic effects.1 It has demonstrated to play a crucial role in PCa biology and to be implicated in both mitogenic and anti-apoptotic events in PCa cell lines.15

The Insulin-Like Growth Factor family involves the combination of two ligands (IGF-I and IGF-II), two receptors (IGF-IR and IGF-IIR), six high-affinity binding proteins (IGFBPs 1–6), a large group of IGFBP proteases and a new group of proteins, which is low-affinity IGFBP-related proteins (IGFBP-rPs). Members of this family form a network of interactions both among themselves and with other GF families and their signalling pathways.16

Several studies have related serum levels of IGF-I to PCa risk, both among cases and controls, and some of these studies, but not others, have shown a direct association between IGF-I and cancer risk. One of the most informative studies is a prospective nested case-control investigation of 152 PCa patients and controls derived from the Physicians’ Health Study. Elevated serum IGF-I could be observed in men at least 5 years prior to
European population, high circulating IGF-I concentration is positively associated with risk for PCa over the short and long term, circulating IGF-I concentration was associated with a significant increased risk for PCa \[ OR \text{ for highest vs. lowest quartile, } 1.69; 95\% \text{ confidence interval (CI), } 1.35-2.13; P(trend) = 0.0002 \].

Sexually Transmitted Disease (STD)

Several epidemiologic studies have suggested that factors related to sexual behaviour and STDs may be associated with PCa. In 1990, McNicol and Dodd reported that HPV type 16 and 18 are present in normal and cancer tissues of human prostate. Since 1990, many studies have detected high-risk HPVs in PCa tissues by Southern Blot and/or polymerase chain reaction (PCR) analysis. It conclude that infection and subsequent inflammation in the prostate is speculated to be several microorganisms that cause prostatitis or sexually transmitted infections may be an important risk factor in the pathogenesis of PCa. Approximately 13 published studies looked for the presence of HPVs in prostate carcinomas. These investigations revealed that the presence of these viruses vary from 4.2\% to 53\%. Meta analysis from Taylor et al examined the current epidemiological evidence for the association between specific STD and PCa. Significant elevated ORs for PCa were demonstrated for any STDs (1.48, 95\% confidence interval [CI] 1.26-1.73), gonorrhea (1.35, 95\% CI 1.05-1.83), and human papillomavirus (1.39, 95\% CI 1.12-2.06). This meta-analysis provides evidence of a higher rate of PCa in men with a history of an exposure to gonorrhea, HPV, or any STD.

Stark et al suggest men who had been infected with the STD trichomoniasis were only slightly more likely to develop PCa years later, compared to men with no documented evidence of prior infection, they were nearly three times as likely to die of the disease once they had PCa. The finding suggests that infection may make PCa more aggressive and more likely to progress. This large prospective case control study obtained further support for an association between a seropositive status for antibodies against Trichomonas vaginalis and the risk of PCa, with statistically significant associations

<table>
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<tr>
<td>1q42-43</td>
<td>PCaP</td>
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<tr>
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Adapted from Tortajada and castell. The diagnosis of PCa. Clinical and pathologic parameters were correlated with IGF-1 receptor intensity and frequency of staining. Only 2–3 staining on a scale of 0–3 was considered positive in this evaluation. These data show that the IGF-1 receptor is expressed in PCas and node metastases. The data showed that stromal expression of the receptor is associated with higher Gleason score support the hypothesis that there is an association between IGF-1 receptor and a more aggressive tumor phenotype. In the
identified for the risk of extraprostatic PCa and for clinically relevant, potentially lethal PCa.21

**Obesity**

Obesity is suspected to be a risk factor for aggressive PCa due to its associations with altered circulating levels of metabolic and sex steroid hormones involved in prostate development as well as oncogenesis.22 It was hypothesized that underlying the relationship between adiposity and tumor development involve adiposity related changes in metabolism and endogenous hormone levels.2 An important specific metabolic consequence of obesity, particularly when combined with physical inactivity, is a reduced tissue response to insulin, especially in terms of reduced uptake of glucose. This insulin resistance leads to chronically elevated blood levels of insulin, which is a growth-enhancing hormone and thus is a biologically plausible risk factor for cancer development and progression.23

One possible explanation for the lower risk of PCa diagnosis among obese men is that cancers may be more difficult to detect.24,25 Consequently, obese men are less likely to have an elevated PSA, less likely to undergo a biopsy, and thus less likely to be diagnosed with PCa, moreover obese men have larger prostate size making cancer detection at biopsy more difficult.25 Because obesity is a potential factor leading to lower detection of PCa, clinicians should consider Body Mass Index (BMI) when interpreting PSA concentration. Inclusion of BMI along with other factors that are currently included (race, rectal screening, and family history) in the existing PCa risk calculator, improve its performance.26

Three meta analyses reported a positive association between obesity and PCa incidence. The relative risks (RRs) in these studies were modest yet consistent, from 1.01 (95% confidence interval [CI], 1.0–1.02) per 1 kg/m² increase in BMI to 1.05 (95% CI, 1.01–1.08) and 1.03 (95% CI, 1.0–1.07) per 5 kg/m² increment in BMI.24 Data from three National Survey that present study linking evidence from 3 large nationally representative samples of the US population notes that obesity is associated with higher PCa progression and mortality despite an association with lower prostate ca incidence.26

**Smoking**

Tobacco and cigarette smoke contains over 4,000 chemicals, among which more than 60 are listed as class 1 or class 2 carcinogens according to the International Agency for Research on Cancer (IARC).27 However, constituents of cigarette smoke, such as polycyclic aromatic hydrocarbons (PAH), required metabolic activation, evasion of detoxification processes, and subsequent binding to DNA to exert their carcinogenic action. Therefore, functional polymorphisms in genes involved in PAH metabolism and detoxification may modify the effect of smoking on PCa.28 An association with smoking could also have a hormonal basis: male smokers were found to have elevated levels of circulating androsterone and testosterone, which may increase PCa risk or contribute to cancer progression.27,29

A meta-analysis from Huncharek et al27 with 24 prospective cohort studies evaluated the relationship between smoking and PCa. The studies enrolling 21579 PCa case participants for a general variance-based meta-analysis. Results. In the pooled data, current smokers had no increased risk of incident PCa (RR=1.04; 95% CI=0.87-1.24), but it was stratified by amount of smoking. It had statistically significant elevated risk (cigarettes per day or years: RR=1.22; 95% CI=1.01, 1.46; pack years of smoking: RR=1.11; 95% CI=1.01, 1.22). Former smokers had an increased risk (RR=1.09; 95% CI=1.02, 1.16). Current smokers had an increased risk of fatal PCa (RR=1.14; 95% CI=1.06, 1.19). The heaviest smokers had a 24% to 30% greater risk of death from PCa than did nonsmokers. This observational cohort studies showed an association of smoking with PCa incidence and mortality.27,29

Most studies examining relationship between smoking and PCa recurrence or PCa related mortality demonstrated that smoking related to an increasing in PCa recurrence and mortality, even after controlling for multiple factors including the more advanced malignant disease at presentation. Gutt et al reported follow-up data from 434 patients after external-beam radiation therapy with curative intent. In patients who
had been current smokers at the time of therapy, they found a recurrence rate 5.2 times greater than the rate of life-long nonsmokers, and in former smokers, the recurrence rate was 2.9 times greater.30

**Alcohol Consumption**

Alcohol consumption is one of the most important risk factors for human cancers, but also potentially one of the largest avoidable factors. Alcohol consumption is generally measured in drinks per day, with a “typical” drink of alcohol containing about 15 g of ethanol irrespective of the type of beverage consumed (beer, wine and liquor, straight or mixed). Alcohol use, and particularly heavy use, may be a possible risks factor of cancers including prostate.31

Evidence suggests that the effect of alcohol is modulated by polymorphisms in genes encoding enzymes for ethanol metabolism (e.g. alcohol dehydrogenases), folate metabolism and DNA repair.32

Dennis et al reported that there was a significant relationship between higher PCa risk and higher number of alcohol intake. It showed that RR of PCa risk increased from 1.05 for one alcoholic drink per day to 1.21 for four alcoholic drinks per day.33,34

**Vasectomy**

Vasectomy is the most frequent of male contraception in the United States, with approximately 500,000 procedures performed annually. It has been associated in some studies with increased PCa risk.35 There is no proven biological mechanism that might explain an association between vasectomy and PCa has been identified. In studies demonstrating small relative risks, data were limited by methodological shortcomings and potential biases, including detection and misclassification bias.36

**Diet**

1. Saturated animal fat

A high caloric intake of saturated animal fat has often been associated with an increased risk of PCa due to increasing testosterone levels.37-39

Mucci et al, Platz et al and Pauwels et al concluded that animal fat consumption per capita are positively associated with the incidence and mortality of PCa. The studies revealed a relation between fat intake and advanced PCa with OR=1.6-2.9.38

A recent case control population based study in patients ≤60 years found a statistically significant PCa risk comparing high and low intake of total fat to PCa risk 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 polysaturated fat with OR = 2.34 (CI 95%: 1.59-3.46).40

The possible biological mechanisms involved between saturated animal fat and PCa risks are the following: (a) high energy intake increases basal metabolism and insulin growth factors, tumor proliferation, (b) lipid metabolism generates free radicals, leukotrienes, prostaglandins, (c) promotes prostate carcinogenesis via androgen.41,42

2. Meat (red, smoked, and seasoned)

Meat has been related to carcinogenesis as observed in the high correlations between per capita meat consumption and cancer incidence and mortality.43

World Research Cancer and Fund (WCRF) study showed that consumption of <500 g of red meat per week (OR = 0.77; 95% CI: 0.61, 0.98) was significant predictor of decreased risk of a highly aggressive Pca. Recent studies directly associate the high intake of these varieties of meat with risk of PCa and PCa mortality. Cooking at elevated temperature (125-300oC) causes the formation of mutagenic heterocyclic amines.38,39,43

Rohman et al showed that men consuming ≥5 servings/week of processed meat had higher risk of PCa compared with men who eat ≤1 servings/week.44 Similarly, high consumption of red meats increased PCa risk among black men in U.S.

3. Calcium, Milk and Dairy Products

Milk and dairy products contribute to the increase of saturated animal fats level as it provides high calcium content.40A 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 significant higher risks of PCa than men with lower dietary 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.\textsuperscript{41,43} Dairy products, significantly increased the risk of PCa when compared with those who consumed the most versus the least; a 63%, 53%, and 52% increased risk, respectively.\textsuperscript{45,46}

There is a biological possibility for the role for calcium in prostate carcinogenesis. Intracellular calcium pools have been shown to control PCa cell growth and susceptibility to apoptosis. Therefore, small alterations in calcium homeostasis could result in increased proliferation, differentiation, and apoptosis in PCa cells.\textsuperscript{47,48}

**PREVENTION OF PROSTATE CANCER**

**Soy**

Soy, containing protein and phytoestrogens, has been identified as dietary component that may play an important role in reducing the incidence of PCa.\textsuperscript{49} The family of phytoestrogens is composed of four classes such as isoflavones, flavonoids, coumestans, and lignans. In soy, the primary isoflavone correlated with PCa is genistein and biochanin-A.\textsuperscript{50}

Genistein has been shown to exhibit potent anti-proliferative effect on various cancers. The study indicates that genistein consumption is associated with a lower incidence of clinical PCa metastasis through its effect on PCa cell invasion inhibition. Meta analyses of the two studies including men with identified risk of prostate cancer found a significant reduction in PCa diagnosis following administration of soy isoflavones (RR = 0.49, 95%CI 0.26, 0.95).\textsuperscript{30,51}

**Lycopene**

Lycopene is a bright red phytochemical in the carotenoid family that have potent antioxidant properties.

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.\textsuperscript{52} Giovannucci et al highlighted the reduction in PCa risk associated with both tomato product consumption and lycopene intake in a large, multicenter cohort of health professionals. From five major carotenoids, only lycopene intake was associated with reduced risk (RR=0.79, 95% CI=0.64-0.99, for high versus low quintile of intake). A phase II randomized clinical trial of 15 mg of lycopene supplementation twice daily for 3 weeks before radical prostatectomy exhibited a decrease in the plasma IGF-I levels with no significant changes in Bax and Bcl-2.\textsuperscript{52,53}

Lycopene and other carotenoids have a number of cancer-preventive biological effects including (a) inhibition of growth and induction of differentiation in prostate cancer (b) up-regulation of connexin 43 (Cx43) and increased gap junctional intercellular communication, and (c) prevention of oxidative DNA damage.\textsuperscript{54,55}

**Green Tea (EGCG)**

Based on epidemiological data the incidence of Pca is very low in East Asian countries where green tea is a highly consumed beverage. This might be explained partly by the fact that oral consumption of green tea polyphenols containing one of the catechins called epigallocatechin-3-gallate (EGCG) that has chemopreventive effects in PCa experimental models.\textsuperscript{56,57}

Administration of a green tea polyphenol infusion (0.1% in drinking water) to the Transgenic Adenocarcinoma of the Mouse Prostate (TRAMP) mice for 24 weeks markedly inhibited PCa development and distant site metastases.\textsuperscript{56,57}

It has been suggested that EGCG in green tea possesses the most potent activity against all stages of multistage carcinogenesis. After supplementation of EGCG, plasma concentration has increased up to 4,400 pmol/mL, enough to exert antioxidant activity in the blood stream.\textsuperscript{56-58}

Nam et al reported that EGCG potently and specifically inhibits the chymotrypsin-like activity of the proteasome in vitro (50% inhibitory concentration [IC 50] = 86–194 nmol/L) at the concentrations found in the serum of green tea drinkers.\textsuperscript{58}

**Supplementation**

a. **Vitamin E**

Vitamin is a main liposoluble antioxidant of the human organism with additional anti PCa effects.\textsuperscript{59,50} Vitamin E consists of tocopherols and tocotrienols. Tocopherols are the major source of vitamin E in the diet. The relationship
between vitamin E nutrition and PCa risk has been investigated in many epidemiologic studies. It showed controversial result, which 7 of 14 case control studies showed an inverse association between dietary or blood levels of tocopherols and PCa risks.\textsuperscript{61,62} \(\alpha\)-tocopherols supplementation was found to be significantly associated with lower incidence of PCa (as a secondary endpoint), and higher serum \(\alpha\)-Tocopherol was associated with a reduced risk of PCa.\textsuperscript{59,62} These results encouraged the launching of the Selenium and Vitamin E Cancer Prevention Trial (SELECT).\textsuperscript{59,61,62}

b. Vitamin D

Vitamin D acts as a regulatory hormone for multiple cell activities in the human body. The activated form of vitamin D is 1,25-OH2 vitamin D can potentially play a role in cancer pathogenesis.\textsuperscript{63,64} John et al. demonstrated a significant inverse association between UVR and PCa risk.\textsuperscript{64} Barnett et al. collected data from cancer registries of several countries that were categorized as sunny or less sunny. It was found that the risk of secondary solid cancer after melanoma was significantly lower in sunny countries compared with less sunny countries. It concluded that vitamin D production in the skin reduced the risk of several solid tumors, including PCa.\textsuperscript{63}

Ma et al. found an inverse association was observed between vitamin D receptor polymorphisms and PCa risk in men with low serum vitamin D levels, strengthened by Tuohimaa et al.\textsuperscript{65-67}

Shui et al conclude Higher 25(OH)D levels were associated with a 57\% reduction in the risk of lethal PCa (OR=0.43, 95\% CI=0.24-0.76).\textsuperscript{67}

c. Selenium (Se)

Selenium concentration is accumulated in plants (cereals, legumes, and tubers) and animals (eggs, meat, fish, and seafood). The trace element selenium used to be treated as a very toxic substance, but modern science now regards it as essential but in small quantities.\textsuperscript{67}

Epidemiologic studies show lower mortality of PCa in countries and regions with soils rich in selenium (Se). Meta-analysis of 16 epidemiological studies (11 cohorts and 5 case-controls) documents PCa risk reductions between 16\%-28\% when comparing high to low selenium consumption.\textsuperscript{68} Another systematic review and meta analysis from The World Cancer Research Fund/American Institute for Cancer Research Continuous Update Project database with 12 studies including total of 13,254 participants and 5007 cases of PCa. The relationship between serum selenium and PCa in meta-analysis showed that the risk decreased with increasing plasma/serum selenium up to 170 ng/mL.\textsuperscript{69}

Exercise

Exercise is one of the modified lifestyle therapy that appear to offer many benefits and relatively few side effects. Lack of exercise has also been linked to increased PCa risk. Antonelli et al found that veterans who exercised were significantly less PCa risks.\textsuperscript{70}

Several studies showed that physically active PCa patients have significantly greater quality of life, less fatigue, and lower PSA levels and delay in initiating ADT by two years compared with less active PCa peers. They also have significantly lower serum insulin and insulin-like growth factor (IGF-1), higher IGF binding protein (IGFBP-1), and a lower risk of high-grade disease (Gleason score 7 or greater) compared with less active PCa patients.\textsuperscript{70}

CONCLUSION

Numerous epidemiologic studies have linked PCa risk to various factors, i.e. age, ethnicity, family history, insulin like-growth factors, lifestyle, diet, environmental and occupational exposures. The results of epidemiological, in vivo, in vitro, and early clinical studies suggested that selected dietary products and supplementation may play a role in PCa prevention. More studies are still needed to explore and find the risk factors and preventive methods of PCa development. It is important for clinician to elaborate these informations for education to lower PCa risks and encourage PCa prevention.

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screening committee (UKNSC) the policy review process is described in detail at http://www.screening.nhs.uk/policyreview. 2010.


