Principles and Practice of Cancer Prevention and Control

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Normal Prostatic Structures

Anatomy and histology

The prostate is the male sexual accessory gland. It is located on the floor of the pelvis and surrounds the neck of the bladder and urethra. In man, the urethra runs from the bladder through the prostate and to the tip of the penis, it serves two purposes that including the urination and ejaculation. The section of the urethra running through the prostate is known as the prostatic urethra.

The average weight of a healthy prostate is ranging between 7 and 16 grams [1]. The prostatic parenchyma can be classified into several biologically distinct regions. The peripheral zone (PZ) forms about 70% of the prostate and surrounds the urethra. Nearly, 80% of prostatic cancers develop in the PZ. The central zone (CZ) surrounds the ejaculatory ducts and forms 25% of the prostate. Only 2.5% of prostatic cancers arise in this region, however the cancers that do develop in this region are more aggressive [2]. The transition zone (TZ) accounts for around 20% of prostatic cancers and surrounds the proximal urethra. The TZ grows larger over time; benign prostatic enlargement originates in this region. The final region, the anterior fibro-muscular zone consists of muscle and fibrous tissue only (Figure 1) [3]. Histologically, the prostate gland is lined with two epithelial cell layers, which consist of the outer layer is composed of simple cuboidal and the inner layer is composed of columnar epithelium that named transitional epithelium or urothelium has the ability to contract and expand according to the volume of fluid [4].

Prostate Physiology

The primary functions of the prostate gland are to store part of seminal fluid and assist ejaculation during sexual activity. The smooth muscles in the prostate might help to expel the semen during ejaculation. A major constituent of prostatic secretions are prostate specific antigen (PSA), along with citrate, zinc, spermine and cholesterol (78 mg/ml) [5]. The slightly alkaline fluid produced by the prostate makes up 25% of seminal fluid and allows sperm motility and viability; because the vaginal tract is acidic therefore the alkalinity of the semen neutralizes the environment to allow the sperm to stay viable. The prostate is regulated by dihydrotestosterone, it is synthesized from testosterone in the peripheral tissue, whereas the main male hormone is testosterone and is produced in the testicles.

Prostate Tumour and Carcinogenesis

Tumours are described as unregulated growth and consequent spread of cells to other parts of the body [6]. Cancers (carcinomas) are characterized by their unregulated growth and spread of cells to other parts of the body [7]. The normal cells in the human body can undergo such malignant changes and become cancers. In the process of carcinogenesis, normal cells are transformed into cancer cells due to an uncontrolled cell division and disrupted [8], however the disrupted new “tumour” cells overgrow in a localized region at first, and then spread to surrounding tissues or to other parts of the body via the lymphatic or vascular system [9]. The resulting mass can either be benign, which does not spread to other parts of the body, or be malignant which can invade other organs and spread to distant locations [10].

A possible prostatic carcinoma is prostatic intraepithelial neoplasia (PIN) that involves the abnormal development of the epithelial cells which line the prostate glands. It may divides into two types according to the grade level. Low grade is characterized by crowded and irregularly spaced epithelial cells where the nuclei are hyperchromatic and pleomorphic, while the high grade is characterized by...
higher level of hyperchromatism and pleomorphism exists. PIN is distinguished from adenocarcinoma by the involvement of a cluster of rounded cells, resembling a raspberry shape [11]. Presence of PIN suggests an increased risk for adenocarcinomas, which is a type of cancer arising from epithelial cells of the secretary glands lining the prostatic ducts [12].

**Nodular hyperplasia of the prostate**

Nodular hyperplasia of prostate (Benign Prostatic Hyperplasia (BPH)) is characterized by benign proliferation of stromal and glandular elements. Dihydrotestosterone (DHT) an androgen derived from testosterone, is the major hormonal stimulus for proliferation [13]. Nodular hyperplasia most commonly affects the inner periurethral zone of the prostate, and the nodules compress the prostatic urethra. Microscopically, the nodules have variable proportions of stroma and glands. Hyperplastic glands are lined by two cell layers: an inner columnar layer and an outer layer composed of flattened basal cells (Figure 2). Clinical symptoms are seen in 10% of affected patients and include hesitancy, urgency, nocturia, and poor urinary stream. Chronic obstruction predisposes to recurrent urinary tract infections. Acute urinary obstruction may occur [14].

**Carcinomas of the prostate**

Carcinoma of the prostate is the most common visceral cancer in males, ranking as the second most common cause of cancer-related deaths in men older than 50 years of age with a peak incidence between the ages of 65 and 75 years. Latent cancers of the prostate are even more common than those that are clinically apparent, with an overall frequency of more than 50% in men older than 80 years of age [14].

Carcinomas of the prostate arise most commonly in the outer, peripheral glands and may be palpable by rectal exam. Microscopically, they are adenocarcinomas with variable differentiation and anaplasia. Neoplastic glands are lined by a single layer of cells (Figure 3) [15]. Grading of prostate cancer by the Gleason system correlates with anatomic stage and prognosis. Most localized cancers are clinically silent and are detected by routine monitoring of PSA concentrations in older men. Advanced cancers present with metastases to other organs [14,16].

Although the cause of carcinoma of the prostate remains unknown, the clinical and experimental observations suggesting those hormones, genes and environment factors have a role in its pathogenesis. A hormonal influence is further suggested by the observation that the growth of many carcinomas of the prostate can be inhibited by orchiectomy or by the administration of estrogens such as diethylstilbestrol. As in the case of nodular hyperplasia of the prostate, however, the function of hormones in the pathogenesis of carcinoma of the prostate is not fully understood [17].

**Symptoms and Diagnosis of Prostate Tumour**

**Symptoms**

Prostate tumours are usually slow growing and symptoms may not occur for many years. In the early stages of prostate cancer, there are often no symptoms. However, due to its location surrounding the urethra, symptoms for the disease most commonly affect urination. Prostate cancer symptoms include frequent urination, increased urination during the night (nocturia), and difficulty in maintaining a steady stream of urine, hematuria and dysuria [18]. It can also affect sexual function, such as difficulty in achieving
erection or painful ejaculation. Many of the urinary symptoms also occur in other prostate diseases, such as benign prostate hyperplasia, along with an enlargement of the prostate. If the cancer is advanced, it can spread to other organs. Prostate tumours are only felt in a small percentage of cases during a digital rectal examination (DRE) [19,20].

**Diagnosis of prostate tumour**

There are certain conditions for a diagnostic test to be successful, there must be a significant burden of the disease, the natural history of the disease must be known, and the test must be accurate and have a positive effect on treatment. Diagnosis of prostate cancer must be confirmed by histopathology using of needle biopsy using prostate specific antigen (PSA) as a diagnostic test [21]. Asymptomatic tumours are common in men over the age of 50 years, these are slow growing. However, fast growing tumours can spread to surrounding tissue very quickly. A testing programme would be most effective for cancers confined to metastasize prostate [22]. Serum PSA concentrations less than 4 ng/mL are considered normal, and values over 10 ng/mL are suggestive of prostate cancer. PSA levels may also be elevated above 4 ng/mL in non-neoplastic conditions such as nodular hyperplasia and prostatitis, hence biopsy is required for diagnosis. Later on, the evaluation of PSA concentrations after treatment has great value in monitoring progressive or recurrent disease [16,23].

**Epidemiology of Prostatic Cancer**

The epidemiology of prostate cancer has been extensively studied. Prostate cancer (PC) is the second most common cause of cancer among men worldwide. An increasing incidence of prostate cancer may pose a significant burden on public health and the benefit of screening has been debated for some time. The estimation that a 50 year old man with a 25 year life expectancy has a 42% risk of having prostate cancer.

**Incidence of prostate cancer**

The worldwide PC burden is expected to grow to 1.7 million new cases and 499 000 new deaths by 2030 simply due to the growth and aging of the global population [24]. The PC incidence rates increased over the last 10 year of observation. It is estimated that PC incidence rates remain highest in the highest income regions of the world including North America, Oceania, and western and northern Europe, whereas mortality rates tend to be highest in low- to middle-income settings. The highest increases in incidence rates occurred in less resourced countries with stable or increasing mortality trends. The PC incidence rates increased in nearly all countries, while the PC mortality rates increasing mainly occurred in lower resource settings, with declines largely confined to higher source countries [25].

**Risk Factors**

In comparison to other common cancers, only age, race and family history are considered the risk factors causes of prostate cancer, a combination of both genetic and environmental risk factors at play. Hereditary contributions have also been implicated in light of the increased risk of disease among first-degree relatives of patients with prostate cancer. However, the frequency of incidental prostatic cancers is comparable in all races, suggesting that race figures more importantly in the growth of established lesions than in the initial development of carcinoma [14].

Several factors may have contributed to the prostate cancer are heterogeneous in regards to aggressive potential of incidence or mortality, age group, obesity or high BMI which is a surrogate of energy balance, and multiple hormones may be associated with
prostate cancer risk, including androgens, The insulin-like growth factors (IGFs), insulin, and leptin, and these may have complex relationships with obesity and with each other [26].

Environmental risk factors

A possible role for environmental influences is suggested by the increased frequency of prostatic carcinoma in certain industrial settings and by significant geographic differences in the incidence of the disease. Age is one of the strongest risk factors for the disease; it is more common in men over the age of 65, representing approximately 85% of all cases diagnosed. The PSA testing showed the incidence of prostate cancer in men aged 50-59 years to rise to 50%, which was a dramatic increase [27]. The lowest incidence rates are observed in Asian men, while the African American men have the highest rates. It has been previously hypothesized that the higher rates in African Americans are due to social factors, such as poor access to healthcare systems or poor registry of cancers. However, there is big difference in incidence rates of prostate cancer exists in different ethnic groups. There is an inverse correlation of prostate cancer mortality and exposure to sunlight that might because of the implicating environmental factors, such as Ultraviolet radiation (UVR) exposure plays a role in disease progression. The hypothesis of increasing UVR exposure levels and physical activity (PA) are associated with decreased risk of prostate cancer [20].

Physical activity may promote potential explanatory mechanisms for a possible association between physical activity and prostate cancer. The evidence for a role of PA in cancer etiology is now considered to be fairly strong, consistent and biologically plausible. Several biological mechanisms have been hypothesized to explain how PA reduces prostate cancer risk, including an impact on modifying effect of circulating hormones on endogenous sex and metabolic hormone levels such as testosterone, growth factors, inflammation and insulin resistance, reduced inflammation (IL-6) and increased production of superoxide dismutase which protects against oxidative stress, all of which impact carcinogenesis [28]

A recent meta-analysis suggested that there is approximately a 16% lower risk of prostate cancer among diabetics. However, there seems to be an inverse relationship between diabetes and prostate cancer risk. The relationship between diabetes and prostate cancer is suspected to be causal due to evidence of decreasing prostate cancer risk with increasing diabetes duration and lack of evidence for any confounding of this association. Hypothesized mechanisms for decreased prostate cancer risk among diabetics include (1) decreased levels of hormones and other cancer-related growth factors among diabetics, (2) the impact of diabetes on detection-related factors, such as prostate size, circulating prostate-specific antigen (PSA), and health-care seeking behaviors, (3) protective effects of diabetes medications, and (4) a protective effect of diabetes-induced vascular damage in the prostate [29].

Obesity is an epidemic, particularly in the developed world, which will further intensify the current burden on public health, it is a strong risk factor of increase the incidence of prostate cancer. The correlation between obesity and prostate cancer mortality significantly increased with increasing body mass index (BMI), it is found the BMI above 30 kg/m² had an 18% lower risk of low grade prostate cancer but at the same time had a 29% higher risk of high grade prostate cancer [30]. Overweight and obesity result in a shift in the sex and metabolic hormone balance in the body and influence the availability of a number of growth factors involved in the insulin resistance and inflammation pathways that initiate and promote carcinogenesis, PA can also be used for weight management to reduce cancer risk. In addition, PA may act to decrease cancer risk by decreasing obesity and central adiposity, both established risk factors cancers [31].

Occupational factors and some lifestyle are also may have a heavy responsibility for increased risk of prostate carcinogenesis such occupational exposures to chemical agents as cadmium, poly aromatic hydrocarbons, pesticides, rubbers and benzene [32]. Smoking is associated with increased overall and prostate cancer-specific mortality and recurrence. Accumulating evidence suggests that smoking may increase risk of aggressive prostate cancer and prostate cancer mortality rate [33]. The relationship between tobacco use and prostate cancer risk was assessed. A possible mechanism is the exposure to cadmium. Cadmium is known to increase oxidative stress and cause an increase in androgen levels, which are thought to be mechanisms that promote prostate carcinogenesis. Androgens are responsible for the development and maintenance of the prostate. The two principal androgens in adult men are testosterone and dihydrotestosterone. Androgen deprivation is known to decrease PSA levels and cause apoptosis of prostate cancer cells. Despite this however, it is generally believed that high levels of testosterone are associated with an increased risk of prostate cancer [34].

There are inconsistent associations of alcohol and prostate cancers. Heavy daily drinking alcohol may increase the risk of high-grade prostate cancer. Heavy drinking made finasteride ineffective for reducing prostate cancer risk. Studies have investigated high consumption of red meat found a high risk of disease. It has been suggested that cooking the meat at high temperatures increases the level of carcinogenic substances. A number of epidemiological studies have implicated diet as a potential risk factor, specifically high intake of fat, meat and dairy products. This is consistent with the high incidence rates in developed countries where such diets are common (Table 1) [35].

<table>
<thead>
<tr>
<th>Positive Association</th>
<th>Negative Association</th>
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<tr>
<td>Red meat consumption</td>
<td>Tomatoes/lycopenes</td>
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<td>Smoking</td>
<td>High intake of fruit and vegetables</td>
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<td>Farming</td>
<td>Selenium</td>
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<tr>
<td>Exposure to cadmium, polyaromatic hydrocarbons and pesticides UV exposure</td>
<td>Physical activity</td>
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**Table 1: Possible Risk Factors for Prostate Cancer.**

Prevention of Prostate Cancer

Diet, physical activity and lifestyle

World Cancer Research Fund / American Institute for Cancer Research (2007) reported that processed meat, milk and dairy products and foods containing calcium are thought to increase the risk. Foods containing lycopene and selenium, vitamin E and soya supplements are probably protective against PC. It could be argued that a lifestyle ensures overall well-being that is also protective against cardiovascular diseases, overweight, hypertension and diabetes. However, chemo-preventives, dietary/lifestyle and high level of physical activity have also been suggested as being associated with a decreased risk of PC [36].

Prostate cancer is a common cause of death in developed countries, yet the benefits of screening for prostate cancer still remain
controversial. A prostate-specific antigen (PSA) test result greater than 4 ng/mL (nanograms/millilitre) has commonly been used as the cut-off level for seeking further tests to diagnose the presence or absence of prostate cancer [16]. Despite the uncertainty of the net benefit of early detection and treatment, safe and effective methods to prevent prostate cancer are of value. Consumers, seeking greater involvement in their healthcare, are increasingly turning to lifestyle modification and complementary and alternative medicines (CAMs) to maintain their health and prevent disease [37]. Lycopene is a member of the carotenoid family, which is found abundantly in tomatoes, tomato-based products, strawberries, and watermelon. It has been hypothesised that lycopene is a strong antioxidant, which may lower the risk of prostate cancer and may reduces the incidence of prostate cancer and prostate cancer-specific mortality [37,38].

**Vitamin D and prostate cancer prevention**

Vitamin D deficiency may underlie the major risks for prostate cancer, including age, Black race, and northern latitudes. These factors all are associated with decreased synthesis of Vitamin D. Mortality rates from prostate cancer are inversely correlated with ultraviolet radiation, the principal source of Vitamin D. The hypothesis consistent with known antitumor properties of Vitamin D, and may suggest new avenues for research in prostate cancer. Previous studies supported the hypothesis that UV radiation may protect against clinical prostate cancer. Viewed in conjunction with other recent data, including those demonstrating a differentiating effect of vitamin D on human prostate cancer cells, these findings suggest that vitamin D may have an important role in the natural history of prostate cancer. Men in the US have ten times the risk of developing prostate cancer than Japanese men. This has also been linked to vitamin D consumption as Japanese men have a higher intake due to their high intake of fatty fish which is a good source of vitamin D. Researchers in Norway then published work showing that men diagnosed with prostate cancer during seasons with more sunlight had a significantly better prognosis that those diagnosed with the condition at other times of the year. Patients with advanced prostate cancer were treated with 2000 IU of vitamin D3. Impressively, showed a reducing in, or prevention of further rises in PSA showing that vitamin D could play a role in prostate cancer. An adequate vitamin D should be maintained and it might decrease the risk of prostate cancer and prevent metastatic disease should it develop [39,40].

**Hormonal therapy**

Prostate cancer remains one of the most common malignancies in Western countries and is also increasing in Asian countries. According to American Cancer Society statistics for 2006, prostate cancer is the most frequently diagnosed cancer, and is a leading cause of cancer death in men in the US). Surgery and external beam radiation or radioactive seed implants may be used to treat early-stage disease. Androgen ablation therapy, chemotherapy, and radiation are used for metastatic disease. Hormonal therapy can control prostate cancer for long periods by shrinking the size of the tumor, but tumors often become androgen-independent, leading to a relapse within 2 years [41].

There are three main established risk factors for prostate cancer: age, ethnic group, and family history. In addition, exposure to androgen is also a well documented risk factor for prostate cancer, estrogen and insulin-like growth factor 1 (IGF-1) may also influence prostate cancer development. High levels of the circulating insulin-like growth factor 1 (IGF-1) pathway may be involved in prostate carcinogenesis. Estrogen is another steroid hormone which has evidence in prostatic carcinogenesis and possesses the ability to influence androgen-response gene expression. Androgens stimulate proliferation and impede apoptosis of normal prostate epithelial cells as well as androgen-responsive prostate cancer cells [42].

The male sex hormone, androgen, is required for normal prostate cell growth and development. The efficiency of androgen ablation in the treatment of hormone-dependent metastatic prostate cancer is largely resulted from the induction of apoptosis of neoplastic epithelial cells, with incidental apoptosis of the normal prostate epithelium. However, androgen is also known to be associated with prostate carcinogenesis. Androgen has been showed to up-regulate IGF-1R protein expression and sensitize prostate cancer cells to the biological effects of IGF-1. It can reverse the effects of the dihydrotestosterone hormone and can induce apoptosis of human prostate cancer cells [42].

**Dietary factors**

The precise impact of increased dietary consumption in humans, however, remains uncertain of prostatic cancer. The association between diet and prostate cancer (PC) risk, although suggestive, still remains largely elusive, whereas the hypothesis that total fat may increase PC risk and tomatoes/tomato, garlic and other nutritional supplements products may protect patients against PC.

**Bioactive food**: Cancer chemoprevention has developed as a major field of scientific investigation. Cancer chemoprevention is defined as is a means of cancer control by which may inhibit, or reverse carcinogenesis, or prevent the development of invasive cancer the course of the disease can be entirely prevented, slowed down, or reversed by the administration of one or more naturally occurring and/or synthetic agents. The concept of chemoprevention is gaining increasing attention because it is a cost-effective alternative to cancer treatment. Bioactive food components are increasingly being evaluated as potential chemopreventive agents [43].

Dietary consumption of foods and herbal medicines is a convenient method of administering potentially chemopreventive phytochemicals in a cost-effective manner. Bioactive food components are increasingly being evaluated as potential prostate chemopreventive agents. The dietary intervention strategies offer intriguing possibilities for maintaining normal cell function by modifying a process that is essential for a change in inflammation-mediated development and progression prostate cancer. Dietary and lifestyle interventions are of particular interest in prostate cancer because of the often long disease latency. The dietary factors have been intensively studied because of the lifestyle might associate with prostate cancer. However some studies have found an association between high fat intake and prostate cancer. Dietary fat and saturated fat are perhaps the most common dietary variables associated with prostate cancer. In particular, high consumption of red meat and high-fat dairy products has been linked to increased risk for prostate cancer. In contrast, the omega-3 fats found in certain fish (salmon, sardines, fresh tuna) may be protective. Fish oil supplements rich in omega-3 fatty acids have been shown to reduce production of the cytokines interleukin (IL)-1, IL-6, and TNF in normal volunteers [43,44].

**Vegetables and fruits**: Vegetables and Fruits contain chemicals, such as phytochemicals and indole-3 carbinol, which reduce cancer cell growth. These chemicals are believed to act through induction of antioxidant proteins, thereby lowering the oxidative damage in the normal cells. A diet rich in vegetables, fruits, and legumes appears to protect against prostate cancer. However, it is not clear whether this is due to the nutrients contained in these foods, or the fact that these foods are low in fat. No specific vegetable or fruit has been proven to decrease risk. Lycopene, which is found in tomatoes, has been a target of research interest, but the evidence for its protective
benefit is still inconclusive. Modification of diet by increasing vegetable and fruit intake could potentially prevent approximately prevent 20% cancer-related deaths annually. Because of their safety, low toxicity, antioxidant properties, and general acceptance as dietary supplements, fruits, vegetables, and other dietary elements are being investigated for the prevention of cancer [45,46].

Nutritious foods that are part of a healthy diet are the best sources for vitamins and minerals. A high intake of calcium has been linked to an increased risk of prostate cancer. A combination of vitamin E, selenium, and lycopene dramatically inhibited prostate cancer. Although there was no main effect of multivitamin use on localized prostate cancer, the findings of an increased risk of localized prostate cancer among those who took multivitamins more than seven times per week versus never use, in men also taking vitamin E, selenium, or folate supplements. The risk of advanced prostate cancer and prostate cancer mortality associated with heavy multivitamin use was highest in men who reported concomitant use of selenium, β-carotene, or zinc supplements, or who had a positive family history of prostate cancer. Thus, excessive intake of certain individual micronutrients that are used in combination with multivitamins may be the underlying factor that is related to risk and not the multivitamins themselves. In fact, excessive use of multivitamin supplements or a closely related behavior was associated with an increased risk of advanced and fatal prostate cancer. Because multivitamin supplements consist of a combination of several vitamins and men using high levels of multivitamins were also more likely to take a variety of individual supplements [47].

Cancer is due to the accumulation of DNA mutations that confer a growth advantage and invasive properties on clones of cells. A variety of external factors including nutrients in the environment interacting with genetic susceptibility influence the accumulation of mutations in cells. Nutrition is important at every stage of carcinogenesis from initiation to promotion to progression and metastasis. In spite of the fact that prostate cancer is the most common male cancer in many countries in the developed world, little is known of risk factors and predisposing conditions. Oxidative stress has been suggested to play a key role in carcinogenesis. Free radicals have been shown to mediate the anti-cancer actions of many chemotherapeutic regimens. Despite active investigation, knowledge is lacking concerning the local and systemic effects of free radical-generating treatments in cancer. Free radicals are among the environmental factors that might contribute to cancer process. While it has not been conclusively determined whether free radicals are a cause or an effect of prostate cancer, it is clear that characteristic types of free radical damage increase with cancer. However, understanding the nature of that particular tumour can help us to optimize therapy or to design therapeutic approaches. Oxidative stress is generated by a large variety of mechanism, including mitochondrial respiration, ischemia/reperfusion, inflammation and metabolism of foreign compounds. Several studies have demonstrated that H2O2 can induce cell proliferation, apoptosis resistance, increased metastasis and angiogenesis, invasion and metastasis. Free radicals generate a large number of oxidative modifications in DNA, including strand breaks and base oxidations [48].

Key and Priorities Conclusion of Prostatic Cancer Patients

Good communication between health care professionals and men with prostate cancer is essential. Healthcare professionals should adequately inform men with prostate cancer and their partners or carriers about the effects of prostate cancer and the treatment options on their sexual function and physical appearance. Healthcare professionals should ensure that men and their partners have early and ongoing access to specialist for assessment, diagnosis and conservative treatment of troublesome urinary symptoms and erectile dysfunction and services. The healthcare professional decision of prostate specific antigen (PSA) level and digital rectal examination (DRE) estimate of prostate size before the prostate biopsy. Low-risk of prostate cancer patients are considered suitable for radical treatment. Healthcare professionals should seek feedback from men with prostate cancer and their carriers to identify the highest quality information resources. Healthcare professionals should discuss the purpose, duration, frequency and location of follow-up with each man with localised prostate cancer. Men and their partners should be warned about the potential loss of ejaculation and fertility associated with treatment for prostate cancer. The regular assessment of needs should be applied systematically to men with metastatic prostate cancer. Healthcare professionals should ensure that palliative care is available when needed and is not limited to the end of life.

References

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