

Is Male Infertility a Natural Defense or Forerunner of Cancer?

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Abstract

Infertility connotes inability to become pregnant after 12 months or more of regular unprotected sexual intercourse. Male factor is known to be responsible for almost 50% of cases of infertility. There are increasing evidences of possible association between infertility, especially male infertility and cancer. Higher risk of subsequently developing testicular cancer and clinically important prostate cancer has been suggested. Hence, there is possibility of common etiologic factors for male infertility and metastasis of these reproductive organs. The main circulatory androgen in man, testosterone is known to function as prohormone that is converted to active steroid, dihydrotestosterone by the enzyme 5 α -reductase in the prostatic cells. This hormone and enzyme are not only important in spermatogenesis and maturation of sperm cells but important in prostatic growth and development of prostate cancer. The level of 5 α -reductase in particular increased in prostatic intraepithelial neoplasia and prostate cancer and continues to rise as the disease progresses. Mutation and polymorphism of androgen receptor has been related to both prostate cancer and infertility. Furthermore, protosomes which is a small membrane-bound vesicle that are produced within the prostate acini are known to fuse with and transfer proteins to spermatozoa, enhancing their motility and modulating their functions. The corpus function and production of this protosomes in metastasis will directly affect the quality and function of sperm cells, consequently causing infertility. Cancer of the testicular germ cells has also been implicated in decline semen quality and infertility. In addition, testicular dysgenesis syndrome; a theoretical constructs attempted to relate environmental modulators, genetics, and infertility in the development of testicular cancer. Reactive oxygen species and free radicals damages of DNA and faulty DNA repair are also common mechanism implicated in both male infertility and cancer. This article reviews the suggested associations and possible related mechanisms that contribute to cancer of reproductive organs and male infertility.

Keywords: Male infertility; Prostate cancer; Testicular cancer; Androgen; ROS; DNA damage

Introduction

Infertility is generally defined as failure to conceive after frequent unprotected sexual intercourse [1]. Clinically, it is defined as inability to become pregnant after 12 months or more of regular unprotected sexual intercourse [2,3]. It could also be referred to as the biological inability of an individual to contribute to conception, or to a female who is unable to carry a pregnancy to full term. Infertility is a common medical problem globally, and both male and female factors have been observed to contribute almost equally to this problem. Several factors have been implicated to cause infertility, these include endocrinological [4,5], anatomical [1,5], immunological [5] and nutritional [6] and genetic [7,8]. Though, possibility of link between male infertility and cancer has been suggested but not fully elucidated [9].

Testicular cancer is thought to be higher among men seeking infertility treatment when compared with general population [9], thus suggesting that men with male factor infertility have an increased risk of subsequently developing testicular cancer. Therefore, there is the possibility of common etiologic factors for infertility and testicular cancer. Testicular germ cell cancer is the most common cancer among young men in industrialized country [9]. Subjects with testicular germ cell cancer have been reported to have decline semen quality and infertility in industrialized nations [9-11]. Whether a decline in semen

quality and infertility are independently or related to each other remained to be clearly elucidated.

On the other hand, lower risk of prostate cancer has been reported in infertile male [12,13]. Interplay between androgen receptor and ligate binding may play a major role in this relationship. Testosterone, which is the main circulating androgen in men is essential for both spermatogenesis and sperm maturation. Low levels of testosterone are common observation in infertile men [14]. While an increase level of testosterone is associated with risk of prostate cancer [15]. Association between infertility and circulating androgen level on one hand and circulating level of androgens and prostate cancer on the other hand are not well document [16]. However, there is an increasing divergence in the outcome of research attempts to link fertility or male infertility to prostate cancer.

There are other several factors implicated in both male infertility and cancer such as genetic factors, epigenetic modifications, and environmental factors. Knowledge and information on these factors are emerging and is still at the stage of research only. However, prenatal exposure to some chemicals such as Vinclozolin, are known to induce transgenerational inheritance of reproductive diseases including male infertility and prostate cancer [17,18].

Male Infertility and Testicular Cancer

Male reproductive health has declined markedly globally in the recent year with attendant decrease in the quality of semen produced and consequently increased rate of infertility in men. Studies have

shown a six-fold increase in developing gonadal tumors among male with infertility suggesting a possible link between male infertility and testicular cancer [19]. Previous studies have also shown that men who developed testicular cancer had fewer children than age-matched men who do not developed testicular cancer [20]. Petersen et al. [21] Shown that semen quality in men with unilateral testicular cancer was much poorer than that of those with normal testis. Also a pre-cancerous cellular condition (Carcinoma in situ) was reported to be more frequent in testicular biopsies of men evaluated for infertility or sub fertility suggesting that this group of individual is at a higher risk of developing testicular cancer [22]. In addition, studies by Jacobsen et al. [23] and Raman et al. [24] corroborated the fact that there is increased risk of testicular cancer in men with infertility.

However, several studies have shown divergent findings in the association between male infertility and testicular cancer [20,23,24]. While study by Jacobsen et al. [23] on a large Danish Cohort among men with infertility revealed 1.6 times more likelihood of developing subsequent testicular cancer, study by Raman et al. [24] in a Cohort of American men with infertility indicated about 18-fold increased risk of testicular cancer. These studies suggested a possible link or common underlying mechanism between male infertility and testicular cancer. Thus it is evident that male infertility is at crossroads of genetic determinants and environmental effects with the exact genetic mechanisms in male infertility still largely unclear. However, with recent studies it is becoming clearer that male infertility is largely associated with a host of medical diseases particularly testicular cancer [25].

Male Infertility and Prostate Cancer

Prostate cancer in the recent time has earned the reputation of one of the leading causes of cancer-related death in men, second only to lung cancer [26,27]. In the United States with the estimated cases of 220,000 diagnosed yearly; this is expected to increase with the expanding geriatric population [28]. Akinloye et al. [29] opined that prostate cancer has become the most common cancer in Nigeria men. While two percent of Nigerian men are reported to develop prostate cancer with 64% mortality after two years of diagnosis [28 now 30], it remains one of the major cancer-related deaths in the USA [31]. Thus prostate cancer is an increasingly important public health problem among men globally. The etiology and pathogenesis of prostate cancer remains poorly understood [32]. In spite of extensive studies on this disease, the pathogenesis of prostate cancer still remains unknown as the biochemical and molecular mechanisms responsible for and associated specifically with the development and progression of prostate cancer are largely unidentified [33].

Several studies have linked prostate cancer and male infertility [34,35]. There are however increasing conflicting results. While there are increasing evidences of lower risk of prostate cancer in childless men when compared with fathers [12,13,36], lack of clear relationship have also been reported [37]. Several lines of evidence support an association between androgen production, androgen sensitivity, male reproduction and prostate cancer [35]. Previous study had observed lower levels of testosterone in infertile men; resulting in reduced testosterone-to-estradiol ratios in this group when compared to the fertile men [14]. In addition, androgens have been reported to be positively associated with the risk of prostate cancer [15]. Study had shown that growth of the prostate gland depends on circulating androgens and intracellular steroid signaling pathways. The effects of androgens are mediated through the androgen receptor (AR), a

nuclear transcription factor encoded by the AR gene. Mutation and polymorphism in androgen has been reported to precipitate either male infertility or prostate cancer [29,38-42]. The differences in CAG and GGN tender repeats in androgen receptor polymorphism have been implicated in ethnical diversity observed in the risk factors of prostate cancer [29]. A shorter repeat is said to improve the interaction between the receptor and ligand resulting in higher activities of androgen. A shorter repeats associated with black population is translated to relatively higher risk of prostate cancer and increase fertility and vice-visa [29,38]. This may explain the report that black men are disproportionately affected by prostate cancer and their incidence rate is about 1.6 times greater than the rate for white men [43]. In addition to this, report from [44] also showed the prevalence of prostate cancer to be highest among black men. This population is also associated with high fertility rate with increasing uncontrolled population growth that further impoverishes Africa population. Furthermore, It has been shown that male infertility though may not necessarily increase the risk of prostate cancer; as the number of prostate cancer cases between infertile and fertile men did not show any significant difference, but the nature of the prostate cancer between these two groups did [34]. Hence, these authors [34] suggested that male infertility may be an early and identifiable risk factor for the development of clinically significant prostate cancer [37].

Common Underlying Mechanism and Risk Factors of Male Infertility and Cancer

Observations from various published studies are in support of both biological and clinical mechanism responsibility for the possible associations between infertility and testicular cancer. Several studies provided evidences in support of faulty DNA repair [9,45-47] and other specifically extend the role of oxygen radicals in DNA damage and cancer incidence [48]. High level of reactive oxygen species and reduced antioxidants are common underline mechanism implicated in spermatogenic failure and male infertility [49,50]. Thus there is an association between decreased total antioxidant capacity and male infertility [51]. Environmental toxicants are known to contribute significantly to both DNA damage and generation of free radical as exposure to environmental estrogens and pesticides has been linked to alterations in spermatogenesis. This is also true about the toxic effect of heavy metals on sperm quality and sperm production [52]. Testicular dysgenesis syndrome; a theoretical construct that attempts to relate environmental modulators, genetics, and infertility in the development of testicular cancer are clinical condition that have been implored to explain relationship between male infertility and cancer of male reproductive organ [53]. Infection, inflammation and enlargement of reproductive organs such as benign prostate hyperplasia (BPH) are other clinical condition that may increase the risk of both male infertility and prostate cancer.

Hormonal Milieus, Male Infertility and Cancer

It is a general knowledge that testosterone is the main circulating androgen in men [54]. However in the prostate gland and other organs, testosterone functions as prohormone that is converted to Dihydrotestosterone (DHT) by 5 α -reductase (5AR) (an intracellular enzyme present in the prostate, skin and liver) in the prostatic stromal and basal cells [54,55]. In serum the ratio of testosterone to DHT is about 10:1, while the ratio of testosterone to DHT in the prostate gland is about 1:10 [56]. 5 α -reductase plays an important role in normal prostate growth and in the development of prostate cancer as its levels

appear to increase during disease course of prostatic intraepithelial neoplasia and prostate cancer and continues to rise as the disease progresses [43].

In addition, protosomes which is a small membrane-bound vesicle that are produced within the prostate acini play a key role in male fertility. It fuses with and transfer proteins to the sperm cells thereby enhancing their motility and modulating their function. This membrane preserves the integrity of the sperm cells [57]. Study has proposed protosomes as an aetiologic factor for prostate cancer. While the mechanism for this is unclear, opinions are suggesting potential mechanisms such as promotion of tumor angiogenesis, cell cycle dysregulation and immunoprotection of cells that are malignantly transformed [58]. However, there are conflicting report on linkage of reproductive hormones with male infertility and prostate cancer. While some studies showed a biological link between fatherhood status and prostate cancer as that of an association between infertility and low circulating androgen levels which is in turn would be associated with a lowered incidence of prostate cancer; association between infertility and circulating androgen level is however not very well documented and there is no well documented association between circulating level of androgens and prostate cancer [16].

Studies by Suomi et al. [59] and Hsieh et al. [60] showed a strong association between testicular dysgenesis syndrome and reproductive hormones levels as one of the studies of reproductive hormone levels in 3 months- old infants found that cryptorchid boys had significantly elevated FSH and LH serum level and low inhibin B levels when compared with non-testicular dysgenesis syndrome control. However among adult men, there was a shift towards lower serum testosterone levels, testosterone/LH ratio and higher serum LH level in infertile men [61]. Also men with CIS and testicular cancer have impaired spermatogenesis, higher levels of LH and FSH as well as a tendency towards lower testosterone levels [21].

Free Radical-induced Mutagenesis and DNA Base Modification

Exposures of human cell to free radicals result in permanent modification to genetic material resulting from oxidative damage. This oxidative damage is the first step of carcinogenesis involved in mutagenesis [62]. DNA alterations caused by radicals are removed by specific and non-specific repair mechanisms. The repair of DNA base damage is thought to occur mainly by base-excision [63]. In the process of DNA repair, a mis-repair could occur. When this happens, mutations such as base substitution and deletion occurs leading to carcinogenesis [64,65].

Oxygen free radicals damage of DNA produces two common types of lesions which are group into; strand breaks and base modification products [66]. Studies have shown that superoxides from xanthine and xanthine oxidase system cause DNA strand breaks [67]. While on the other hand, free radicals from hydroxyl group react readily with nucleic acids to yield different kinds of products including strand breaks which results from the attack of the hydroxyl free radicals on the sugar portion, probably carbon 3' and 4' of macromolecule [67]. This strand breaks are of pathological significance since their proper repair is tantamount to proper functionality of the cell. However enzymatic repair of DNA strand breaks generally have decreased fidelity hence there is a higher probability of mis-incorporating the wrong base in the repaired DNA.

Furthermore, it was also reported that other modified bases; 8-hydroxy-2-deoxy-guanosine (8-OHdG), 8-hydroxyguanine, 5-hydroxymethyluracil, and thymine glycol which results from hydroxyl free radical attack on DNA could have serious consequences in terms of mutagenesis and carcinogenesis [67]. Valko et al. [48] reported that mutagenic potential is directly proportional to the number of oxidative DNA lesions that escape repair and that repair mechanisms decay with age hence DNA lesions accumulate with age. Men with male factor infertility have been observed to be slightly older at the time of infertility evaluation and had longer duration of infertility care than men without male factor infertility but had the same duration of follow up [9]. Sixty- seven cases of testicular cancer were observed among cohort members. On the overall, these authors [9] revealed that infertility cohort members demonstrated a trend for increased risk of testicular germ cell cancer compared with men from the general California population. Thus, observing an association between infertility in men and subsequent development of testicular cancer. These authors shows that male partners of infertile couples were 1.3 times more likely to develop a testicular germ cell cancer the California population regardless of male fertility status. However, among men with known male factor infertility, the risk of subsequent testicular cancer was more than twice that such that these men were 2.8 times more likely to develop testicular cancer relative to the general population.

Free radicals contribute in a unique ways to carcinogens and the malignant progression of tumor cells, which enhances their metastatic potential. Free radicals cause genomic damage leading to genetic instability; also they participate as intermediaries in mitogenic and survival signals via growth factor receptors and adhesion molecules, promoting cell mobility, inducing inflammation/repair and angiogenesis in the tumor microenvironment [68-77].

As mitogenic signal intermediaries, ROS directly act on antioxidant enzymes to cause reduction on the mitogenic reponse in which Mitogen Activated Protein Kinases (MAPKS) and cytokine-mediated signal participate. de la Cruz-Morcillo [78] documented that MAPKS participate in intracellular signal transduction pathways this leads to cell differentiation and survival, arresting growth, apoptosis and senescence which eventually leads to resistance to radiotherapy and chemotherapy. In addition ROS could act as a second messenger by activating the cascade signal that control various cell events like proliferation, apoptosis and inflammation through inactive receptor transduction [68].

Oxidative Stress, Faulty DNA Repair, Testicular Apoptosis and Pathogenesis

Oxygen is essential for life; however as important as oxygen is to life, it can also play a major role in the destruction and disturbance of the normal function of some cells. In normal or physiological cellular metabolism, Reactive Oxygen Species (ROS) are formed. Normally cell generates free radicals and also degrades that which is strictly necessary to avoid cell and tissue damage; however, in the presence of various circumstances (intrinsic & extrinsic) and biochemical activity of the cell can possibly make it to lose control of the formation and management of free radicals. When this happens, it results into an imbalance in the formation of free radicals in the tissue and the cell or tissue antioxidant of these free radicals lead to a situation known as "oxidative stress" [68,79]. Studies have shown that radical-related damage of DNA and protein could play a key role in the development of diseases such as cancer, neurodegenerative disorders, arthritis,

arteriosclerosis and others [80,81]. This is because all ROS have the potential to interact with cellular components including DNA bases or the deoxyribosyl backbone of DNA to produce damaged bases or strand breaks [82] ROS can also oxidize lipids or proteins to generate an intermediate which can react with DNA [83]. Oxygen radicals are derived from many sources but most importantly are the superoxide radicals which are produced in cells generally by a process of electron transfer reactions. These reactions could be enzymatically or non-enzymatically mediated. Normally free radicals are derived from electron leakage that occurs from electron transport chains, such as those in the mitochondria and endoplasmic reticulum, to molecular oxygen, which generates superoxide [84]. Intracellular sources of superoxide and hydrogen peroxide include mitochondria [85-90], cytochrome P-450 [91], Cytoplasmic oxidases [48] Xanthine oxidase [92] Microsomes and peroxisomes [48]. On the other hand, extracellular source of superoxide includes membrane NADPH oxidases [93]. The primary site of radical oxygen damage from superoxide produced in mitochondria is the mitochondrial DNA (mtDNA). Mammalia spermatozoa are extremely sensitive to oxidative stress [94]. ROS in some cases causes defective sperm function as a result of lipid peroxidation of the poly unsaturated fatty acids in the head and mid-piece of the spermatozoon.

Studies have shown that the testis is sensitive to a variety of stressors and exposure to such agents induces germ cell apoptosis [95,96]. Apoptosis is a process by which the body maintains a cellular balance through regulated cell death. Disturbances in the physiological process of apoptosis result in diseases [97] including infertility [98] or cancer [99]. It must be remembered that the principal function of testicular apoptosis is to help maintain tissue homeostasis during spermatogenesis [98]. It has been hypothesized that that apoptosis limit the germ cell population and prevents maturation of aberrant germ cell [100]. Apoptosis results in chromatin condensation, resulting in a free -OH group at the 3' end of the deoxyribose sugar of the condensed DNA [97,101].

Oxidative stress has been associated with a decrease in SOD activity as a decrease in a germ cell-specific SOD mRNA was observed after Cryptorchidism [102]. The testicular function is primarily controlled by local and endocrine cells through interrelationships between the hypothalamus, pituitary and testis in hypothalamic-pituitary-testicular axis. While normal reproductive function is vital to procreation and sexual satisfaction in humans, reproductive dysfunctions on the other hand possess a major health challenge to couples. Studies have revealed that among male with reproductive dysfunction, oxidative and nitrosative stress play key roles [103-105]. It has been shown that oxidative and nitrosative stress has deleterious effect on normal spermatogenesis and sperm qualities such as motility, capacitation, acrosome reaction, egg penetration and de-condensation of sperm head [103-107].

Furthermore, studies have shown that normal and vital sperm functions require a low level of endogenous ROS activities [108,109]. However, high ROS/RNS compromises the germinal sperm cells activities. Mammalian spermatozoa are reported to be extremely sensitive to oxidative stress (a net increase in ROS level within the cell) [94]. These high levels of ROS therefore adversely affect normal sperm production and quality by interacting with membrane lipids, proteins nuclear and mitochondrial DNA [110-112]. The lipid peroxidation may damage membrane integrity resulting in increased cell membrane permeability leading to enzyme inactivation, structural damage to DNA and cell death [113]. Thus it becomes imperative that generation

of Reactive Oxygen Species (ROS), in male reproductive tract has become a real concern because of their toxic effect, at high levels on sperm quality and function [114].

Environmental and Chemical Risk Factors of Male Infertility and Cancer

Environmental contaminant exposure can cause oxidative stress in the testis, leading to apoptosis in germ, sertoli and Leydig cells. Toxicants triggers oxidative stress induced testicular apoptosis through specific pathways [99]. Thus environmental agents can stimulate or inhibit apoptosis [115]. Environmental agents can cause elevation in ROS levels and decrease ROS-scavenging antioxidants causing oxidative imbalance in the testis thereby altering key processes like apoptosis, spermatogenesis and steroidogenesis. Studies have indicated common mechanism such as up-or down-regulating expression of apoptotic related proteins in addition to directly triggering apoptosis in spermatocytes [116,117]. Loss of normal programmed cell death is a common mechanism in metastasis.

Studies have suggested important roles of environmental and lifestyle factors in testicular carcinogenesis [118,119]. Similarly, maternal lifestyle is known to influence son's reproductive function. Particularly, maternal smoking [120] and alcohol consumption during pregnancy can be harmful to the developing testicles [121].

Environmental compounds including fungicides, plastics, pesticides, dioxin and hydrocarbons can inflict insults which can promote the epigenetic transgenerational inheritance of fetal gonadal sex determination [122]. Many of these chemicals are oncogenic toxicants which can precipitate cell abnormalities such as epigenetic changes that are in turn related to increased susceptibility to disease [123]. Environmental epigenetic transgenerational inheritance involved toxicants used in agriculture. Agricultural fungicide such as vinclozolin and pesticide such as methoxychlor were observed to affect gonadal development and function in the offspring. Increased spermatogenic cell apoptosis and prostate carcinoma have been reported after exposure to vinclozolin. Similarly, methoxychlor; a model environmental endocrine disruptor with estrogenic and anti-androgenic activity has been used to replace DDT for application on agricultural crops and livestock [124]. Its estrogenic and anti-androgenic property will adversely influence androgen sensitive cancers including prostate and breast cancer. This chemical like other phytochemicals has been reported to reduce animal's fertility [124].

Genetic and Epigenetic Modifications of Male Infertility and Cancer

Recent advances in genomics had validated the earlier believe that genetic factor contribute to prostate cancer etiology, as genomes of large numbers of individuals in Genome-Wide Association Studies (GWASs) can be scanned rapidly. Studies reported to date revealed that Single-Nucleotide Polymorphisms (SNPs) are scanned across the genome with a fixed panel of thousands of SNPs, chosen on the basis of regular intervals or SNPs chosen to represent independent variation (tag SNPs) [125]. Study by Manolio et.al [126] has shown that GWAS have discovered over 400 genomic regions in over 75 diseases or human traits. GWAS of prostate cancer have provided strong evidence of genome-wide significance [127-131]. Studies have reported an association with a SNP (rs10993994) on chromosome 10q11.2, in close proximity to the MSMB gene [127,131], this encode a prostatic secretory protein 94 (PSP94), which is also referred to as β -

microseminoprotein. Another gene product of MSMB is secreted in the epithelial cell of the prostate gland. Both the PSP94 and the gene product of MSMB, and its binding protein PSPBP, have been reported to be serum markers for early detection of high-grade prostate cancer [132,133]. These genes and its products are synthesized in the epithelial cell of prostate gland and thereafter secreted into the seminal plasma [134]. Study by Wu et al. [135] reported epidemiologic evidence supporting the involvement of common genetic polymorphism in MSMB gene in spermatogenic failure. These results thus suggest that men carry the variant have increased risk of spermatogenic failure associated with male infertility.

Clinical Condition that may Promote Infertility and/or Cancer

Testicular dysgenesis syndrome; a theoretical construct that attempts to relate environmental modulators, genetics, and infertility in the development of testicular cancer are clinical condition that have been implored to explain relationship between male infertility and cancer of male reproductive organ [53]. Infection, inflammation and enlargement of reproductive organs such as benign prostate hyperplasia (BPH) are other clinical condition that may increase the risk of both male infertility and prostate cancer. Testicular dysgenesis syndrome; manifested by conditions such as cryptorchidism, impaired spermatogenesis, hypospadias and testicular cancer are implicated as risk factors for either male infertility or testicular cancer. Cryptorchidism is an established risk factor for infertility and Testicular Germ Cell Tumor (TGCT) [136]. Studies by Thorup et al. [137] indicated that between 5-10% of men who develop testicular cancer were or are cryptorchidism. In addition, Dalgaard et al. [138] identified an association of subsets of these symptoms to genetic factors, in particular between cryptorchidism and testicular cancer. Several studies have supported that fetal origin of two symptoms of testicular dysgenesis syndrome such as hypospadias and cryptorchidism and provided evidence that testis cancer is of developmental origin [139-141]. Some of these studies suggested that the precursor cells of testis cancer, carcinoma in situ testis (CIS) are similar to fetal gonocytes. There is however an evidence to suggest that most cases of testicular dysgenesis syndrome are because of environmental factors thus supporting the hypothesis that both environmental and genetic factors can cause dysgenesis of the fetal testis. Furthermore, decreased functions of Sertoli and Leydig cells are assumed to be responsible for both impaired germ cell differentiation and androgen insufficiency [142]. Thus testicular dysgenesis syndrome may therefore lead to early symptoms, such as undescended testis and hypospadias, as well as late effects such as testicular cancer and infertility [142]. One of the mildest manifestations of testicular dysgenesis syndrome may probably be impaired spermatogenesis without other symptoms, however in some cases; low testosterone levels are also observed [143].

Conclusion

Observations from different studies suggest a link between infertility and testicular cancer. Studies have shown that both infertility and testicular cancer are probably the late symptoms of testicular dysgenesis which is in most cases genetically or/and environmentally mediated. Although, there is no known direct link between infertility and risk of prostate cancer, never the less, the pattern of prostate cancer between these groups has been shown to differ. Thus, while infertility and testicular cancer goes neck and neck,

it can still not be clearly stated that infertility is a forerunner of cancer or vice versa. However, several mechanisms implicated in the etiology of male infertility are now known to predispose to prostate or testicular cancer.

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