Abstract – Objective: The aims of this review study were to provide awareness about PCa as well as an updated knowledge about the incidence, risk factors, and knowledge of PCa in Iran and all over the world.


Results: Incidence rates are relatively high in certain less developed regions. The lowest incidence rates are observed in Central and Eastern European countries and also in Asian populations. Mortality rates are generally high in predominantly black populations. The main risk factors associated with PCa are as follow: smoking and drinking, low intake of fresh fruit and vegetables, geographical area, family medical history, genetic changes, race/ethnicity, occupation, excessive use of micronutrient, estrogen metabolism, obesity, inflammation of the prostate, vasectomy and sexual activity/sexually transmitted diseases.

Conclusions: This study may provide considerable evidence for PCa’s major and minor risk factors. This may be helpful in identifying subsets of the population who are more at risk of developing PCa. Effective preventive actions, such as health education, nutritional intervention, and screening programs, are needed especially in high-risk areas of the world.

KEYWORDS: Prostate cancer, Incidence, Mortality, Risk factors, Iran, World.
INTRODUCTION

Prostate cancer (PCa) is the second most common cancer and the sixth leading cause of cancer death among men worldwide, with an estimated recorded amount of 1.1 million cases and 307,000 deaths in 2012\(^1\)\(^2\), which allocates 15% of all new cases of cancer in men (3). Prostate cancer sufferers are the diagnosed men, (almost 70% of the cases numbered: 759,000) in more developed regions\(^1\). Approximately, 42% of PCa cases occur in men over the ages of 50 years old and the majority of them are often seen after 60 years old\(^6\). Few studies have been implemented about the epidemiology of PCa in Iran\(^4\)\(^5\), although it is the second most common cancer in men and the sixth most common cancer in Iran\(^6\). Therefore, PCa has become an important public health concern as a chronic disease\(^3\).

Epidemiologic studies have shown that there are geographical and racial distribution differences about PCa; it happens more often in Western countries than Asian ones, such as Iran\(^2\)\(^9\). The considerable geographical variation demonstrated that different causal factors are influencing the increasing of PCa rate. Therefore, this study aimed at investigating the incidence, risk factors and the knowledge about PCa in Iran and worldwide.

METHODS

A rapid literature search strategy was conducted for all English language literature published before March 2017. The search was conducted using the electronic databases PubMed and Embase, Scopus and Web of Sciences. The search strategy included the keywords ‘prostate cancer’, ‘epidemiology’, ‘incidence’, ‘mortality’, ‘risk factor’, ‘survival’, ‘Iran’, and ‘worldwide’. The search strategy was adjusted according to different requirements for each database. The specific search was also performed in cancer-related websites for Iran related information.

The incidence and mortality of PCa worldwide and in Iran

The incidence rate of PCa varies by more than 25-fold worldwide; the highest rates were estimated in Northern and Western European countries such as Norway and France\(^10\) and in Australia/New Zealand and Northern America\(^1\) (ASR of 111.6 and 97.2 per 100,000, respectively). Incidence rates are also relatively high in certain less developed regions such as the Caribbean (79.8), Southern Africa (61.8)\(^2\) and South America (60.1), and the lowest rates are in Central and Eastern European countries such as Albania\(^13\) and Republic of Moldova\(^10\) and also in Asian populations\(^4\) with estimated rates of 10.5 and 4.5 in Eastern and South-Central Asia\(^1\). With an estimated number of 307,000 deaths in 2012, PCa is the sixth leading cause of death from cancers in men worldwide (6.6% of total men deaths). Since PSA testing is more effective on incidence than mortality\(^23\), there are less variations in mortality rates than incidence worldwide (ten-fold from approximately 3 to 30 numbers per 100,000 people) as the number of prostate cancer deaths are higher in less developed regions compared to more developed (165,000 and 142,000 numbers, respectively).

Mortality rates are generally high in predominantly black populations (Caribbean, 29 per 100,000 people and in Sub-Saharan Africa, ASRs are 19-24 per 100,000 people), they are very low in Asia (for instance 2.9 per 100,000 people in South-Central Asia) and are intermediate in the America and Oceania\(^1\).

PCa is the sixth most common cancer and as the study of Pakzad et al\(^16\) reported, PCa is the sixth leading cause of death from cancer in Iran, with an estimated number of 4,111 new cases and 2,297 deaths in 2012\(^17\). A study conducted in Iran during a 6-year period (2003-2008) showed that 9-7% of all cancers in Iranian men were PCa. In total, in the six-year study, 16,071 cases of PCa were recorded\(^4\). Different conducted studies in Iran showed that more PCa cases occur after 50 years of age and PCa is mostly frequent in ages of 70-79 years old\(^18\)\(^-\)\(^21\), which is related to the morphology of adenocarcinoma. Pakzad et al\(^17\) also reported that the most common morphology (adenocarcinoma) decreased from 97.6% in 2003 to 90.97% in 2008; this reduction was significant with an APC of -3.3 (CI: -7.4 to 0.9)\(^4\). Compared to the Western countries like the United States, Iran has a remarkable lower incidence rate of PCa\(^22\). This large disparity in the incidence of PCa may be due to a combination of genetic, environmental factors, diet, lifestyle, widespread clinical examinations, and most importantly access to preventive and diagnostic services like PSA testing in developed countries\(^23\)\(^-\)\(^25\).

The incidence of PCa is also affected by geographical region in Iran\(^4\). Few studies have been conducted on the epidemiology of PCa in Iran\(^7\). The results of Sadjadi et al\(^23\) (based on Iran Ministry of Health Guidelines) showed that there were evident regional differences in the incidence of PCa in Iran. The results of the first report of cancer incidence in Tehran at 2009\(^26\), showed that after stomach cancer, PCa is the second most common cancer among men in Tehran, with an ASR of 15.6. According to the results of another report\(^23\)
However, the PCa mortality rate in Asia, Africa and Central America is lower than other parts of the world. The exact causes of this difference are not known, but one of the possible causes of this difference can be the advance in diagnostic methods and difference in lifestyle. For example, the risk of PCa among Asian-Americans is lower than white Americans. Also, due to the higher life expectancy in developed countries, the incidence of PCa in these countries has often increased with age.

**Major Risk factors of PCa**

**Drinking and Smoking**

In terms of diet and nutrition, some studies have found a significant association between smoking and beverage consumption. Findings of meta-analysis studies of Fillmore et al., Rota et al., and Zhao et al., showed a significant relationship between high consumption of alcoholic beverages and PCa incidence. In terms of tobacco consumption, the findings of a meta-analysis study indicated that the incidence and mortality associated with PCa have increased significantly with the increase in tobacco use. Various studies have provided various mechanisms about the development of tumors and morbidity caused by smoking. For example, researchers have found that smoking increases the serum estrogen metabolism and subsequently promotes a more aggressive tumor phenotype, resulting in increased PCA-related deaths.

**Lack of Fresh Fruit and Vegetables**

Several studies have shown that a diet containing certain vegetables (including tomatoes, cruciferous vegetables, soy beans, and other legumes) or fruit juices (such as pomegranate) is associated with lower incidence of PCa. In this regard, results of a systematic study showed that there is a significant association between receiving tomato-rich vegetables and tomato-rich products with reduced PCa incidence. Some case-control studies also indicated that the risk of PCa in people who intake cruciferous is significantly lower than others.

**Geography**

Geographically, the most commonly affected regions of PCa include North America, Australia, New Zealand, and Western and Northern Europe. The highest PCa mortality rate is estimated in low and middle-income regions, including sub-tropical Africa, South America, and the Caribbean.

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### Geographical Considerations

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Vitamin D (1, 25 dihydroxyvitamin D₃) also, is an essential vitamin that is from the super family of the steroid hormones. Human sources include both dietary intake and conversion from an inactive to active vitamin D in the skin through sunlight exposure. Interest in vitamin D as a determinant of PCa risk, comes from several epidemiologic studies that suggest PCa occurs more frequently in older men, with more common vitamin D deficiency. Also, a dietary intake of dairy products rich in calcium, which depresses the serum levels of vitamin D, is associated with a higher risk of PCa. Although, many studies show no association or a weak association between vitamin D levels and PCa risk.

The Cancer Prevention Study II Nutrition Cohort, a prospective cohort of 65,321 men, demonstrated a modestly increased (relative risk) RR of 1.2 for total calcium intake (dietary and supplements) and 1.6 for just high dietary calcium intake (≥2000 mg/day vs <700 mg/day), but not for dairy intake. The results demonstrate that very high calcium intake, more than daily recommendation, may modestly increase cancer risks. These conflicting results regarding vitamin D, calcium, and PCa risk, may be explained by variants in the vitamin D receptor (VDR). Polymorphisms resulting in a VDR with lower activity have been related to increased risk of PCa, as well as increased risk of biochemical recurrence following radical prostatectomy.

**Estrogens**

In contrast to the early study about estrogen that has been considered as protective factor against PCa and has been used as a treatment for advanced disease, evidence suggests that estrogens may play a significant role in predisposing or even cause PCa. There is correlative evidence in humans, which indicates the effect of estrogen on the prostate gland being conducive to cancer onset. Although, blood circulating estrogen levels may not correlate well with intraprostatic levels, particularly in light of recent evidence about the intraprostatic estrogen production, serum values offer an easily accessible surrogate marker to investigate associations between estrogen and PCa risk. Estrogen metabolism (CYP1B1 and CYP19) and PCa risk, may be explained by variants in the vitamin D receptor (VDR). Polymorphisms resulting in a VDR with lower activity may contribute to prostate carcinogenesis and cancer. However, the data on serum estrogen levels and PCa risk/ethnicity

Highest PCa incidence rates were observed in African-American Caribbean men. The mortality rate from PCa among African-American men is about double than of white men. The occurrence of PCa in Asian-American and Hispanic/Latino men was lower compared to non-Hispanic white men.

**Occupation**

Several studies have been carried out on occupational risk factors. The findings of a case-control study in 2016 showed that the PCA risk among forestry workers, police officers, administrative and clerical workers, white-collar occupations, and industries, such as public service, was lower compared to other occupations. A study conducted in 2013 also suggested that the risk of PCA in farmers is 4 times higher than others. One of the reasons why PCa is higher in farmers is the exposure to pesticides. Parent et al. also found that the exposure to various chemicals such as pesticides, acetic acid, arsenic compounds, polycyclic aromatic, gasoline and diesel engine emissions, mono-nuclear aromatic hydrocarbons, lubricating oils has significantly increased the risk for PCA. This study also found that the risk of PCa is generally twice in farmers using pesticides than others. Other study findings also indicate that PCA risk is 6 times higher for farmers exposed to diesel engine exhaust. The results of a case-control study in Taiwan (2016) showed that the risk of PCa among hairdressers using hair dye was significantly higher than other hairdressers. In fact, hair dye products contain over 5,000 mutagenic and carcinogenic chemicals.

**Factors with less clear effect on PCa risk**

**Excessive use of micronutrient**

Many studies recommend that use of vitamins, supplements, and specific foods are frequently reported among PCa patients. A Swedish study in 2010, showed that, overall, participants with PCa were more likely to have used supplements than healthy population-based control subjects. In a Canadian study, complementary and alternative medicine (CAM) use was reported among 39% of recently diagnosed PCa patients, and the most commonly used forms of CAM were herbas, vitamins, and minerals. Within those categories, saw palmetto, vitamin E, and selenium were the most popular ones.
risk are conflicting. Complicating interpretation of serum measurements is the fact that estradiol can be produced from testosterone by intraprostatic aromatase. Therefore, future research is needed in order to reach confirmation on estrogen’s role in development and progression of PCa.

**Obesity**

There are contradictory results about the risk of obesity. Several studies have found that, despite the lower incidence of low-risk diseases in obese men, the risk of PCa in these individuals is higher than others. The reason for this finding is not clear. Some other studies also indicated that PCa-related risk and mortality rates in obese men were significantly higher than others. However, all surveys are not consistent with this finding. So, further studies are needed.

**Prostatitis**

Some studies have found that there was a significant association between prostatitis and PCa. However, some other studies did not confirm this finding. Cohort study findings in California (2010) also indicated that PCa risk increased in people with prostatitis [RR = 1.30; 95%, CI: 1.10-1.54]. There is a lot of evidence of long-term affliction to asymptomatic inflammatory prostatitis caused by infectious microorganisms and PCa. One of the organisms associated with PPH and PCa is the infection with E. coli bacteria. Other studies also indicated that the protozoan T. vaginalis infection caused by sexually transmitted diseases (STIs) was associated with prostatitis and PCa. In general, the association between prostatitis and PCa has not been definitely demonstrated, and further studies are needed in this field.

**Vasectomy**

Existence of a relationship between vasectomy and PCa risk was initially suggested in 1993 with a RR of 1.6 based on two large cohort studies. The risk increased by aging, so that men who underwent vasectomy at an early age, had a lower risk. A recent meta-analysis reported a pooled RR of 1.37, with a linear trend suggesting a 10% increase for each additional 10 years since vasectomy. On the other hand, a meta-analysis of cohort studies suggested that vasectomy was not associated with increased risk of PCa. Therefore, research on this possible association is still under way.

**Sexual Activity/Sexually Transmitted Diseases**

Some studies have found that there is a significant relationship between the incidence of STIs and the incidence of PCa. It is assumed that sexual behavior and associated exposure to infectious agents increases the risk of PCa. Meta-analysis study findings also confirmed a significant relationship between PCa and STI (odds ratio [OR] = 1.48, 95% CI = 1.26 to 1.73), gonorrhea (OR = 1.35, 95% CI = 1.05 to 1.83) and human papillomavirus (OR = 1.39, 95% CI = 1.12 to 2.06). Some other studies also show a significant relationship between ejaculation frequency and PCa, so that ejaculation is a protective factor in prevention of PCa. Findings by Doolan et al. (2014) also indicated that men who ejaculated more than 5 times a week had a lower risk of developing PCa. Leitzmann et al. found in a Cohort study that more than 21 ejaculations per week decrease the risk of developing PCa. The causes and mechanism of the protective effect of ejaculation are still unknown.

**Survival**

Most cases of PCa develop in older men. In many cases the cancer is slow growing and non-invasive. Therefore, it has a lower risk and only one out of 36 cases died from PCa. Likewise, most people with PCa die for different causes than PCa, such as stroke and cardiovascular diseases. The five-year relative survival rate is 100% in the local stage and 28% in the regional stage. The American Cancer Society has also estimated the PCa’s 10-year survival rate to be 91%. The PCa survival rate in developing countries is lower compared to developed countries due to delayed diagnosis and lack of adequate health care access.

**Conclusions**

PCa is characterized by wide variations in incidence and mortality all over the world, combined with evidence of increasing load of incidence in several areas. The rates are in the highest amounts in Australia/New Zealand and Northern America and in Western and Northern Europe but remain low in Asian populations. Compared to the Western countries like the United States, Iran has a remarkably lower incidence rate of PCa. This large disparity in the incidence of PCa may be due to a combination of genetic, environmental factors, diet, lifestyle, widespread clinical examinations, and most importantly, access to...
preventive and diagnostic services such as PSA testing in developed countries. These studies may provide considerable evidence for major and minor risk factors, which may be helpful in identifying subsets of the population which are more predisposing in developing PCa. This will lead to the use of effective preventive actions, such as health education, nutritional intervention, and screening, especially in high-risk areas in the world. Furthermore, a screening program for PCa by PSA testing is highly recommended in order to discover latent asymptomatic PCa cases and to clarify the real burden of the disease, especially in developing countries such as Iran. In addition, future investigations are needed to improve our knowledge about unclear risk factors of PCa, which have been mentioned in this article.

REFERENCES


