Risk Factors for Prostate Cancer

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Abstract: Prostate cancer is one of the representative cancers that show a marked difference in morbidity by race and region. In the U.S.A., the annual frequency for the diagnosis of prostate cancer is ranked first among all cancers excluding skin cancer, and it is the second leading cause of death following lung cancer. Meanwhile, the incidence of prostate cancer in Asian countries, including Japan, is considerably low. It is actually reported that the difference in incidence between African Americans, showing the highest prevalence, and the Japanese, is at least ten times. Based on epidemiological information, it is speculated that the long-term exposure to certain environmental factors, including diet, acts as a risk for prostate cancer. Certain genetic factors also participate. Recent epidemiological studies on human cancer not only demonstrate the risk factors for cancer, but also greatly contribute in illuminating the processes of carcinogenesis, enabling the identification of highly suspected groups of carcinogens, and finally, establishing an effective strategy of preventive measures against cancer. In the control of prostate cancer, the identification of risk factors and the promotion of active preventive medicine can provide enormous benefits to the super-aging society of our future.

Key words: Prostate cancer; Epidemiology; Environmental factors; Genetic factors

Introduction

External environmental factors have a large influence on the development of human cancers. If all carcinogenic environmental factors could be eliminated, 90% of all cancer would probably be preventable.1) Meanwhile, host susceptibility to the carcinogenic environmental factors is influenced by various factors such as gender, age, nutritional state, and genetic factors. If it is possible to identify the carcinogenic environmental factors and to estimate their susceptibility to external factors, it would appear that cancers could effectively be prevented by combining various approaches.

Cancer epidemiology is a classic scientific approach of investigating clues involving external environmental factors. The types of approach

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in cancer epidemiology include descriptive and analytical epidemiology. The former examines the morbidity, mortality, etc., and draws various conclusions based on examination, while the latter analyzes the relationships between certain diseases and various factors that are thought to contribute to the disease. In this review, I would like to explain the risk factors for prostate cancer from an epidemiological point of view by looking at recent descriptive epidemiological trends concerning prostate cancer, secondly, at external factors involved in prostate cancer, based on analytical epidemiology, and finally, at overall features concerning the risk factors for prostate cancer introducing research on genetic factors.

Descriptive Epidemiological Trends Concerning Prostate Cancer

Prostate cancer is one of the representative cancers that shows a marked difference in morbidity by race and region. In the U.S.A., the annual frequency for the diagnosis of prostate cancer is ranked first among all cancers excluding skin cancer, and it is the second leading cause of death following lung cancer. An epidemiological survey of prostate cancer in the U.S.A. in 2001 reported 31,500 deaths, while 198,100 patients were newly diagnosed.

Meanwhile, the incidence of prostate cancer in Asian countries, including Japan, is considerably low. It is actually reported that the difference in incidence between African Americans, showing the highest prevalence, and the Japanese is at least ten times. Further, from 1988 to 1992, the age-adjusted mortality rate of prostate cancer was only four per 100,000 of the population for Japanese, compared with 36, the highest rate, in African Americans. In recent years, however, the prevalence of prostate cancer shows a tendency to increase regardless of high or low incidence regions. The cancer statistics white paper for 1999 shows that the actual mortality of prostate cancer in Japan was 7,005 in 1999, and is expected to be 15,801 in 2015, and it would consequently ascend to the seventh place for cancers in males, ranking under esophageal and rectal carcinomas.

Another characteristic of prostate cancer is that the prevalence increases with age. The morbidity/mortality rate increases exponentially with age.2)

Risk Factors of Prostate Cancer Based on Analytical Epidemiology

As mentioned above, the descriptive epidemiological data accumulated up to the present shows that only age and race (regional difference) are established as risk factors for prostate cancer. Based on the epidemiological information, it is speculated that long-term exposure to certain environmental factors, including diet, acts as a risk for prostate cancer. Certain genetic factors also participate.

1. Dietary factors (Table 1)
(1) Fat intake

In general, fatty acids are classified as saturated or unsaturated. Of these acids, it seems that saturated fatty acids, which are mostly found in animal fats, enhance the risk for prostate cancer, and several case-control studies

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<td>Total calorie intake (obesity)</td>
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<td>Saturated fatty acids</td>
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<td>Factors that may decrease risks</td>
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<td>Soy protein</td>
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<td>Isoflavonoid</td>
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<td>Vitamin A (lycopene)</td>
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<td>Selenium</td>
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have reported a significant association between a high intake of saturated fat and prostate cancer. However, in a recent cohort study that compensated for caloric intake, no significant relationship was detected although a tendency for the risk to increase was recognized. Kolonel et al. reviewed the previous epidemiological studies, and reported that the relationship between the intake of saturated fatty acids and prostate cancer had been suggested in many case-control studies. They also inferred that the rate at which excessive intake of saturated fatty acids contributed to the incidence of prostate cancer was 20 to 25% for European Americans and African Americans and 5 to 10% for Asian Americans. 

(2) **Soy protein**

Isoflavonoid, which is mostly found in soybeans, has an estrogenic structure. It has also been assumed that isoflavonoid probably suppresses prostate cancer because the morbidity of prostate cancer is low in several South-East Asian countries where soy protein is ingested in large amounts. Soybeans contain two kinds of isoflavonoids, namely genistein and daidzein. Nagata et al. suggested that the ingestion of soybean products cause a decrease in the sex hormone concentration in the blood of Japanese males. They speculated that this influence on the sex steroid may be one of the mechanisms involved in preventing the development of prostate cancer. 

(3) **Vegetable, fruit, and the vitamins they contain**

It has been proposed that vitamins contained in vegetables and fruit prevent carcinogenesis. However, the relationship between vegetable and fruit ingestion, and prostate cancer has not been clearly established.

It is suggested that vitamin A and such precursors as retinol and carotinoid, protect against oxidative stress, thus suppressing carcinogenesis. Of these, β-carotene and lycopene have most widely been studied for their relation to prostate cancer. Oishi et al. conducted a study into the relationship between β-carotene ingestion and prostate cancer, and reported that the relative risk for prostate cancer is significantly increased at lower ingestion levels of β-carotene compared to higher ingestion levels. However, no uniform tendency was demonstrated in later reports. Lycopene is mostly found in tomatoes, and has been proven to have an inhibitory effect on the proliferation of prostate cancer cells *in vitro*. A recent report suggested a meaningful inverse correlation between lycopene concentrations in the blood and prostate cancer. Although vitamin E is also considered to suppress carcinogenesis due to its strong antioxidant activity, there are no definite reports indicating a significant association with the prevention of prostate cancer.

Taking all the above facts into consideration, at this point there is no conclusive evidence that clearly supports the preventive effect of vitamin A and E on prostate cancer. However, it is considered necessary to further investigate the possible preventive effect of lycopene and vitamin E on the development of prostate cancer.

(4) **Vitamin D**

Insufficient exposure to sunshine (ultraviolet rays) has a significant association with a high prostate cancer morbidity, and an inhibitory effect of active vitamin D on the development of prostate cancer has been suggested. Actually, active vitamin D (1,25 vitamin D) shows a suppressing effect on the proliferation of prostate cancer cell lines. Additionally, the existence of vitamin D receptors on prostate cancer cells has been proved.

(5) **Selenium**

Selenium is a metal element similar to sulfur, and is found in large amounts in plants that grow in soil and take nutrients from the soil. Recently seven prospective studies reported a possible relation between the prostate cancer risk, and the quantity of selenium in the blood or nails. Of these, two studies reported a significant relationship, while three studies showed a preventive effect of selenium, even though a significant relationship was not demonstrated.
Based on these studies, selenium is expected to show a preventive effect against prostate cancer. At present, a prospective cohort study investigating the effect of chemical prevention by using selenium and vitamin E is being conducted in the U.S.A. 7)

(6) Green tea
One of the differences in dietary habits between Asian and Western countries is the amount of green tea consumed in Asia. The apparent anti-tumor effect of green tea is based on catechin, a polyphenol. Experiments on prostate cancer cell lines have shown that catechin has a suppressing effect on cell proliferation, and a recent large-scale cohort study in Japan reported that the intake of at least 10 cups of green tea a day may cause a delay in the clinical onset as well as a decrease in the prevalence of cancers. 8) Even though there is still no definitive evidence that green tea reduces the risk for developing prostate cancer, green tea is an attractive candidate for use in the prevention of prostate cancer since it is rarely toxic and is readily acceptable as a dietary ingredient.

2. Benign prostate hyperplasia
During the past 30 years, there has been controversy over the relationship between benign prostate hyperplasia and prostate cancer. Like prostate cancer, benign prostate hyperplasia is an age-dependent condition that is evidently related to sex hormones. The weight of the prostate glands of males in Asian countries is smaller than that of Western males, even after correction for physique. There may be a cofactor, e.g. a gene, that exists both in hyperplasia and cancer. However, benign prostate hypertrophy and prostate cancer develop in anatomically different regions of the gland. That is, benign prostate hyperplasia occurs in the central region surrounding the urethra, called the transition zone, whereas approximately 70% of prostate cancers develop in the peripheral zone, closer to the rectum. Also, recent molecular studies have failed to show that benign prostate hyperplasia and prostate cancer share the same genetic base. Summarizing the above facts, though there may be some cofactors that cause both benign prostate hyperplasia and prostate cancer, it is reasonable to say that there is no clear relationship between them.

3. Drinking and smoking
Concerning the relationship between prostate cancer and non-essential substances like alcohol, cigarettes etc., there have been many negative reports. Dennis et al. reported interesting results of their meta-analysis investigating the relationship between prostate cancer and alcohol intake. 9) According to their review, a significant relationship was not recognized in the overall analysis, but appeared as the alcohol intake increased. This result may agree with the report by Tonnesen et al. describing a relationship between prostate cancer and alcohol dependency. 10) Therefore, it is assumed that excessive drinking may act as a risk factor for prostate cancer.

4. Sex hormone
Androgens are essential to the development of a normal prostate. Further, since the proliferation of prostate cancer cell shows androgen dependency, it is assumed that there is a relationship between the concentration of androgens in the body and the risk for prostate cancer. However, more than ten prospective epidemiological studies have not provided constant results yet, and only one study showed a significant relationship between the concentration of testosterone in the serum and prostate cancer. 11) There seems to be various reasons why this controversy has not been solved. In addition to the inevitable fundamental problems of epidemiological studies, other complicated factors may also be involved, for example, a biased hormone measurement system, timing of blood collection, the levels of hormone-binding protein, individual differences in the 5α-reductase activity, etc. Furthermore, it is necessary to consider at what age the concen-
tration of androgens has an influence on prostate carcinogenesis in human beings.

**Genetic Factors for Prostate Cancer**

Another definite risk factor for prostate cancer is a positive family history. Narod et al. reported that in a patient with a history of prostate cancer in either his brother or father, the relative risk increases 2.62 times and 1.22 times, respectively. This seems to provide evidence that a genetic predisposition plays an important role in the development of prostate cancer.

At present, it is estimated that hereditary prostate cancer, in which genetic factors play a decisive role, amounts to only 5 to 10% of all prostate cancers.\(^\text{12}\) Up to now it has been illustrated that 6 gene loci, i.e., 1p36, 1q24-25, 1q42, 17p, 20q13, and Xq27-28 are involved, and some candidate genes have actually been identified. On the other hand, sporadic prostate cancers can develop as a result of interaction between environmental and genetic factors (Fig. 1). Concerning the genes that control the risk for the sporadic development of prostate cancers, or the host susceptibility to prostate cancer, a genetic group (\textit{CYP 17, SRD 5 A 2, Androgen receptor gene, etc.}) involved in androgen biosynthesis and androgen response has been considered a strong candidate. Recently, a new science called molecular epidemiology has come under the spotlight, and studies on genetic polymorphisms (genetic individuality) of susceptible genes are under way at a rapid pitch.

**Conclusion**

Recent epidemiological studies on cancer, including environmental as well as genetic factors, have not only demonstrated the risk factors for cancers, but have also made a great contribution in illuminating the processes of carcinogenesis, enabling the identification of highly susceptible groups of carcinogens, and finally, establishing an effective strategy of preventive measures against cancer. In prostate cancer, the identification of risk factors and the promotion of active preventive medicine can provide enormous benefits to the super-aging society of our future.

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