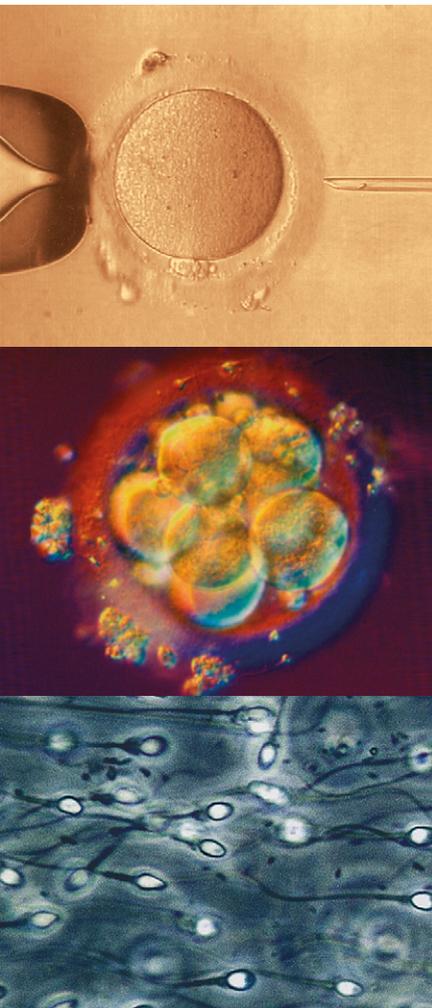


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J. Reproduktionsmed. Endokrinol 2015; 12 (4), 396-398

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Indexed in EMBASE/Excerpta Medica/Scopus

Krause & Pachernegg GmbH, Verlag für Medizin und Wirtschaft, A-3003 Gablitz

Aging Men and Prostate Cancer

B. Thompson, S. Khan

Prostate cancer (PCa) is one of the most commonly diagnosed cancers in men worldwide and its incidence increases with age, mainly affecting elderly men aged 60 and above. Factors known to be associated with the development and progression of PCa are age, family history, and race/ethnicity, with age being the most important factor. The reasons for the increased incidence and mortality due to prostate cancer in elderly men are not entirely clear. Continued exposure to environmental and dietary factors may lead to accumulation of genetic and epigenetic changes over the life-span, leading to altered expression and/or activity of tumor promoter and tumor suppressor genes. Changing levels of endogenous hormones (like androgens) and metabolism in elderly men may also play a role in the development of prostate cancers which may be further influenced by testosterone replacement therapy. For many decades now preventative strategies and treatments such as radiation therapy or hormone therapy, and others have been administered to manage PCa; however current studies and evidence suggest that PCa is undertreated in elderly men, despite evidence of efficacy of these treatments, which leads to higher prevalence of mortality in this age group. Studies involving basic research, preventative and management strategies are still underway to understand the mechanisms of PCa development in elderly men and treatment of this disease in ageing male population. **J Reproduktionsmed Endokrinol_Online 2015; 12 (4): 396–8.**

Key words: prostate cancer, elderly men, prevention and management, cancer treatment

■ Introduction

Prostate cancer (PCa) is one of the most common diseases that affect men worldwide and is among the leading causes of cancer-related deaths in men [1–3]. According to the American Cancer Society in 2015 there is an estimation of about 220,800 new cases of prostate cancer and approximately 27,540 deaths from this disease in the US. About 1 in 7 men will be diagnosed with PCa during his lifetime and about 1 in 38 men will die of this disease [1, 2]. There are several confirmed risk factors which play a major role in PCa incidence: age, genetics, and race/ethnicity in which age is the most important factor. PCa incidence increases with age and has steadily increased over the last decades with increasing population of elderly men due to improved life expectancy [3–6]. Reports show that prostate cancer occurs mainly in men aged 65 or older with approximately 6 in 10 diagnosed cases and will rise in the upcoming years [1]. Due to predicted increase in the prevalence of this disease in the elderly, many studies have been carried out to investigate factors that may be involved in the development and progression of prostate cancer.

PCa is a “hormone-sensitive” disease meaning that its development is strongly influenced by natural hormones that are made in the body and exogenous hormones and chemicals which are derived from food and the environment [6]. The

balance of these hormones is influenced by aging, obesity, high-fat diet, calcium in diet, lack of exercise, smoking and alcohol use, excessive calcium and exposure to hormone-like chemicals from food and the environment [1, 6]. Studies have been carried out to link these risk factors to prostate cancer in men. Research studies also report that genetic variations or mutations may contribute to the increased risk of developing PCa. To explore a possible connection between elderly men and prostate cancer, we will discuss factors that may play a role including hormonal, dietary factors, genetics, and/or environmental factors that may provide an answer to a direct cause-and-effect relationship between age and prostate cancer.

■ Testosterone and Prostate Cancer

Many researchers have designed studies to correlate testosterone levels and the risk for prostate cancer; however, many of these studies have not provided a consistent association between the two. Testosterone is the hormone that is needed for the normal growth and development of the prostate [1, 6] and is also involved in building muscles, burning fat, immune function, and bone density [6–8]. Studies have shown that the levels of testosterone decrease gradually with age and by the age of 65, testosterone levels may be only 20% of those found in young adults [6, 7]. Low levels of testosterone or “hy-

pogonadism” are associated with increased morbidity and mortality [7–10]. Epidemiological studies have demonstrated that the incidence of hypogonadism in aging male increases with every decade of his life [7]. Several studies have found that men with lower testosterone levels have an increased risk of life-threatening diseases such as cardiovascular disease, obesity, osteoporosis, and diabetes [9, 11, 12].

Testosterone replacement therapy (TRT) as its name suggests, has been used in clinical studies for treatments to replace or increase levels of circulating testosterone. It has been hypothesized that increasing the amount of testosterone in elderly men with low testosterone levels into a range that is mid-normal for a healthy young man would improve the overall quality of life [10]. A number of clinical trials have demonstrated minor to moderate improvements in lean mass, increase in bone mineral density and reduced adiposity [6, 11, 12]. However, there are still important concerns regarding health risks associated with long-term use [10]. Testosterone therapy increases the levels of testosterone and may result in improving the quality of one’s life for obesity, bone mineral density, etc., but because testosterone functions to promote the growth and development of the prostate, this may provide a direct link of testosterone promoting the growth of prostate cancer. However, there is no conclusive evidence correlat-

Received and accepted: June 17th, 2015

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ing high testosterone levels and prostate cancer risk [10, 11].

Several reports indicate that prostate cancer can grow very slow and the majority of elderly men diagnosed with prostate cancer had no previous symptoms and this microscopic disease progressed with age [1, 3]. Prostate cancer is androgen-dependent [6–8], and although tumors may have been undetected, the presence of exogenous testosterone may cause these microscopic tumors to grow and spread quickly [8]. Findings from several studies have not provided a direct cause and effect between aging men and prostate cancer but have provided evidence that high levels of testosterone could increase the speed of the disease's growth rate [6, 8].

Linking Testosterone and Diet to Prostate Cancer

Testosterone is an important signaling molecule in regulating multiple cellular metabolic pathways including the regulation of adipogenesis [6, 7]. Several studies have reported evidence of testosterone's role in regulating the body composition by increasing and maintaining muscle mass and reducing fat mass. These findings suggest that low levels of testosterone may contribute to obesity. Elderly men have low levels of testosterone which have declined with age and may correlate with slower metabolism and result in an increased risk of obesity and diabetes. Studies have shown that men with high cholesterol levels have a 50% increased incidence of developing prostate cancer compared to men with normal levels [6, 11, 12]. In addition, men over 60 years of age or older showed an increase in cholesterol levels and resulted in an increase in prostate cancer compared to their younger counterparts [9, 11–13]. Even though the direct cause of prostate cancer is not completely understood, researchers have found that high-fat diets are linked to prostate cancer [11].

Genetics and Prostate Cancer

Studies have shown that genetic variations/alterations are key factors involved in developing prostate cancer. Genetic alterations (changes in the DNA sequence) such as deletions and/or mutations in genes that regulate different aspects of prostate cell development and behavior play a key role in the develop-

ment and progression of prostate cancer [14, 15]. During genetic alterations, tumor suppressor genes such as PTEN and ATBF1 and oncogenes such as BCL2, RAS, MYC and others often have mutations in which they either lose their function or have a gain of function, respectively [14–18]. Therefore, accumulation of these mutations over time leads to the aggressive progression of prostate cancer as seen in elderly men. Several genes such as BRCA1, BRCA2, and CHEK2 have been shown to be implicated as high risk for breast cancer and ovarian cancer and have also been shown to increase the risk of PCa [14, 16, 17]. Reports have also shown that younger men have precancerous prostatic intraepithelial neoplasia (lesions) but prostate cancer is not clinically detectable until a man reaches 60 years of age and this disease is manifested [14, 19]. These genetic changes in early adulthood and the accumulation of these changes (mutations) leading to the progression of prostate cancer may be a result of aging.

Prevention and Management of Prostate Cancer

The ultimate goal is to understand the underlying mechanisms which are involved in the development of prostate cancer in elderly men and then set measures to prevent this disease from developing. Although significant progress has been made to reduce the progression of prostate cancer (early testing, yearly rectal examination, and PSA test), the evidence of risk factors and correlations that are associated with this disease are not conclusive enough to make definite recommendations [1, 5, 13]. On the other hand, for elderly men, age is a risk factor that cannot be changed; the development of effective preventative strategies may delay the onset of prostate cancer beyond their expected life span. There are several preventive initiatives that are currently being discussed or being studied in clinical trials. Although high testosterone levels have been implicated as a risk factor for prostate cancer [8, 11], its role in elderly men remains less defined. Testosterone levels decline steadily with age [6, 7], therefore the strategy of decreasing prostate exposure to androgenic stimuli is less obvious as a preventive strategy. In fact, a more common issue facing elderly men is the potential need for TRT. Although studies have reported

that this therapy may have long-term side effects, evidence is not completely conclusive.

Treatments for Prostate Cancer

After a patient has been diagnosed with prostate cancer, the prognosis and treatment options available depend on several factors including the stage of prostate cancer (the level of prostate specific antigen, PSA), Gleason score, grade of the tumor, how much of the prostate is affected, how fast the cancer is growing, how much of it has spread to other body areas, reoccurrence or 1st time diagnosed, age and overall health of patient, and also the benefits and potential side effects associated with treatments [1, 5, 15]. Immediate treatment may not be necessary for men diagnosed with very early-stage prostate cancer, instead active surveillance including regular follow up tests, exams, and biopsies may be performed to monitor the progression of cancer. Treatment options used to treat more advanced prostate cancers include surgery (removal of the prostate), radiation therapy (high-powered energy to kill cancer cells), hormone therapy (treatment used to stop the production or block actions of male hormone, testosterone), chemotherapy (use of drugs to kill rapidly growing cancerous cells), and others. Most or all of these treatments for prostate cancer carry several risk complications, side effects, and other impacts that will affect the patient's long-term quality of life [6, 15, 20].

Impact of Age on Prostate Cancer Treatment

Age plays a vital role in prostate cancer treatment decisions. Elderly men with high-risk prostate cancer are usually under-treated because they are offered fewer and less effective choices of treatment compared to younger men that may result in higher rates of cancer mortality in this group, according to a study at University of California San Francisco (UCSF) [21]. This study addressed whether or not age played a pivotal role with prostate cancer risk and survival following treatments. In this study, researchers studied men in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database (a longitudinal, observational disease registry of

men with prostate cancer in the US); and found that elderly men 75 years and older with high-risk prostate cancer are often not treated with potentially curative treatments such as surgery and radiation therapy, but instead are under-treated with hormone therapy or go through a period of watchful waiting/active surveillance. This study analyzed elderly men with localized prostate cancer that were treated with curative treatments (surgery, radiation therapy and several others) or conventional methods and showed a decrease in mortality compared to men who were treated with hormone therapy or active surveillance [20–22]. This study highlights the importance of the need of treatments to be selected based on disease risk (tumor size, metastases rate) and not based on the age of the patient [21, 23]. Another study compared the outcomes of chemotherapy in men ≥ 75 with younger patients who exhibit similar prognosis (stage of cancer and tumor grade) with 1 year of treatment and found that there was no age specific difference with survival rates, indicating that elderly men are able to tolerate this treatment [22–25]. Despite the age of patients, both age groups should have the same choice of considering different treatment options that may benefit them in increasing their life expectancy.

■ Conclusion

Prostate cancer is a disease that largely affects the elderly male population aver-

aging 65 years old and above and a large percentage of deaths due to this disease occur in men 75 years and older. Treatments used for prostate cancer are given based on the perception of a patient's age, current illness, ability to tolerate therapy, which causes many elderly patients to be undertreated, but should be treated based on disease risk. On the other hand, even though some treatments may benefit the older population the same as the younger counterparts, they may be more likely to suffer from side effects from more aggressive treatments.

■ Conflict of Interest

The authors declare no conflict of interest.

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