

## Prevention and Early Detection of Urologic Cancers: A Mini-Review

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### Abstract

Urological cancers are among the commonest cancers in western countries. Progress in the domain of prevention and early detection of cancer is well known by researchers but studies have shown that advices for patients are sparse, inconsistent and even contradictory. The possible beneficial effects for prevention and early detection of urologic cancers are addressed in this mini-review. Emphasis will be placed on the role of alcohol and tobacco use, natural compounds, dietary supplements, early detection and pharmacological therapy on the risk of each urologic cancer. Most evidence suggests that alcoholic beverages contain a variety of carcinogenic contaminants that are introduced during fermentation and production. Many chemicals are present in tobacco smoke, including at least 69 known carcinogens. Smokeless tobacco, chewing tobacco and dipping snuff contains at least 28 carcinogens. Calorie restricted diet is associated with improvement of urologic cancer outcomes. Obesity is an established risk factor for kidney and prostate cancer. There is an association between obesity and cancer-specific mortality in bladder cancer. There is limited evidence indicating no association between physical activity and testicular or bladder cancers but a growing body of research suggests a modest risk reduction for kidney cancer and advanced prostate cancer. It seems to be no effect of lycopene and carbohydrates with prostate cancer chemoprevention. In addition, there is little evidence to support daily use of multivitamins to protect against urologic cancers. The tremendous potential benefits of catechins in tea, pomegranate, luteolin and flavanoid, needs further studies to confirm their role in urologic cancers chemoprevention. For medical agents, statins and 5 alpha reductases inhibitors are good candidates for future studies. Screening is not recommended for all urologic cancers except for prostate cancer where controversies remain. In contrast, opportunistic screening leads to early detection and decrease specific cancer mortality for almost all urologic cancers.

**Keywords:** Urologic cancers; Prevention; Screening; Early detection

### Introduction

Cancer has overtaken cardiovascular disease to become the leading cause of death among men and women younger than 85 years in the United States, and the number of cancer deaths continues to increase [1]. Urological cancers (prostate, bladder, kidney and testicular) are among the commonest cancers in western countries. They affect both men and women, although more common in men. They account for one in three of all cancers in men, and one in five of all cancers in the general population [2].

In many respects, cancer could be considered as a preventable disease. Estimates indicate that approximately half of the cancers occurring today either arise from modifiable risk factors or can be detected as precursor lesions before the development of disease with metastatic potential [1]. In addition, about one-third of cancers in high-income Western countries are attributable to factors relating to food, nutrition, and physical activity [3]. Although diet, obesity, and physical inactivity are modifiable causes of cancer, it is challenging to identify with confidence specific associations between these factors and cancer over a lifetime, because of the long latent period for cancer development and its complex pathogenesis.

Prevention of cancer can take place on several different levels: primary prevention addresses the cause of cancer to protect healthy people from developing it, secondary prevention identifies disease in its earliest stages to slow its progression, and tertiary prevention reduces complications of disease to maximize quality of life. In most cases, a combination of primary, secondary and tertiary interventions are needed to achieve a meaningful degree of prevention and protection.

Although progress in the domain of prevention of cancer is well known by researchers, studies have shown that advices for patients are sparse, inconsistent and even contradictory. Very few top cancer centers provide online specific recommendations about cancer prevention. Moreover, practitioners are facing an increase demand from the patients for nutritional recommendations before and especially after treatment of cancer.

For urological cancers, the problem is more profound. Finding an association between common dietary regimen or natural compounds or common prescribed medication in elderly and prostate cancer which is a common disease in elderly is difficult. In addition, assessing the association of risk factors with less common cancers like kidney and testicular cancer is more challenging and evidence base is more limited. Another difficulty stems from the long latency period for urologic cancers which makes epidemiological studies and surveys difficult to realize.

In clinical practice, assessment of an individual's risk is a key step in urologic cancer prevention; Review of personal and family medical history, work history, and lifestyle can help identify cancer risk factors, which may be modifiable or nonmodifiable. Combinations of these risk factors place some people at particularly high risk. In this mini-review, we address the possible beneficial effects studied for prevention of urologic cancers. Emphasis will be placed on the role of alcohol and tobacco use, natural compounds, dietary supplements, early detection and pharmacological therapy on the risk of each urologic cancer.

### Lifestyle and Dietary Factors

#### Alcohol

Alcohol is a common term for ethanol or ethyl alcohol, a chemical substance found in alcoholic drinks as well as in some medicines,

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mouthwashes, household products, and essential oils. Alcohol is produced by the fermentation of sugars and starches by yeast. Alcoholic drinks contain different percentages of ethanol, but in general a standard size drink of any type-12 ounces of beer, 5 ounces of wine, or 1.5 ounces of 80-proof liquor contains about the same amount of ethanol (about half an ounce). There is some evidence in the literature suggesting that the amount of alcohol consumed over time and not the type of alcoholic beverage is the most important factor in raising cancer risk [4].

Most evidence suggests that alcoholic beverages contain a variety of carcinogenic contaminants that are introduced during fermentation and production, such as nitrosamines, asbestos fibres, phenols, and hydrocarbons. In addition, acetaldehyde, a metabolite of ethanol is a well established toxic chemical. By damaging DNA and proteins, it is incriminated by researchers to be a probable human carcinogen. Ethanol may also generate reactive oxygen species which can damage DNA and proteins. Another mechanism of carcinogenesis could be by interfering with the absorption of a variety of nutrients known to influence the process of carcinogenesis [5].

In their meta-analysis, Song et al. found that alcoholic beverage intake was inversely associated with a lower risk of renal cell cancer, with moderate consumption conferring the protection and higher consumption conferring no additional benefits [6]. The association was found in each sub group (wine, beer, whiskey). For testicular and prostate cancers, numerous studies have examined their association with alcohol consumption. For these cancers, either no association with alcohol use had been found or the evidence for an association was inconsistent [7,8]. However for bladder cancer, there is strong evidence suggesting that alcohol consumption slightly increase the risk [9].

### Tobacco use

Tobacco consumption is common, and thus its epidemiologic impact is massive. An estimated 20% of adults in the United States and Europe are current cigarette smokers. Tobacco use accounts for approximately one third of cancer deaths in the US [10]. Of these, kidney and bladder cancer mortality have also been linked to smoking [11]. Many chemicals are present in tobacco smoke, including at least 69 known carcinogens [12]. Smokeless tobacco chewing tobacco and dipping snuff contains at least 28 carcinogens [13]. Smoking may also promote more aggressive forms of cancer: for example, tobacco use was associated with higher-grade and higher-stage prostate cancer in large scale epidemiological studies [14,15].

Smoking is recognized as an etiologic factor for urothelial cancer accounting for 50% of tumours [16]. Tobacco smoke contains aromatic amines, such as b-naphthylamine, and polycyclic aromatic hydrocarbons known to cause urothelial cancers. These are renally excreted and exert a carcinogenic effect on the entire urinary system. There is some evidence suggesting that pipe, cigar and environmental smoking slightly increase the risk of urothelial bladder tumour [16].

The association between renal cell cancer and cigarette smoking is also well established, although reported risk increases for ever-smokers compared with never-smokers are moderate. In a recent meta-analysis, ever-smoking produced a relative risk for renal cell cancer of 1.38, and risk increases were generally greater among men than women [17]. There is also strong evidence suggesting that smoking cessation confers protective effects in kidney cancers [17].

If smoking is a well known risk factor for kidney and bladder cancers, its relationship with prostate cancer risk is less clear. In a recent meta-analysis, current smoking was not associated with risk of

prostate cancer, but there was an increased risk among heavy smokers. However, in that study, current smoking was associated with increased prostate cancer mortality and a recent study showed that smoking at the time of diagnosis was related to a higher risk of prostate cancer-specific mortality [15].

### Alimentary habits and physical activity

The assumption that calorie restricted diet is associated with improvement of cancer outcomes is corroborated by both animal experiments and epidemiological studies. Mice fed a calorie-restricted diet had significantly slower tumour growth than those fed their regular diet [18]. Multiple population-based studies of underweight patients have revealed a significantly lower cancer incidence than in the general population [19,20]. Furthermore, obesity was an established risk factor for kidney and prostate cancer in a comprehensive systematic review of epidemiological studies by the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) [21,22]. Prospective studies have also demonstrated an association between obesity and cancer-specific mortality, in bladder cancer [23]. For physical activity, if there is convincing evidence that it protects against colon and breast cancers, association with urologic cancers is less well explored. There is limited evidence indicating no association between physical activity and testicular or bladder cancers but a growing body of research suggests a modest risk reduction for kidney cancer [24-26]. Also, a large number (>30) of studies suggests a probable small decrease in prostate cancer risk which is likely driven by the effect on advanced/aggressive tumors [26-29]. The role of physical activity in decreasing urologic cancer risk is thus likely limited to advanced prostate and possibly kidney cancers with no association in testicular or bladder cancers.

For diet and alimentary habits, evidence has also accumulated, over the last years, suggesting that by systematically reducing the amount of dietary carbohydrates (CHOs) one could suppress, or at least delay, the emergence of cancer, and that proliferation of already existing tumor cells could be slowed down [30]. This hypothesis is supported by the association between modern chronic diseases like the metabolic syndrome and the risk of developing or dying from cancer [31]. CHOs or glucose, to which more complex carbohydrates are ultimately digested, can have direct and indirect effects on tumor cell proliferation: first, contrary to normal cells, most malignant cells depend on steady glucose availability in the blood for their energy and biomass generating demands and are not able to metabolize significant amounts of fatty acids or ketone bodies due to mitochondrial dysfunction. Second, high insulin and Insulin-like Growth Factor (IGF)-1 level resulting from chronic ingestion of CHO-rich Western diet meals, can directly promote tumor cell proliferation via the insulin/IGF1 signaling pathway. Third, ketone bodies that are elevated when insulin and blood glucose levels are low, have been found to negatively affect proliferation of different malignant cells in vitro or not to be usable by tumor cells for metabolic demands, and a multitude of mouse models have shown antitumorigenic properties of very low CHO ketogenic diets [32,33]. Large observational studies suggest that high intake of refined carbohydrates may be associated with increased risk of prostate cancer [34]. However no significant associations with high-risk prostate cancer are found and not all foods that are typically high in refined carbohydrates were associated with prostate cancer [35].

Alimentary regimens rich in animal fat are known to be carcinogenic for several cancers but the evidence in urology is less clear. For kidney cancer, a pooled analysis of 13 prospective studies in 2008 found a statistically significant positive associations or trends

in pooled age-adjusted models for intakes of total fat, saturated fat, monounsaturated fat, polyunsaturated fat, cholesterol, total protein, and animal protein. However, these associations were attenuated and no longer statistically significant after adjusting for body mass index, fruit and vegetable intake, and alcohol intake. Intakes of fat and protein or their subtypes, red meat, processed meat, poultry, and seafood were not associated with risk of renal cell cancer as there were no clear associations between intakes of coffee, tea, milk, juice, soda, punch, and water and risk of renal cell cancer. Greater total fluid intake didn't reduce the risk of renal cell cancer [36].

For bladder cancer, there is no strong evidence in the literature suggesting an association of bladder cancer with beverages of coffee, tea, milk, juice, soda, punch, and water. Like for kidney cancer, greater total fluid intake doesn't reduce the risk of bladder cancer. A diet rich in fruits was found to slightly decrease the risk of bladder cancer [37].

There are some prospective studies suggesting a positive association between prostate cancer and high intake of red meat cooked at high temperatures, pan-fried, or well-done [38]. Processed meat intake was also associated with bladder cancer in two prospective studies [39]. Summary of findings of multiple studies for each urologic cancer are shown in Tables 1, 2 and 3.

### Chemoprevention

Cancer chemoprevention is defined as pharmacological intervention with synthetic or naturally occurring compounds that may prevent, inhibit, or reverse carcinogenesis, or prevent the development of invasive cancer. An ideal chemopreventive agent is expected to be nontoxic, effective at low doses, orally taken, and inexpensive.

### Nutrients

If epidemiologic studies have consistently found that a diet rich in fruits and vegetables is associated with reduced risk for cancer, it remains unclear whether daily multivitamins can result in a similar benefit. Multivitamin use is widespread among adults in the United States, with nearly one half of all Americans taking some form of dietary supplement and one third taking a daily multivitamin. Despite the popular belief that daily multivitamins protect against cancer, there is little evidence to support such claims in human trials. Several large-scale observational studies have found no association between multivitamin use and cancer [40,41], and some have even reported increased mortality among patients taking multivitamins [42,43].

For prostate cancer, high dietary intake of zinc was associated with lower prostate cancer specific mortality after diagnosis particularly in men with localized disease in a Swedish cohort published in 2011 [44]. In vitro studies had demonstrated that Zinc-citrate compound can induce apoptotic cell death in castration resistant prostate cancer cell line, by caspase-3 activation through up-regulation of apoptotic proteins and down-regulation of antiapoptotic proteins [45]. Vitamin D3 supplementation at 4000 international units per day for one year had resulted in a decrease of positive cores at repeat biopsy in subjects with low-risk prostate cancer under active surveillance in an interventional study [46]. Several studies have shown that folate and vitamin B12 supplementation was not associated with a reduced bladder, kidney or prostate cancer risk [47-50].

As for selenium and vitamin E, there is considerable preclinical evidence suggesting a reduction of prostate cancer risk. Three large scale epidemiological studies have examined the impact of these nutrients

| Evidence                     | Convincing*                | Probable**   | Possible***                                    |
|------------------------------|----------------------------|--|--|
| Substantially increased risk |                            | -  | -  |
| Moderately increased risk    | First degree relatives     | Intakes of fat   | Surgery for Benign Prostatic Enlargment (RRx8) |
| Slightly increase risk       |                            | Carbohydrates intake<br>Vitamine E (400 UI/d)<br>Obesity<br>Milk diary | Surgery for Benign Prostatic Enlargment (RRx2) |
| No association               |                            | Selenium<br>Lycopene   |  |
| Slightly decreased risk      |                            | Zinc<br>Circumcision<br>Physical activity                              | Quercetin, Genistein, Resveratrol, Curcumin    |
| Moderately decreased risk    | Dutasteride<br>Finasteride | Fruit and vegetable intake<br>Epigallocatechin-3-Gallate               | Vitamine D                                     |
| Substantially decreased risk | -                          | -  | -  |

- \*>15 prospective study + mechanistic explanation
- \*\*5 <study < 15+mechanistic explanation
- \*\*\*<5 study with mechanistic explanation or 5<study <15 without mechanistic explanation

Table 1 : Prostate cancer and Prevention.

| Evidence                     | Convincing                  | Probable   | Possible                               |
|------------------------------|-----------------------------|--|--|
| Substantially increased risk | Cigarette smoking           | -  | -                                      |
| Moderately increased risk    | -                           | -  | -                                      |
| Slightly increase risk       | Alcohol consumption for men | -  | Pipe<br>Cigar<br>Environmental smoking |
| No association               | -                           | Coffee, Tea, Vegetable<br>Vitamin A (carotenoids)<br>Vitamin C | Total fluid<br>Folate                  |
| Slightly decreased risk      | -                           | Fruit  | -                                      |
| Moderately Decreased risk    | -                           | Selenium   | Vitamin E                              |
| Substantially decreased risk | -                           | -  | -                                      |

Table 2: Bladder Cancer and Prevention.

| Evidence                     | Convincing   | Probable   | Possible  |
|------------------------------|--|--|---|
| Substantially increased risk | Cigarette smoking<br>Obesity                               | -  | -   |
| Moderately increased risk    | HTA<br>First degree relatives                              | -  | -   |
| Slightly increase risk       | -  | -  | Pipe, cigar<br>Environmental smoking            |
| No association               | High alcoholic consumption<br>total fluid intake           | Intakes of fat and protein (red meat, processed<br>meat, poultry, and seafood) | coffee, tea, milk, juice, soda,<br>punch, water |
| Slightly decreased risk      | Moderate alcoholic consumption (beer,<br>wine and whiskey) | -  | -   |
| Moderately Decreased risk    | fruit and vegetable intake                                 | -  | -   |
| Substantially decreased risk | -  | -  | -   |

Table 3: Kidney Cancer and Prevention.

on prostate cancer. The Alpha-Tocopherol, Beta Carotene (ATBC) trial reported a 35% risk reduction for prostate cancer in men taking 50 mg/d of vitamin E for a median of 6.1 years [51]. Another large prospective randomized trial that had examined the effect of these 2 agents for prostate cancer prevention was The Selenium and Vitamin E Cancer Prevention Trial (SELECT) which had randomized in 2001 135 533 men into 4 groups: selenium with matching placebo, vitamin E with matching placebo, both agents, or placebo [52]. Initial data from SELECT, reported in late 2008, showed that daily selenium and vitamin E supplements, taken either alone or together for a median of 5.5 years, did not prevent prostate cancer [52]. The data also showed two concerning trends: a small increase in the number of prostate cancer cases in men taking only vitamin E, and a small increase in the number of cases of diabetes in men taking only selenium. Updated data from SELECT, reported in 2011, show that, after an average of 7 years (5.5 years on supplements and 1.5 off supplements), there were 17 percent more cases of prostate cancer in men taking only vitamin E than in men taking only placebos [53]. This difference, an absolute increase of 11 cases per 1,000 men, was statistically significant. The Physicians Health Study II (PHS II) conducted contemporaneously with SELECT intervention with 400 IU of vitamin E every other day for a median of 8 years had no effect on the incidence or overall mortality of prostate cancer [54].

The increased incidence of prostate cancer seen in SELECT, the previously reported increased incidence of lung cancer with high-dose beta carotene in both ATBC [51] and the Beta-Carotene and Retinol Efficacy Trial (CARET) [55], and the increased risk of colon polyps seen in a trial administering high-dose folate [56], suggest that caution should be used when recommending or studying high doses of micronutrients. As opposed to synthetic pharmaceuticals, these naturally occurring dietary constituents are part of normal physiology, and a U-shaped-dose response curve may exist where either deficiency or supraphysiological doses are harmful. Furthermore, the fact that the increased risk of prostate cancer in the vitamin E group of participants in SELECT was only apparent after extended follow-up suggests that health effects from these agents may continue even after the intervention is stopped, emphasizing the need for long-term follow-up even in trials closed before the planned intervention period is completed.

### Natural compounds

There is growing interest in medicinal botanicals as part of complementary medicine in the United States. Approximately 40% of Americans use alternative remedies, including herbal medicine, for disease prevention and therapy [57]. The high cost, side effects, and therapeutic limitations of conventional medications are key factors

that are driving the revival of herbal remedies. People can easily obtain herbal medicines or botanical supplements on an over-the-counter basis, and feel comfortable consuming these products, even though safety and efficacy are generally not established on a rigorous scientific basis. Moreover, dietary compounds have drawn a great deal of attention because of their safety and potential ability to reduce the risk of cancer.

### Tea beverages

Next to water, tea, a complex chemical compounds made from the leaves of *Camellia sinensis*, an evergreen shrub of the *Theaceae* family, is the most popular beverage consumed in the world and is distinguished by the presence of a group of polyphenols called catechins. A growing body of evidence from laboratory animal studies demonstrates that tea consumption has an inhibitory effect on carcinogenesis at various organ sites [58]. The bioavailability and biotransformation of tea polyphenols, however, are the key factors for the abovementioned chemopreventive effects of tea against tumorigenesis [59,60].

At present, epidemiological studies have not yielded conclusive evidence of the protective effect of tea consumption against the development of human cancers [61-63]. However, limited epidemiological studies suggest that people drinking more cups of tea regularly have a lower risk of prostate cancer [64].

Four major tea components epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin (EC), present in green, black and other teas act by inhibiting mutagenesis [65,66], genotoxicity [67,68], transformation [69-71], cell proliferation, [72-80] and angiogenesis [59,60]. Each mechanism involves multiple potential molecular targets. Although both black tea and green tea have been studied for their chemopreventive potential, green tea showed greater efficacy against prostate cancer probably because the concentration of EGCG is increased in green tea [74]. Studies of large populations of men have shown that those who consume green tea regularly are less likely to develop prostate cancer than men who shun the beverage [81]. In other studies, researchers found that the risk of prostate cancer decreases proportionally as the amount, frequency, and duration of green tea consumption increases [82]. In terms of amount of tea consumed, men who drank more than three cups of green tea daily showed a reduced risk of prostate cancer. In a large study that evaluated the green tea drinking habits of 49,920 men aged 40 to 69 who were followed for at least 10 years, the investigators found that men who consumed five or more cups of green tea daily had a reduced risk of advanced prostate cancer when compared with men who drank less than one cup daily [83].

It also appears that catechins in green tea may benefit men who have High Grade Prostatic Intraepithelial Neoplasia (HG PIN). In a 2006 a study published in Cancer Research, randomized 60 men who had high-grade PIN in a double-blind, placebo-controlled study. Men in the treatment group receiving three 200-mg capsules of catechins daily had significantly fewer cancer on the one year control biopsy compared with controls. For other urologic cancers no association was found [84].

### Carotenoids

Carotenoids are pigments that give yellow, red, and orange vegetables and fruits their colors. They are known for their antioxidant activity and their potential protective role against cancer. The body uses some types of carotenoids to make vitamin A. studies of vitamin A's possible role in urologic cancer prevention have been generally disappointing. There have been no consistent findings showing, in clinical trials, lower risk of cancers of bladder, or prostate due to diet rich in vitamin A [85]. Lycopene is another carotenoid compound that gives tomatoes and certain other fruits and vegetables their color. Though not considered an essential nutrient for humans, it is one of the major carotenoids in the diet of North Americans and Europeans. People who have diets rich in tomatoes, which contain lycopene, appear in some studies to have a lower risk of certain types of cancer, especially cancers of the prostate [86-88]. This finding has piqued interested in its use for prostate cancer prevention. Studies have examined the effects of lycopene on prostatic growth. In one study, normal human prostate epithelial cells were treated with synthetic lycopene [88]. High doses of lycopene inhibited the growth of prostatic epithelial cells supporting the notion that lycopene could be used clinically. A systematic review of the literature identified eight randomized controlled trials comparing lycopene with placebo for the treatment of prostate cancer [89]. A meta-analysis did not identify a significant decrease in the incidence of prostate cancer [90]. Consequently, there is insufficient evidence for or against the use of lycopene in prostate cancer.

### Saw palmitto

Saw palmetto is the common name for the plant *Serenoa repens*. Its putative mechanism of action may be to reduce dihydro-testosterone in prostatic tissue [91]. The use of saw palmetto for the prevention of prostate cancer was evaluated in a large epidemiologic study of 35,171 men [92]. Saw palmetto had no detectable effect on prostate cancer risk. There is currently no evidence to justify the use of saw palmetto for the prevention of prostate cancer.

### Pomegranate and luteolin

The fruit of the tree *Punica granatum* grown mainly in the Mediterranean region, has been shown to possess many medicinal properties such as being anti-oxidant and anti-inflammatory [93]. The antioxidant activity of flavonoids obtained from pomegranate juice was observed to be close to that of green tea and significantly greater than red wine [94-96]. Malik et al. observed growth inhibition in prostate cancer cells and decreased serum level of PSA [97]. Pomegranate extract also inhibited the proliferation of Human Umbilical Vein Endothelial Cells (HUVEC) and decrease the xenografted prostate cancer size, tumor micro vessel density, Vascular Endothelial Growth Factor (VEGF) levels, and Hypoxia-Inducible Factor (HIF) [98]. Pantuck et al. found a statistically significant prolongation of PSA doubling time in patients with rising PSA and treated with 8 ounces of pomegranate juice daily until disease progression suggesting a potential role for pomegranate in prostate cancer prevention. Pomegranate consumption may retard prostate cancer progression and improve patient's quality of life [99].

Luteolin, another flavonoid found in a variety of vegetables, especially in broccoli, celery, cabbage, spinach, green pepper, and cauliflower had the same anti-oxidant and anti-inflammatory properties as pomegranate [100]. Luteolin has been found to induce cell cycle arrest and apoptosis in a variety of cancer cells including prostate cancer cells both in vitro and in vivo [101].

### Soy isoflavones

Soy isoflavones include genistein, daidzein, and glycitein. Genistein is the most active and abundant isoflavone found in soybeans and soy products. It has Selective Estrogen Receptor Modulator (SERM) properties similar to tamoxifen and raloxifene [102]. Epidemiological studies show an inverse association between dietary soy consumption and the risk of prostate cancer [103]. Consumption of a soy isoflavone mixture consisting of genistein and daidzein inhibited prostate cancer cell growth in culture by inducing G2/M arrest and apoptosis, inhibited the secretion of PSA, and increased the radiation effect against prostate cancer in cell culture and in orthotopic and metastatic in vivo models [104,105]. On the basis of these observations, several early clinical trials either with genistein or soy products have been completed. A pilot study conducted in patients with prostate cancer and rising serum PSA levels suggested that soy isoflavones may benefit some patients with prostate cancer [106]. Another phase II trial in biochemically relapsed prostate cancer patients showed a significant decrease in the serum PSA level [107]. Moreover, soy isoflavones have shown potent anti-oxidant and anti-inflammatory properties and therefore could potentially protect normal tissues from radiation toxicity, thereby decreasing urinary, intestinal, and sexual adverse effects in patients receiving radiation therapy for prostate cancer [108-112].

## Pharmacological Therapy

### Alpha reductases inhibitors

Although two large randomized double-blind, placebo-controlled, multicenter trials have demonstrated that 5 $\alpha$ -reductase inhibitors reduce prostate cancer risk by 20% to 25% [113,114]; the use of these agents is controversial because of concerns related to an observed increased risk of high-grade disease. In the Prostate Cancer Prevention Trial (PCPT), finasteride significantly reduced by 26% the risk of prostate cancer compared to placebo. Reduction in risk was limited to Gleason score 6. However, a significant increased incidence of Gleason score 8-10 with finasteride compared to placebo (1.8% versus 1.1%, respectively) was noted [113]. In the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study, dutasteride significantly reduced by 23% overall risk of biopsy detectable prostate cancer when compared to placebo. This overall risk reduction was limited to a decrease in Gleason score 6 and an increased incidence of Gleason score 8-10 with dutasteride versus placebo (1% versus 0.5%, respectively) [114]. The possible induction of high-grade tumors is an area of concern with the use of 5-alpha reductase. FDA Drug Safety Communication had stated "5-alpha reductase inhibitors (5-ARIs) may increase the risk of a more serious form of prostate cancer".

A REDUCE Follow-Up Study assessed the occurrence of prostate cancer in the two years following the conclusion of the REDUCE study (REDEM). This study shows that with 2 years further follow-up beyond the original REDUCE trial there were no Gleason 8-10 tumors diagnosed. A possible reason for this difference is that any prostate cancer that may have been suppressed by dutasteride during REDUCE was no longer being suppressed for those subjects who did not continue 5ARI therapy [115].

Even if PCPT and REDUCE studies showed a decrease of cancers with the use of 5 alpha-reductase (5ARI) but with side effects, there is no indication for prostate cancer prevention by these drugs. In the same way, despite the results of REEDEM study, there is no indication of these drugs in active surveillance. Committee of Cancerology of the French Association of Urology noted that no recommendation can be given for indications of 5ARI in prevention or treatment of prostate cancer.

### Statins

Statin drugs are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the enzyme that controls conversion of 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, an essential precursor of cholesterol [116].

Statins are used to treat hypercholesterolemia and have been shown to reduce cardiovascular disease incidence and mortality [117]. Thus, use of statins has increased exponentially in the United States over the last decade [118]. Numerous in vitro experimental data have shown that statins exhibit antitumor effects against various leukemia cells and solid tumor cells of different origins. These effects primarily resulted from the suppression of proliferation and the induction of apoptosis [119]. Epidemiologic studies of statin use in relation to prostate cancer risk have been inconclusive. Recent evidence, however, suggests that longer-term use may reduce risk of more advanced disease [120].

By inhibiting the synthesis of cholesterol, a precursor of androgens, statin use could have beneficial effects in prostate cancer [121]. In experimental models, statins inhibit cell proliferation, inflammation, oxidative stress, angiogenesis, and metastasis in prostate cancer cells [122,123].

When interpreting studies linking statins to prostate cancer, four concepts should be kept in mind. First, different statins have different antiproliferative and proapoptotic effects on various tumor cell lines of differing origins. Second, the antitumor effects were found only when lipophilic statins (fluvastatin, lovastatin, cerivastatin, atorvastatin and simvastatin) were examined. Third statins differ significantly in their antitumor potential due to different physicochemical properties. Fourth, statin cytotoxicity may depend on the target tumour type [124].

Available evidence on bladder cancer is conflicting. The findings of a meta-analysis done by Zhang et al. suggested that there was no association between statin use and risk of bladder cancer. They concluded that more studies, especially RCTs, are needed to confirm the absence of association [125]. For kidney cancer, clinical studies have shown that statin use may modify the risk. However, these studies yielded different results. The findings of a meta-analysis done by the same authors, suggested that there was no association between statin use and risk of kidney cancer. They also concluded that more studies especially randomized controlled trials and high quality cohort studies with larger sample size, well controlled confounding factors are needed to confirm this association in the future [126]. The effects of statins on urologic cancers are described in Table 3.

### Biguanides

In the 1920s, biguanides were identified as the active ingredient of *Galega officinalis* and in the 1950s, they were developed as therapeutics. Since then, metformin has become the drug of choice for the treatment of type 2 diabetes. In addition, metformin can inhibit cancer cell growth in vitro [127-129]. Hirsch et al. explained that metformin selectively kills cancer stem cells and blocks tumor growth [130]. They also observed a synergistic action of metformin with chemotherapeutic

drugs in order to reduce tumor mass and prolongation of remission in nude mice. Meta-analyses of metformin and cancer risk in diabetic patients described around one-third reduction in overall cancer risk and cancer mortality in metformin users compared with other antidiabetic drugs [131,132]. However, a large multicenter study did not find an association between metformin use and risk of prostate cancer among older men with diabetes, regardless of cancer grade or method of diagnosis [133].

### Nonsteroidal anti-inflammatory drugs

The rationale for using aspirin and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in prostate cancer prevention stems from laboratory studies suggesting inflammation plays a role in prostate carcinogenesis [134]. Elevated levels of prostaglandin and cyclooxygenase-2 enzyme (COX-2) have been found in prostate cancer cell lines [135], and regression of HGPIN has been observed in mouse xenograft models treated with NSAIDs [136]. Several cohort studies examined the association between NSAIDs and prostate cancer risk. A meta-analysis in 2010 incorporated 24 observational studies [137]. Aspirin was associated with a 17% reduction in prostate cancer overall and a 19% reduction in advanced prostate cancer. Studies on NSAIDs without aspirin, had also demonstrated a reduced prostate cancer risk but the decrease was modest and they were not associated with reduced advanced cancer risk.

### Screening tests and early detection

There are two types of screening: organised screening programmes and opportunistic screening programmes. Organised screening programmes should be of a high standard, checked and monitored by people from outside the programme. Organised screening programmes refer to universal screening, mass screening or population screening and include tests and exams used to find a cancer in the absence of any symptoms.

Opportunistic screening refers to selective screening or individual early detection and takes place when someone asks their doctor for a check or test, or when the doctor offers a check or test to people who are known to be at higher risk of developing cancer.

Screening, however, is not without harms. The extent and magnitude of harms must be considered before screening is recommended. The harms of screening are to be individualized and weighed against the risks of disease and benefits of early detection. If the relative risk for disease is greater for the individual and the relative harms of screening is reduced, then screening with early disease detection is therefore desirable. Conversely, if the risk for disease is low, then the relative harms of screening may outweigh the relative benefits, and, consequently, it would be less attractive to screen. The harms of screening may be associated with true-positive and -negative and false-positive and -negative results. The diagnosis of inconsequential true-positive diseases may lead to investigation and treatment of diseases that may or may not affect an individual's life. A true-negative result is reassuring but can incur costs during the investigative process. False-negative results are potentially dangerous because they provide false assurances, which subsequently lead to delay and misdiagnoses. False-positive findings may result in inappropriate and excessive investigations that could be harmful. Guidelines should therefore provide explicit, unbiased, and relevant evidence to inform an individual's overall risk of disease, benefits, and harms when making the eventual decisions on screening [138].

## Kidney cancer

Kidney cancer is one of the rare cancer models explaining that screening should be individualized and weighed against the risks of disease and benefits of early detection. In the era of medical imaging, the annual incidence of renal cell carcinoma has been rising, with the greatest increase observed for cases with localized tumors [139-142]. Ablative surgery for small renal masses had paralleled their rising incidence with the assumption that early intervention will achieve netter survival outcomes [143,144]. However, this assumption is not supported by population-based mortality data [139,140]. This suggests a need for careful assessment of the benefits of screening that may lead to investigation and treatment of diseases that may or may not affect an individual's life. The significance of early detection of small renal masses is under debate that's why, in the present base of knowledge, all professional organizations recommend against kidney cancer mass screening. Opportunistic screening with annual kidney ultrasound should be offered only to high risk population: chronic kidney failure, dialysis and kidney transplants. In patients with a family history of hereditary kidney tumour, genetic counselling is advised. Depending on the histological and syndromic features, genetic testing for a particular mutation can be initiated in an affected member. In most cases, this provides presymptomatic diagnosis, or confirms the diagnosis, especially in cases in which a family mutation is already known. Mutation negative cases can be reassured that there is no significantly higher risk for renal cancer in them or their children. Mutation carriers can be entered into a screening program. Patients harbouring the same mutation should be offered kidney ultrasound every two years from the age of 30 years or 10 years before the earliest tumour was diagnosed in a family member.

## Testicular cancer

There is no standard or routine screening test used for early detection of testicular cancer. Most often, testicular cancer is first found by patients themselves, either by chance or during self-exam. Sometimes the cancer is found by doctors during a routine physical exam or for unspecific scrotal complaints. No studies have been done to find out if would decrease the risk of dying from this disease. A Cochrane review identified no randomised controlled trials that have evaluated the effectiveness of testicular self-exams, regular exams by a doctor, or other screening tests in men with no symptoms on the risk of dying from the disease [145]. In the absence of any evidence from high quality randomised controlled trials, there is insufficient evidence to unequivocally support, or refute, screening for testicular cancer. The USPSTF (United States Preventive Services Task Force) recommends against routine screening for testicular cancer in asymptomatic adolescent and adult males [146]. The USPSTF based this recommendation on the relative rarity of testicular cancer, the lack of evidence showing the accuracy of clinical or self-examination, and highly favourable outcomes from treatment even with advanced disease. However, The USPSTF did not review the evidence for screening among men with at increased risk for testicular cancer. Furthermore, routine screening probably would not decrease the risk of dying from testicular cancer but finding it early may make it easier to treat. Patients who are diagnosed with testicular cancer that has not spread to other parts of the body may need less chemotherapy and surgery, resulting in fewer side effects. The ACSP states « check up for men > 20 years should include examination for testicular cancer » and the EAU states « self physical examination is advisable for individuals with clinical risk factors » [147].

## Bladder cancer

Screening test used in primary care include urine dipstick or microscopic urinalysis for hematuria, urine cytology, and tests for urine biomarkers. Positive screening results are referred to a urologist for cystoscopy and biopsy/resection, imaging, and other studies if tumour is found. Urinary cytology is convenient and detects bladder cancer with high specificity, but its diagnostic ability is rather disappointing due to its low sensitivity (40-76%) [148]. Cystoscopy is highly invasive and relatively expensive, and thus, majority of the patients would be distressed. In clinical practice, the positive predictive value of screening is <10% in asymptomatic persons [148]. For urine biomarkers, a number of urine-based tests have been developed. These include tests based on Bladder Tumour Antigen (BTA), Nuclear Matrix Protein 22 (NMP22), urine fibrin and Fibrinogen Degradation Products (FDP), ImmunoCyt, and FISH (UroVysion) [149-151]. However, the diagnostic capability of all of these tests is insufficient to recommend them in clinical practice. Furthermore no randomized trials or high-quality controlled observational studies had evaluated clinical outcomes associated with screening compared to no screening, or treatment of screen-detected bladder cancer compared to no treatment. In addition, no study had evaluated the sensitivity or specificity of tests for hematuria, urinary cytology, or urinary biomarkers for bladder cancer in asymptomatic persons without a prior history of bladder cancer and harms associated with treatment for screen-detected bladder cancer compared to no treatment. This explains why major organizations do not recommend screening for bladder cancer in asymptomatic adults. For example, the USPSTF in 2010 recommended against routine screening for bladder cancer in asymptomatic adults (I recommendation: insufficient data) [152]. In 2011, the American Academy of Family Physicians endorsed the U.S. Preventive Services Task Force (USPSTF) recommendation. The European Association of Urology states that the best approach to primary prevention of muscle-invasive bladder cancer is to eliminate active and passive smoking. The American Cancer Society states that prompt attention to bladder symptoms is the best approach for finding bladder cancer in its earliest, most treatable stages in persons with no known risk factors. For symptomatic adults (painless macroscopic hematuria, storage LUTS) and high risk population (smoker, occupational exposure, pelvic radiotherapy, chemotherapy) with microscopic hematuria, opportunistic screening by at least a flexible cystoscopy and cytology is mandatory.

## Prostate cancer

The results of screening by PSA and DRE every year from the age of 50 years are contradictory because of cost and uncertain long-term benefits to patients. However, evidence from randomized trials on the effects of screening for prostate cancer on disease-specific mortality and screening-associated harms accumulates slowly with increasing follow-up. The European Randomized Study of Screening for Prostate Cancer (ERSPC) study documented that screening resulted in a 20 percent reduction in prostate cancer mortality [153]. Recently, the ERSPC has published its 11 years follow-up results. They demonstrated that screening does significantly reduce death from prostate cancer. The latest study confirms that a man who undergoes PSA testing will have his risk of dying from prostate cancer reduced by 29%. After unblinding of the ERSPC trial results, the Swedish part of ERSPC was the first centre that published its results, showing a 44% prostate cancer mortality reduction in favour of screening with a follow-up of 14 yr [154]. Recently, the Rotterdam centre reported a significant 32% prostate specific mortality reduction in favour of screening in men aged 55-69 yr at the start of the trial after a median follow-up of almost 13 years [155]. The Finnish centre reported a nonsignificant 15%

| Type de cancer        | Statins   | Comments  |
|-----------------------|---|---|
| Prostate Cancer Cells | Lovastatin, fluvastatin et simvastatin                                  | Antitumoral effect <i>in vitro</i>                                      |
| Prostate Cancer       | Controversy (protective effect of lipophilic statins /advanced cancer?) | Clinical trials: influence of statins on the risk of cancer             |
| Bladder Cancer        | Contradictory   | Clinical trails: influence of statins on the risk of cancer             |
| Kidney Cancer         | Protective effect of lipophilic statins                                 | Clinical trails: influence of statins on the risk of cancer             |
| Prostate Cancer       | Lovastatin  | One Clinical trial using Lovastatin as an anticancer agent              |
| Prostate Cancer Cells | Celecoxib+atorvastatin  | Action <i>In vitro</i> of statins combined with other anticancer agents |
| Bladder Cancer        | Sorafenib+statins   | Action <i>In vitro</i> of statins combined with other anticancer agents |

Table 4 : Statins and cancer: current and future prospects. Cancer lett 2012 Nov 1;324(1):1-12.

| Organization                          | year | Recommandations   |
|---------------------------------------|------|---|
| European Association of Urology       | 2011 | 1-Widespread screening not appropriate.<br>2-Offer early detection to well-informed men.<br>3-Baseline PSA at age 40 yr has been suggested on which subsequent screening interval may be based.<br>4-Screening interval of 8 yr might be enough in men with initial PSA < 1 ng/ml.<br>5-Further PSA testing is not necessary in men >75 yr of age and a baseline PSA < 3 ng/ml  |
| American Urological Association       | 2009 | 1-Offer early detection to asymptomatic men > 40 yr of age who wish to be screened and who have an estimated life expectancy >10 yr.<br>2-Screening intervals should be based on this baseline PSA level.<br>3-Assess the individual patient's health status to determine the appropriateness of PSA testing at any given age.  |
| American Cancer Society               | 2010 | 1-Asymptomatic men who have at least a 10-yr life expectancy should have an opportunity to make an informed decision with their health care provider about whether to be screened.<br>2-Men at average risk should receive this information beginning at 50 yr of age.<br>3-African American men and men who have a first-degree relative diagnosed with PCa < 65 yr should receive this information beginning at age 45 yr.<br>4-Men with multiple family members diagnosed with PCa < 65 yr should receive this information beginning at age 40 yr. |
| National Comprehensive Cancer Network | 2010 | 1-Offer baseline digital rectal examination and PSA testing at age 40 after providing counseling on the pros and cons of early detection.<br>2-If African American, if there is a family history of PCa, or if the PSA level is >1.0 ng/ml, repeat annually.<br>3-Otherwise, repeat at age 45 and annually starting at 50. Screening in men >75 yr should be considered individually.   |

Table 5: Recommendations.

mortality reduction with 13 yr of follow-up [156]. This is in contrast to the U.S. Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial which has been unable to demonstrate any difference in prostate cancer mortality between the two arms of the study [157]. The USPSTF recommended in 2011 against PSA screening in healthy men [158]. The American Cancer Society states also that it does not support routine screening for prostate cancer because the benefits are unclear or unproven [159]. The European Association of Urology recommended to offer early detection to well informed men [160,161]. According to the section of Rotterdam and Goteborg in the ERSPC study, the trend actually is to have a PSA value at the age of 40 years and to recommend screening by a DRE and a PSA every two years for a high risk population. Opportunistic screening is, in contrast, offered to every patient after discussion with his physician. Summary of the recommendation of professional organizations are stated in Table 4.

## Conclusion

Prevention offers the most cost-effective long-term strategy for the control of cancer. It plays a major role at various stages of carcinogenesis. For urologic cancers, avoiding all kind of smoking, moderate alcohol intake, and a safe cardiovascular regimen are beneficial. Given the tremendous potential benefits of catechins in tea, pomegranate, luteolin and flavanoid, further studies are needed especially in prostate cancer chemoprevention. It seems to be no effect of lycopene and carbohydrates with prostate cancer chemoprevention. In addition, there is little evidence to support daily use of multivitamins to protect against urologic cancers. For medical agents, statins and 5 alpha reductases inhibitors are good candidates for future studies. Screening is not recommended for all urologic cancers except for prostate cancer where controversies remain. In contrast, opportunistic screening leads to early detection and decrease specific cancer mortality for almost all urologic cancers (Table 5).

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