Chapter 12
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Global Development on Causes, Epidemiology, Aetiology, and Risk Factors of Prostate Cancer: An Advanced Study

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ABSTRACT

As the second most recurring cancer in men globally, prostate cancer is a major concern to men's health. It is estimated that approximately 1.3 million new cases are diagnosed every year, those cases are leading to the casualties of nearly 360,000 men during 2018, which represents about 3.8% of all male cancer related deaths. Increasing of age among men can be correlated with global prostate cancer incidence and mortality, with the average age of diagnosis is 66 years old. Prostate cancer is usually asymptomatic or with minimal symptoms in the early stages of the disease, during this period there is minimal to no need of treatment. At early stage, the symptoms of prostate cancer are similar to those observed in prostatic hypertrophy. But in more advanced stages of prostate cancer, more painful symptoms may appear. Elevated levels of Prostate Specific Antigen (PSA) are the main marker used to detect prostate cancer. The disease can be confirmed with a biopsy of the prostate gland. In this work, we try to review the prostate cancer's causes, epidemiology, aetiology, and risk factors globally, as we think that it is a pivotal way to keep update our understanding on this increasingly important health threat to men.

Keywords: Prostate cancer; statistics; epidemiology; mortality; risk factors and prevention.

1. INTRODUCTION

Prostate cancer is considered to be the second most recurring cancer in men globally, with estimated 1,276,106 new cases and a leading to 358,989 casualties (3.8% of all casualties by cancer in men) during 2018 [1,2]. Global Prostate Cancer incidence and mortality is correlated with increasing age, 66 years is the average age when diagnosed. To be noted, the incidence rate is higher in African-American men when compared to white men, with almost 159 new cases diagnosed per 100,000 men and with a mortality rate of almost double than White men [3]. This variation is hypothetically attributed to the differences in social, environmental and genetic aspects. While 2,293,818 new cases are expected until 2040, there will be a small variation in mortality with an increase of 1.05% [4]. Globally prostate cancer is the second most familiar and fifth-most hostile neoplasm among male individuals. One of the emerging issues in men is prostate cancer. The Prostate is a ductal small walnut-shaped gland situated in men below the urinary bladder that produces the seminal fluid for sperms provision and transportation. The risk of emerging prostate cancer during the man's lifetime is one out of seven. According to the epidemiological studies, different environmental and genetic factors are associated with the progression of abnormal prostate cell growth which ultimately causes the development of cancerous cells [210,211]. Many risk factors have been implicated in the etiology of cancer including; tobacco and alcohol consumption, unhealthy diet, physical inactivity, viral infection, bacterial infection, urban air pollution, ionizing radiation and indoor smoke [212].

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A prostate cancer patient may not present any symptoms at the early stages of the disease and usually has an indolent course, and probably needs minimal or no treatment at all. Still, the most frequent complaint presented is difficulty of urination, increased frequency, and nocturia, all these symptoms may show in prostatic hypertrophy. Later in advanced stages of the disease more symptoms may arise, like urinary retention and back pain.

Prostate cancer is mainly detected on the basis of increased plasma levels of prostate-specific antigen (PSA > 4 ng/mL), which is a glycoprotein expressed normally by the prostate tissue. Due to the fact the men without prostate cancer may express elevated levels of PSA, a tissue biopsy is better used to confirm the cancer's case. Numerous countries have implemented a PSA-based screening to better understand the differences in incidence and mortality rates and trends. In the USA, it was recommended by the American Cancer Society [5] and the American Urological Association in 2009 [6] that males at an average risk, aged ≥ 50 years, with life expectancy of ≥ 10 years to give a decision about undertaking PSA testing after being informed about the benefits, uncertainties and associated risks of testing. In 2013, the European Association of Urology and the Prostate Cancer Foundation of South Africa both gave a recommendation that PSA screening should be offered to men with life expectancy of 10 years at least [7,8].

Physical activity and dietary intake are major influencers in the development and progression of prostate cancer. Global ethnic variation in the incidence rates of prostate cancer may be attributed to dietary factors [9-13].

As a great deal of studies are trying to identify the genes and mutations behind prostate cancer, it will be very beneficial to have a detailed analysis of prostate cancer epidemiology and risk factors evaluation in order to understand the connection between genetic mutations and the role of the environment in triggering such mutations towards tumor progression. Having more comprehension and understanding of etiology and causative risk factors of prostate cancer will give us more means to identify males who are at risk and may lead to better development of more effective screening and prevention methods.

2. EPIDEMIOLOGY

Data presented in this paper is based on GLOBOCAN 2018 databases.

2.1 Incidence

Prostate cancer incidence rate differs across various regions and populations (fig. 1) [2]. In 2018, the number of new prostate cancer registered reached 1,276,106 cases, depicting 7.1% of all cancers in males [1]. Prostate cancer incidence rates vary highly globally. The age-standardized rate exhibited the highest levels in Oceania (79.1 per 100,000 people) and North America (73.7), they were followed be Europe (62.1). Africa and Asia contrarily have lower incidence rates than those from developed countries (26.6 and 11.5, respectively) [2]. A difference of 190-fold was seen between the populations with the highest incident rates (France, Guadeloupe, 189.1) and the ones with the lowest rate (Bhutan, 1.0) [2].

As age increases, the incidence of prostate cancer increases [2]. Even though only 1 in 350 males aged under 50 will be diagnosed with prostate cancer [14], the incidence rate will go up to 1 male in every 52 males aged between 50 to 59. The incidence rate is almost 60% in men aged 60 and over [15].

The causes of these variations amongst countries is not entirely understandable. The global variations in the incidence of prostate cancer might be accounted to PSA tested [16]. As an example, in Europe, 24% of all new cancers diagnosed in men were prostate cancer cases in 2018, with estimated 450,000 new prostate cancer cases to be diagnosed in 2018 [17]. On the other hand in the USA, prostate cancer is considered to be the second most common cancer responsible for 9.5% of all new cancer cases (164,690 new prostate cancer cases) registered in 2018 [18]. Recently conducted

research studies have shown that that about 20-40% of prostate cancer cases registered in the USA and Europe could be attributed to overdiagnosis made through the vast PSA testing [16,19,20].

As shown in many studies, the highest incidence of prostate cancer globally is in African-American males, they are more prone to develop prostate cancer earlier in life when compared to other racial and ethnic groups [21]. Caribbean and Black males in Europe also reflect the same data as African-Americans, this suggest that they share a common genetic background more susceptible to the development of cancer. To be noted, Chu et al [22] revealed that African-American males have 40 times the incidence rate than those in Africa. These variations propose that environmental factors also may contribute an important role in the etiology of prostate cancer and differences in incidence may be acclaimed to underdiagnosis, screening methods differences and the gap in health care access.

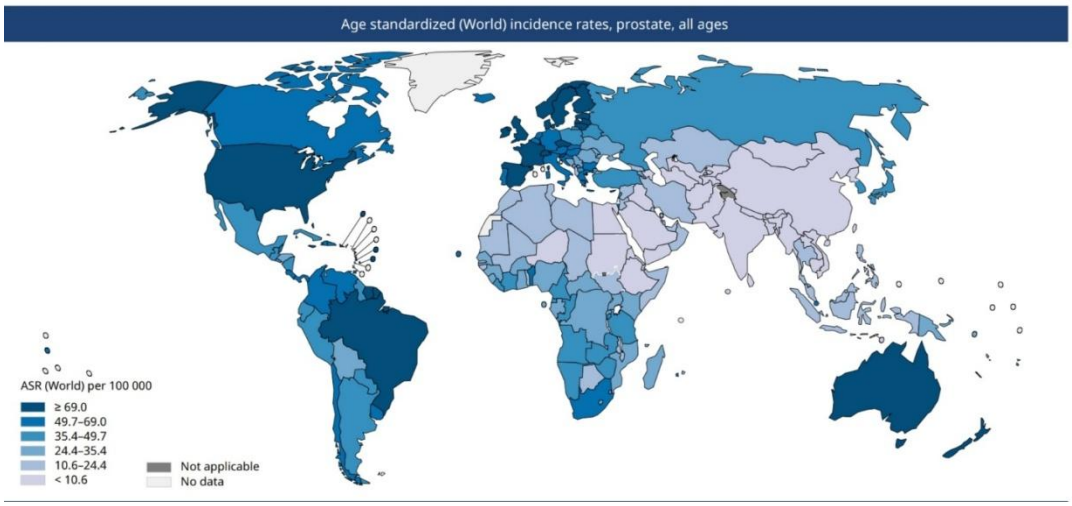

Fig. 1. International variation in age-standardized prostate cancer incidence rates
Source: GLOBOCAN 2018 [2]

2.2 Mortality

Prostate cancer international mortality rates markedly differ worldwide (Fig. 2) [2]. In 2018, mortality rates highest level was documented in Central America (10.7 per 100,000 people), then came Australia and New Zealand (10.2) and Western Europe (10.1) [2]. On the other hand, the lowest rates were recorded in the Asian countries (South-Central, 3,3, Eastern, 4.7, and South-Eastern, 5.4) and Northern Africa (5.8) [2]. One-third of prostate cancer deaths were in Asia (33.0%, 118,427 of deaths), Europe followed by (29.9%, 107,315 of deaths). Prostate cancer mortality rate increases with age, and almost 55% of all deaths happen after 65 years of age [2].

US Preventive Task Force (USPSTF, 2018) has announced that PSA screening can potentially be effective in decreasing deaths attributed to prostate cancer in males aged 55 – 69 years [23]. Unfortunately, the data are less convincing for men over 70 years of age of all races [24]. The highest prostate cancer incidence and mortality rates are in African-American males. This proposes that not only African-American males may have some specific genes that are more prone to mutations in prostate cancer, but generally these mutations are linked to a more aggressive type of cancer. Oliver in 2007 [25] noted that African-American males were less likely to identify early symptoms of prostate cancer correctly when compared to Caucasian males.

2.3 Trends

Prostate cancer incidence and mortality temporal trends differed in a significant matter during the past years, and they look tightly correlated to the endorsement of PSA testing for early disease detection especially in Western countries [26].

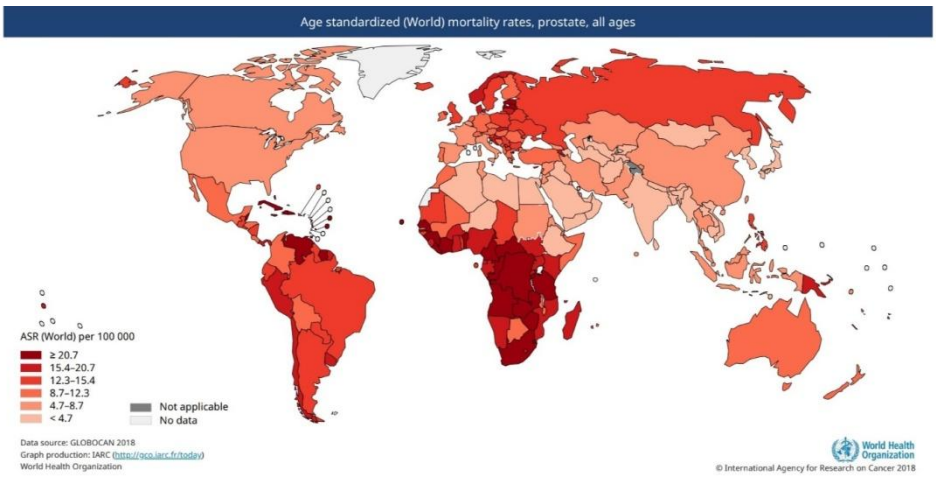

Fig. 2. International variation in age-standardized prostate cancer mortality rates
Source: GLOBOCAN 2018 [2]

Incidence rates in the USA, Australia, and Canada have shown an increase between the 1980s and 1990s but now is showing a decline due to fast distribution of PSA testing [25,26]. On the other hand, European countries exhibit a slight increase in incidence rates due to the increased understanding of PSA screening and starting to gradually adopt PSA testing, without undermining the probability of other factors being involved, like diet and ultraviolet radiation overexposure [27].

Interestingly, prostate cancer incidence will tend towards an increase globally with 1,017,712 new cases (+79.9% overall change) up to 2040 is estimated (Table I) [4]. Africa will have the highest incidence of prostate cancer with (+120.6%), to be followed by Latin America and the Caribbean (+101.1%) and Asia (100.9%). On the other hand, Europe will have the lowest incidence rate at {+30%). This increase in the incidence rate may be attributed to an increased life expectancy. Developing countries increased incidence rates may be due to better access to medical services as well as increased reporting and documentation of cases. Finally, increasing incidence rates in these regions where PSA is not performed on a routine base suggests that this event exhibit westernization of the lifestyle including physical inactivity, obesity and dietary factors [28].

Table 1. Estimated Number of incident cases from 2018 to 2040, prostate Cancer, Males, all ages

	2018	**2040**			
	Number	**Number**	**Demographic Change**	**Change in risk**	**Overall Change**
Africa Males (APC 0%)	80,971	178,634	97,663 (+120.6%)	97,663 (+120.6%)	97,663 (+120.6%)
Latin America and the Caribbean Males (APC 0%)	190,385	382,808	192,423 (+101.1%)	192,423 (+101.1%)	192,423 (+101.1%)
North America Males (APC 0%)	234,278	312,901	78,623 (+33.6)	78,623 (+33.6)	78,623 (+33.6)
Europe Males (APC 0%)	449,761	585,143	135,373 (+30.1%)	135,373 (+30.1%)	135,373 (+30.1%)
Asia Males (APC 0%)	297,215	597,180	299.965 (+100.9%)	299.965 (+100.9%)	299.965 (+100.9%)

Data obtained from GLABOCAN 2018 [4].

Prostate cancer mortality rates in most western countries including North America and in Western and North Europe have been declining steadily [26,28]. The reasons for this decline are not clear, but it

possibly reflects both early detection and treatment improvement [29-31]. O the other hand, in the USA, a randomized controlled trial recently failed to show benefits of PSA testing in lowering down prostate cancer deaths, although another research study conducted in Europe demonstrated benefits of PSA testing [32,33]. Analysis of ethnicity-specific showed that the decline in mortality in African-American males was higher than that in White males during 2001 and 2015 [15,34]. A study by Negoita et al suggested that newer and improved modalities of cancer detection and treatments and improved treatment of resistant and metastatic prostate cancer may explain this trend [24].

It is estimated that during the period from 2018 to 2040 the mortality rate will double with 379,005 deaths globally [4]. Africa will have the highest mortality rate with (+124.4%), to be followed by Asia (116.7%), while Europe will have the lowest estimated mortality rate with (+58.3%) [4]. The finding above is not unusual, due to the lack of resources for screening and detection of prostate cancer which makes it fairly likely of being detected during the late stages. Additionally, lack of accessibility to medical care in developing countries, may give a possible reasoning for the high mortality despite the lower incidence.

2.4 Survival

Despite prostate cancer incidence rates are elevated, much prostate cancer cases are identified when the cancer is still confined inside the prostate. In the USA, the 5-year survival rate for males diagnosed with cancer is near 98% [15]. On the other hand, data collected from the Eurocare project (EUROCARE-5) of patients diagnosed with prostate cancer through the interval from 2003 to 2007 demonstrated that the 5-year survival rates were 83% [17]. Eastern European countries had a survival rate of 76%, where it rises to 88% in Southern and Central European countries. Additionally, survival has risen over time in all over Europe with the largest improvement being noticed in Eastern European countries [35].

2.5 Etiology and Risk Factors

Unlike common cancers, the etiology of prostate cancer is largely unknown despite many studies aimed towards it. Yet, it was established that advanced age, ethnicity, genetic factors and family history are risk factors of prostate cancer [36-38]. Amongst positively linked risk-factors are diet (saturated animal fat and red meat consumption, decreased consumption of vegetables, fruits, vitamins and coffee), obesity and decreased physical activity, hyperglycemia, inflammation, infections and being subjected to chemicals or ionizing radiation in the environment [37, 39-43].

2.6 Age

Prostate cancer is considered to be the most commonly diagnosed cancer amongst elderly males [1]. More elderly men are diagnosed with prostate cancer due to the fact that life expectancy and PSA screening has increased. The risk increases particularly in white males aged 50 and above who have no familial history of prostate cancer, and in black males aged 50 and above who also have no familial history [18]. It was noticed that 30% of males aged 50 and above who have deceased to reasons other than prostate cancer presented histological evidence of prostate cancer during autopsy [44].

2.7 Ethnicity

Different racial groups highly vary in prostate cancer prevalence. In the USA for example, American Indian/Alaskan demonstrate the lowest incidence (46.9), whilst in Native and Asian/Pacific Islanders (52.4), to be followed by White (93.3). Finally, African-American men have the highest incidence rate at (157.6) [15].

This variance can be explained by both socioeconomic states and biologic factors [45]. As an example, African-American males have less access to good health services which leads to inadequate PSA screening [46]. To be noted, when compared to White males, considerably higher PSA levels were found in Black males, with or without prostate cancer [47,48].

As proposed by numerous studies, genetic predisposition may be a factor. For instance, African-American males have a certain chromosome (8q24 variants), which correlates with elevated prostate cancer risk [49-52]. Also, high rate of genetic variation in African-American males leads to tumor suppression such as EphB2 [53] or that control cell apoptosis such as BCL2 [54]. In addition, a more aggressive form of the cancer is shown in African-American males, which also can be attributed to genetic and biologic differences, putting in mind the lack of proper screening and delayed presentation [45].

2.8 Family History and Genetic Factors

Family history is demonstrated in 20% of prostate cancer patients, it may develop not only due to shared genes but also for similar type of exposure to environmental carcinogens and similar lifestyle manners [55,56]. Some studies have shown that increased risk for prostate cancer is correlated with inherited genetic background, responsible for 5% of disease risk [57,58].

Studies of gene linkage demonstrate high susceptibility loci for prostate carcinoma on genes in seven distinct loci. Chromosome 1q24-25 that is known as HPC1 gene encodes the enzyme ribonuclease L (RNASEL) [59], which plays a role in the intrinsic immune defense mechanisms and the interferon (IFN)-mediated signaling [60]. It has a major role in the reduction of antiviral activity and the regulation of cell apoptosis [61]. To be noted, analyzing samples of human prostate cancer with RNASEL mutations revealed the presence of retrovirus, which indicates the importance of antiviral defenses to the development of prostate cancer [62]. In addition, discovering of retroviral infection in a number of prostate cancer cases also demonstrated the possible connection of chronic retroviral infection and the resultant inflammation of the tissue with cancer initiation [63,64]. HPC2/ELAC2 gene which is another HPC gene was found on chromosome 17p11 and encodes a protein with insufficiently understood function [65]. ELAC2, a gene participating in the development of prostate cancer by binding SMAD2, which leads to the up-regulation of the proliferation through TGF-beta signaling pathway activation [66]. Macrophage scavenger receptor 1 (MSR1) is the third identified HPC gene, it is located on chromosome 8p22 [67]. Although, due to the low penetrance of this allele , a number of studies were unsuccessful to prove it association with HPC [68,69]. In addition, an HPC subset was noted to occur in males with BRCA1 and 2 mutations that demonstrated a form of prostate cancer that was clinically aggressive [70]. Furthermore, BRCA2 mutations were linked with an increased prostate cancer incidence, and PALB2, BRCA2-interacting protein, were engaged in familial prostate cancer [71].

Another player in prostate cancer inheritance is the X chromosome, due to the fact that it contains the androgen receptor (AR) and due to small deletions in Xq26.3-q27.3 region were detected in hereditary and sporadic types of prostate cancer [72,73]. The latest studies on 301 families affected with hereditary prostate cancer showed a number of other loci that may have a role to hereditary prostate cancer [74].

2.9 Diet

Dietary factors may have a key role in prostate cancer development as shown by many studies on immigrants relocating for developing countries (low-risk areas) to industrialized countries (higher risk), that demonstrated that changing to a western lifestyle started a shift towards prostate cancer incidence increase. For example, it was reported that incidence rate in African-Americans is higher by 40 times when compared to those of Africa [22]. On the other hand, Chinese males living in the USA have an incidence rate for prostate cancer 16 times higher than males in China [75], implementing that environmental factors may possess a vital role.

Numerous studies show that certain foods are associated at increased risk, while others play a protective role.

Saturated animal fat: Numerous ecological studies have demonstrated a positive correlation between the mortality of prostate cancer and intake of meat per individual, fat and dairy products [76, 77]. Recently, a case-control study in patients less than or equal to 60 years of age showed that high

consumption of total fat was correlated with a statistically significant increase in the risk of prostate cancer [78].

There are a number of biological mechanisms that are thought to be implicated between saturated animal fat consumption and prostate cancer risk: 1) encouraging prostate carcinogenesis through androgen; 2) elevating the levels of reactive oxygen species (ROS) and rising the levels of leukotrienes and prostaglandins from lipid metabolism; 3) enhancing basal metabolism, insulin growth factor and tumor proliferation.

High-calorie consumption of saturated animal fat has led to elevate the growth of prostate cancer cells by rising the circulating levels of androgen [79,80]. Additionally, randomized cross-over studies about low-fat and high-fat diets demonstrated that the androgen level is lower post-prandial and in vegetarians [81]. Finally, a number of studies mentioned that reducing lipid level in the diet reduces testosterone levels [82-84].

Extra fat leads to an increase in oxidative stress and ROS levels that will attack the cells leading to peroxidation and finally DNA damage. Lipid metabolism and its metabolite have an observed role in mice, it has been found that dietary fat is an essential modulator of the growth of prostate cancer. For instance, while a number of studies did not show any differences in tumor growth and survival of mice feeding on a Western diet, other studies mentioned a delay in the growth of cancer cells in mice feeding on low-fat corn-oil diets, implying that both amount and type of fat are critical [85].

Corn-oil may endorse cancer growth through linoleic acid, which has the most omega-6 fat in the oil. Arachidonic acid, a metabolite of linoleic acid, initiates the formation of many pro-inflammatory prostaglandins (PG), amongst is PGE2 which promotes proliferation of the cells, and 5-hydroxyeicosatetraenoic acid which is a result of 5-lipoxygenase action, which is known to be highly expressed in malignant prostate cancer. Therefore, decreasing omega-6 fatty acid consumption can decreased cancer growth. Oemga-3 fats are known to have advantageous effects against cancer growth in opposite to omega-6 pro-inflammatory effect [86].

Red meat: Prostate cancer has been associated with dietary meat consumption when comparing cancer incidence and mortality with meat consumption per capita [87]. It has been shown that a weekly consumption of five or more servings of processed meat lead to a higher risk of prostate cancer when compared to a one or less serving weekly, This has not been the case in African-Americans [88]. On the other hand, consuming meat at a high temperature lead to a 20% increase in the risk of non-advanced prostate cancer [89]. Chemical compounds such as aromatic hydrocarbons and mutagenic heterocyclic amines can be formed due to high temperature cooking [90,91]. Lipid peroxidating and DNA damaging compounds such as N-nitroso compounds can formed by grilling or barbecuing meat [92,93].

Milk, dairy products and calcium: From a genetic aspect, dairy foods have been correlated with high prostate cancer risk [88,94-97]. Calcium from dairy and from supplements both contribute to a higher risk of prostate cancer in men. A dose of more than 2,000 mg daily of calcium was linked to an elevated risk of prostate cancer [98].

Vegetables: It was established that there is great correlation between Brassica vegetables and prostate cancer reduction. It is believed that they have prostate cancer reducing characteristics. These anticancer characteristics are due to presence of phenylethyl isothiocyanate, sulphoraphane, phytochemicals and indole-3-carbinol [99]. On the other hand, some studies showed no anticancer characteristics of Brassica vegetables [100-103].

Green tea and soy: Compared to North America, Asia has a low prostate cancer incidence rate. Knowing that green tea and soy a big part of their diet, studies were initiated to discover their promising cancer prevention potential. Consuming green tea and soy has been noted in decreased levels of prostate cancer amongst other cancers [104-107]. Catechins observed in green tea and isoflavones found in soy beans exhibit anticarcinogenic activity, and they hinder different stages of

carcinogenesis [108,109] and metastasis [110-112]. In addition, polyphenols found in green tea leads to a reduction of IGF-1 levels [113-115].

Tomatoes: Prostate cancer risk seems to be reduced by tomatoes. Due to their high content of lycopene which possesses high anticancer characteristics in addition to cancer-preventive traits [116-120]. In addition, lycopene exerts its action on the androgen receptor receptors and overturns dihydrotestosterone's effects and also leads to the inhibition of insulin growth factor (IGF-I)-stimulation via Akt and GSK3β and GSK3 tyrosine phosphorylation [121].

Decreased risk of prostate cancer is associated with both tomato consumption and lycopene intake [122]. Oppositely, no clinical benefit has been found of lycopene in an open phase II study of advanced prostate cancer [123]. Two other small epidemiological studies have shown the same results [124,125]. Therefore, additional studies need to be conducted to explore the connection between tomatoes consumption and prostate cancer risk.

2.10 Vitamin and Mineral Supplements

Vitamin D: The relationship between sun light (UVB exposure) and prostate cancer incidence has been found as inversed [126,127], implying that prostate cancer risk development might be increased by vitamin D deficiency [128]. Likewise, studies have showed that people residing in countries with sunny climates are at lower risk of acquiring secondary solid cancer after melanoma in comparison to people residing in countries with less sun exposure [129].

Vitamin D has a role in the growth of the prostate, as supported by biochemical evidence [130,131]. Vitamin D and its analogues can inhibit cell proliferation and invasion, and promote cellular differentiation and apoptosis in prostate cancer cells, also in tumor progression in animal models [131-133]. Such discoveries suggests the use of vitamin D and its analogues as alternative therapeutic agents for prostate cancer if the androgen deprivation therapy is unsuccessful [134].

Selenium: Selenium is considered to be an essential micronutrient. It can be found in plants such as tubers, cereals and legumes, it can also be found in animal products such as meat, eggs and seafood in the form of selenomethionine and selenocysteine. Many cancers, including prostate cancer, are inversely associated with selenium.

A number of studies indicate that high consumption of selenium can lead to a 50-60% reduction of prostate cancer risk when compared with low selenium consumption [135,136]. The NPC trial has demonstrated that men consuming selenium have 50% reduction in prostate cancer incidence [137]. Selenomethionine exerts its action on cancer cells inducing cell cycle arrest [138,139]. Inducing apoptosis and inhibiting angiogenesis is another way it can act [139,140]. Methylseleninic acid induces apoptosis through a caspase-mediated pathway [141].

Folate and vitamin B12: Decreased levels of folate and vitaminB12 can cause modified methylation and cause cancer growth due to reason that these essential vitamins play a role in DNA methylation, synthesis and repair [142]. The role of folate in developing an aggressive type of prostate cancer is represented in *in vitro* [143], *in vivo* [144] and genetic studies [145,146]. In addition, increased serum concentration of folate was correlated with an elevated proliferation of prostate cancer cells, this was founded in some samples gathered from patients who had radical prostatectomy surgery [147].

Nevertheless, it was reported in a recent meta-analysis that elevated concentrations of vitamin B12 and folate give a low 12% increase in prostate cancer risk [148]. In prostate cancer patients, folate consumption does not have any effect on disease progression [149], or survival [150]. To conclude, further investigation is needed to determine the association between vitamin B12 and folate and prostate cancer.

3. ALCOHOL CONSUMPTION

It has been noticed that there is a relationship between alcohol consumption and many types of malignancies, including prostate cancer [151]. Intense consumption of alcohol (>15 g ethanol/day)

tend to be a risk factor for many malignancies including prostate cancer [152]. On the other hand, many cohort studies imply that there is a weak relationship between alcohol consumption and prostate cancer mortality [153-156], whereas no relationship with increased risk was found by other studies [157]. Contradictory to that, a considerable correlation between elevated alcohol consumption and prostate cancer risk was found, with a relative risk (RR) valued from 1.05 to 1.21 for one or four drinks containing alcohol daily, respectively [158,159].

Coffee: Increased prostate cancer risk has been inversely correlated with coffee consumption. It was shown in observational studies and a number of animal studies that there is a correlation between long-term coffee consumption and better glucose metabolism and secretion of insulin [160].

It was showed by a large prospective study that coffee consumption was inadequately inversely correlated with overall prostate cancer risk, whereas it considerably decreased the risk of lethal and advanced prostate cancer when comparing people who extensively consume coffee to those who consume less coffee [161].

Obesity, physical activity and insulin: Prostate of the aggressive and advanced types was found to be linked to obesity [162,163]. Also, high body mass index (BMI) is found to be correlated with a more aggressive type of prostate cancer and a worse outcome [122,164].

This can probably be justified by the change of circulating concentrations of metabolic and sex steroid hormones in obese males, which are recognized to play a role in the development of the prostate as well as oncogenesis [165].

The development of insulin resistance with decreased glucose uptake can be caused by obesity, especially when it is combined with physical inactivity. As a result, it will cause chronically increased levels of inulin in the blood. Insulin is known as a hormone the stimulates growth and proliferation, therefore it can be considered as a risk factor that may promote the initiation and/or progression of prostate cancer [166]. Furthermore, adipose cells are considered to be a source of inflammation an addition to macrophages present in adipose, which in turn secrete inflammatory mediators [167]. It was shown by three meta-analysis studies that there is a small but steady correlation between obesity and prostate cancer incidence regardless of BMI increase [168]. Three national surveys conducted in the USA represented data that implied that obesity is correlated with a more aggressive type of prostate cancer and an elevated mortality in spite of the lower incidence [169].

Diagnosing obese men with prostate cancer could be challenging, as their circulating plasma levels are higher which leads to haemodilution of PSA [170]. Eventually, undergoing a biopsy is less likely which will lead to a later detection until a late advanced stage [166,168].

Physical activity is thought to be the simplest adjustable risk factor to handle, as it possesses many advantages and less side effects that lead to the prevention of prostate cancer. A study shows a significant lower risk of prostate cancer in ex-soldiers who exercised [171].

Cigarette smoking: Exposure to cigarette smoking, both passive and active, is deemed to be carcinogenic for many types of human cancers [172].

Linking smoking to prostate cancer may be attributed to either a hormonal or some unknown genetic factors. For example, elevated levels of sex hormones in male smokers may elevate the risk of prostate cancer or assist in cancer progression [173,174]. Alternatively, functional polymorphisms found in genes engaged in polycyclic aromatic hydrocarbons (PAHs) metabolism, one of the chemicals found in cigarette smoke that is carcinogenic [172], may exert an effect on cancer onset and progression [175].

Epidemiological studies have failed to establish a relationship between smoking and prostate cancer incidence. On the other hand, an number of cohort studies have noted a 2-3 fold increase in risk in smokers consuming more than one pack per day when compared to non-smokers [176,177].

Insulin and insulin-like growth factor: Malignancies such as breast, pancreatic and colorectal cancers have been positively correlated to hyperglycaemia [178]. Though, its relationship with prostate carcinogenesis is inconsistent. Numerous studies discovered proof of elevated risk of more aggressive prostate cancer amongst males with unusual levels of glucose, with the correlation found not significant in two of the studies [179-182].

On the other hand, a protective effect of hyperglycaemia against advanced prostate cancer had been reported in several other studies [183-185]. It has been documented early on that glucose is a vital source of energy for fast proliferation of tumour cells [186]. Data from genetic and clinical studies pointed to the link between the hyperglycaemic environment and carcinogenic processes like apoptosis, oxidative stress, DNA damage and chronic inflammation, all may control the cancer's aggressiveness and progression [187-190].

Insulin directly controls serum glucose; therefore, an elevated level of glucose stimulates insulin secretion from the pancreas. A previous study has noted that patients with high-risk prostate cancer had elevated levels of insulin [191]. Lastly, the elevated level of circulating insulin leads to a lower level of production of insulin-like growth factor (IGF-1)- binding proteins, rises IGF-1 levels and rises advanced glycation production end products leading to a promoting of carcinogenesis [192].

Chronic inflammation and prostatitis: It has been found that there is a strong affiliation between prostate cancer and inflammation, both epidemiological and biological studies supplied evidence that inflammation is responsible of high-grade or aggressive prostate malignancies and eventually metastatic spread [193,194]. The information proven by evidence-based practices thus far backs the function of inflammatory response in the management of tumour microenvironment via the remodelling of the extracellular matrix (ECM) and launching of epithelial-mesenchymal transition (EMT). Truly, growth factors and cytokines are released by inflammatory cells inside the tumour microenvironment in order to stimulate ECM's angiogenesis and remodelling, while in the reactive stroma, further cytokines are released which stimulate EMT-mediated responses [195].

Biopsies have shown that patients with high PSA levels frequently show intraprostatic inflammation [196]. Chronic prostatitis leads to proliferative inflammatory atrophy (PIA) [193], which may cause prostatic interepithelial neoplasia (PIN) a known prostate cancer precursor [197].

Inflammation of the prostate cancer is referred to as prostatitis, it is asymptomatic, thus hard to diagnose [198]. It has been noted that patients diagnosed with prostate cancer usually exhibit prostatitis symptoms, this may be attributed to the increased frequency of biopsy [199]. A meta-analysis of studies conducted between 1990 and 2012 provided statistical evidence that prostatitis is major risk factor in prostate cancer [200].

Sexually transmitted disease (STD): Evidence provided by a number of epidemiological studies show that elements correlated to sexual conduct and STD's may be linked with prostate cancer [201]. Prostatitis and prostate atrophy caused by gonorrhoea and other bacterial infections may lead to prostate cancer, viral infections on the other hand role may be attributed to the transforming properties of the viruses, especially HSV [200].

A big case-control study based on the population of the USA including African-American and white men, showed that men with history of gonorrhoea or syphilis have a higher risk of prostate cancer [202][203].

4. MEDICATIONS

For high risk prostate cancer, utilising a shortened course of docetaxel as a hormonal therapy following radical prostatectomy (or radiation therapy) has been proven to be a safe and feasible choice [203][204]. The utilization of docetaxel as a hormonal therapy has been demonstrated to be well tolerated and with minimal toxicity [204]. Patients with an elevated risk for prostate cancer have a much better outcome when using adjuvant vinblastine, doxorubicin and mitomycin [203][204].

However, long-term androgen ablation therapy targeted at prostate cancer has been associated with substantial adverse effects affecting both quality of life and total health [204][205].

4,5-dicaffeolquinic acid, as demonstrated in studies, exerts an inhibitory effect against prostate cancer cells, it causes cessation of the cell cycle [205]. On the other hand, clinical trials imply that using docetaxel is associated with improved survival, additionally , combining docetaxel with estramustine give a better outcome [206]. More important, a significant number of patients undergoing docetaxel-estramusine therapy had as much as 50% PSA decline when compared with those undergoing mitoxantrone- prednisone treatment [206]. Many preliminary studies suggest that carboplatin and oxaliplatin may have some action and could be used as a second-line route in chemotherapy [207].

An oral platinum complex called satraplatin exerts its action against hormone refractory prostate cancer in cisplatin-resistant human tumour lines [208]. Satraplatin-prednisone therapy had a median overall survival of 14.9 months, compared to 11.9 months on prednisone alone, demonstrating a markedly decrease in PSA levels [208].

It has been reported that abiraterone, enzalutamide and many other agents may paly a role in improving the outcomes in men treated for metastatic prostate cancer resistant to conventional hormonal therapy [209]. Options for treating prostate cancer are presented in Table 2.

Table 2. Options treating prostate cancer

Surgical	**Therapeutic**		**Radiotherapy**
Radical prostatectomy	Hormonal therapy	Vinblastine	Iridium implant
	Doxorubicin	Mitomycin	
	Oxaliplatin	Docetaxel	
Androgen ablation therapy	Mitoxantrone	Prednisone	External-beam radiation
	Estramustine	Taxane	
	Satraplatin	Abiraterone	
	Enzalutamide		

5. CONCLUSION

Prostate cancer is the second most common malignancy in men, coming after lung cancer [1]. Having a biomarker like PSA which is correlated in positive manner to prostate cancer made a very positive impact on epidemiological studies of the disease. As a result of utilizing PSA as biomarker, the number of diagnosed cases of prostate cancer has doubled in the USA since early 80's [209]. Similarly, other countries, especially western, have shown the same increase.

It is possible to say that the most exciting statistic about the incidence and mortality of prostate cancer is the manner that prevalence fluctuates amongst various racial groups, showing the highest prevalence in African-American males [18]. This variation can be attributed to biologic and socioeconomic factors, and here comes the urge to study which genes may be involved and how do they correlate with the environment.

In human prostate cancer recently, a thorough analysis of genetic and epigenetic alterations was made possible by the development of innovative genetic technologies. In combination to targeted functional studies, this information aided to detect key signalling pathways that are usually correlated to the initiation and progression of prostate cancer. These findings will give a chance for the development of innovative targeted methods for therapeutic interventions. More studies are carried out to discover genes correlated to an increased risk of prostate cancer, more insights about the role of specific genetic changes on prostate cancer advancement are gathered by researchers.

On another aspect, not enough studies have proven that there is a correlation between dietary intake and risk and prevention of prostate cancer, but some preclinical studies researching the ties between specific eating behaviours and prostate cancer suggest that there might be a link. Hence, there is a need to design better trials that imitate preclinical findings to validate the role of dietary consumption

in prostate cancer. Finally, early intervention and personalised molecularly targeted approaches should be added to future chemoprevention studies, in order to select a treatment for patients with prostate cancer that yields a better and effective outcome.

AUTHOR CONTRIBUTIONS

These authors contributed equally to this work. BTA is supported by a PhD studentship from the Faculty of Medicine, Northern Borders University, Saudi Arabia. MHA is supported by a PhD studentship from the College of Pharmacy, Taibah University, Madinah, Saudi Arabia.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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