Review Article

Prostate Cancer Etiological Factors

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Abstract

Introduction: Prostate cancer is the more frequent extracutaneous malignity in males, presenting a high morbimortality rate. **Methodology:** search was done in Pubmed, using keywords "prostate cancer; epidemiology; etiologic factors and risk factors". Articles in English published in a 10-year period (1996-2006) about etiologic factors of prostate cancer. **Results:** Amongst the factors found regarding prostate cancer, age, ethnicity, family history, and dietary habits stand out. But no clear way was found to determine the events sequence and the initiation factors for this neoplasia in genetically predisposed tissues. Currently, cares men receive in the risk age group are carried through for early diagnosis and treatment of a lesion already existent, with the clear intention of stopping the progression of the disease. However, it is important to consider that therapeutic options for treating prostate cancer are far from being free from side effects. Today it is recognized that the development of prostate cancer has a direct link to a multiplicity of causes the combination of which would be the conditions for the disease to appear. Genetic susceptibility has no doubt an important role, but it is the interaction between this susceptibility and the factors or conditions resulting from life styles and the environment that determine the risk of having cancer.

Key words: Prostate. Cancer. Etiology. Risk Factors.

Introduction

According to World Health Organization (WHO), the prevalence of cancer in the world has had an exponential increase, with a perspective for 2020 of 30 million people living with this disease.[1] In Brazil, we have the same situation, since the incidence of cancer increases in a par with population ageing, due to the rising of life expectancy, urbanization and the new alimentary habits.

From the total of new cases of cancer estimated for 2006 in Brazil, more than 230.000 will develop in men. Prostate cancer accounts for 26% of total cases, being the most incident in this sex, second only to non-melanoma skin cancer.[2]

These data makes vital knowledge regarding etiologic factors related to prostate cancer, aiming to establish effective preventive measures. Because of the high incidence of prostate cancer, the fact this neoplasia incidence increases with age, and the fact that people are living more, knowing clearer and more precisely prostate cancer etiology is a more adequate way for suggesting preventive measures for at least preventing in part so high a casuistry.

Research of etiologic factors of prostate cancer has involved ever more investments in the medical, biological, social, and epidemiologic areas due to the multiplicity of causes.[2]

Risk Factors

The risk factors for prostate cancer known for more than 30 years by epidemiologic research are age, ethnicity and family history.[3]

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Age and Ethnicity

As happens to other cancer types, age is an important risk factor, and it has an special meaning in prostate cancer, since its incidence increases exponentially after age 60. Family history of prostate cancer before age 60 is another important risk factor that may increase the risk 3 to 10 times compared to the general population; besides, this may reflect both inheritance and shared life styles among family members.[2] Ethnicity is also a factor to be considered and analyzed. Blacks have a higher predisposition to developing prostate cancer, mainly when compared to Caucasians and Asians, and the latter are the ones less affected by this type of cancer. Some hypotheses for this ethnic difference exist, and this may be related to the level of circulating testosterone, the amount of melanin, together with vitamin D synthesis, besides differences in life style. This last factor is the object of observational studies where one perceives the rise of the incidence of prostate cancer in Asians who migrated to places where a high prevalence of cancer exists.[4-6]

Some researches add to the importance of epidemiologic factors genetics as a condition able to explain up to 40% of cases of this type of cancer.[7] According to a population-based case-control study, 6.8% of diagnosed African-American with prostate cancer had allele Asp174Tyr MSR1, while only 3.6% of those without the disease had it.[8] In other studies a comparison of the incidence of prostate cancer between monozygotic and bizygotic twins has shown a strong hereditary component for prostate cancer.[9, 10-12]

Diet

The influence diet may have on the development of prostate cancer is uncertain, and one does not know accurately the components or mechanisms through which diet can promote carcinogenesis. However, researchers from the Karolinska Institute suggested in a recent meta-analysis that diet takes part in the initiation, development and progression of this neoplasia.[12]

Epidemiological stud point to a positive relation between milk products and the progression of cancer.[12] Studies involving a broad dietary evaluation considered that the presence of fat in milk products would be responsible for the carcinogenous action, but no confirmation exists for this.[13-14] Another hypothesis points to the rise of serum levels of IGF-1 (insulin-like growth factor-1) from milk ingestion.[15]

Also controversial is excessive meat consumption. Kolonel suggested in a meta-analysis that high consumption of meat can increase in up to 30% prostate cancer risk.[16] Studies in which different types of meat had been analyzed, one observed that red meat has a higher carcinogenous effect than other types, and it modifies the progression of this neoplasia.[13,16]

The biological mechanism of this interaction is not completely elucidated, but there are some possible explanations. The first one relates to meat's fat levels.[16] Other authors point out that diet with large quantities of meat and other animal products could replace an adequate ingestion of fruits, vegetables, cereals and grains, which are rich in constituent anticarcinogenic agents.[17] Meat preparation in high temperatures is also questioned, since gives origin to heterocyclic amines to form that have a powerful carcinogenous effect.[18] Finally, zinc, an essential mineral for some cellular processes is also a cofactor of more than 70 enzymes, having an important role in the maintenance of the immune system. Zinc is found in high concentrations in these products, and is an essential component for testosterone synthesis besides raising IGF-1.20 serum levels.

On the other hand, the consumption of fruits,[19-20] carotenoid-rich vegetables[21] (such as carrots), tomatoes (due to the action of lycopene[21-22] and isoflavone-rich leguminous plants[23] (such as beans, peas and soy) have been considered protective agents. Besides these, some natural components of foods, as vitamins (C, D and E) and[24-25] minerals[24,26-27] (selenium) may also have a protective role. Fish consumption is also considered beneficial due to the presence of anticarcinogenic substances (vitamin D and selenium), and also to the action of eicosapentatenoic and docosahexaenoic acids, which inhibit the growth of neoplastic cells and induce apoptosis in vitro.[28]

Beyond these dietary protective factors, studies has demonstrated a positive association between physical activity and the reduction of the incidence of this prostate cancer.[29]

A correlation is observed between the distributional and epidemiologic patterns of prostate cancer and vitamin D deficiency. Amongst the analyzed factors are age, ethnicity and geographic aspects.[30] The increase of the prevalence of prostate cancer in older men would be associated to a gradual deficiency of vitamin D, besides the fact that these individuals has problems linked to age, such as a reduction of physical activity and other restrictions, less exposition to sunrays and, consequently, lesser levels of vitamin D activation.[31-32] Blacks, by their turn, having a higher amount of melanin, would have vitamin D deficiency, since melanin inhibits its synthesis.[33-34] On the other hand, the traditional diet of Asians, heavily based in fish oil (rich in vitamin D) would give them an additional protection.[35] The less expressive correlation is observed regarding geographic localization: regions presenting

lesser rates of ultraviolet radiation would be more inclined to have more individuals with prostate cancer.[36]

Others Factors

Heavy alcohol and tobacco consumption also are being studied, but no conclusive results regarding its action in prostate cancer development has been found.[37]

Besides behavioral factors already mentioned, we find in the literature studies relating prostate cancer to obesity,[38-41] diabetes mellitus,[42] hyperinsulinemia,[42] hormone replacement therapies[43] and even to acromegaly,[44] spinal cord injury,[45] relaxation and meditation,[46] green tea consumption[47] and cannabis sativa consumptiom.[47] However as these studies present epidemiologic, methodological bias, studies are needed.

A fact deserving discussion is the association between prostate inflammatory processes and the risk of developing cancer.[48] A positive correlation was detected between the symptoms of prostatitis and/or sexually transmissible infections, regardles of the pathogenic agent with this type of cancer. The possible biological mechanism can be explained by an inflammatory response of the host against the infection or by a direct action of the infectious agent on prostatic tissue in individuals having genetic predisposition.[49-50]

However, critiques have been done to this assumption on account of the fact that patients with asymptomatic prostatitis are not included in population-based research[51-52] and neoplastic injuries supposedly are already present and the more exuberant symptomatology of inflammations would make the patient visit a doctor with the resultant increase of the possibility of diagnosis,[51,53] amongst others.

Another factor of great interest that is being investigated is the role of finasteride as a chemoprotective agent; widely used in cases of benign prostate hyperplasia and considered a drug able to stop the progression of prostate cancer, or even delay prostate cancer early detection.[54] Recently, data from the "Prostate Cancer Prevention Trial" with more than 7000 men showed a reduction of up to 30% in the incidence of this neoplasia in men taking finasteride, but with a 30% increase of a more aggressive histology. Whether this finding represents a histologic result of the use of this drug or a real increase in the incidence of more aggressive tumors only a long-term analysis would show.[55-57]

Finally, there is currently a strong debate about a possible association between testosterone replacement therapy (TRT) and the initiation, progression and aggressiveness of prostate cancer. TRT is being used to improve the quality of life of men who suffer with the symptoms of testosterone levels reduction due to advanced age. Studies that analyzed this hypothesis are still controversial and inconclusive, but nevertheless make us think on the risk-benefit of TRT. The current recommendations are to exclude the presence of prostate cancer before beginning replacement therapy in men more than age 40 and monitoring the patient in the first year of replacement.[43]

Final Remarks

Today it is recognized that the development of prostate cancer has a direct link to a multiplicity of causes the combination of which would be the conditions for the disease to appear. Genetic susceptibility has no doubt an important role, but it is the interaction between this susceptibility and the factors or conditions resulting from life styles and the environment that determine the risk of having cancer.

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