A Review of the Risk Factors for Prostate Cancer

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INTRODUCTION

Prostate cancer is responsible for 7% of all male cancers and is the most common malignant tumor of the male genitourinary tract. By 80 years of age, 80% of men show some degree of adenocarcinoma within the gland, although it may be asymptomatic and dormant. Tumors are rarely found in patients less than 60 years of age. Symptomatic patients usually show symptoms of bladder outflow obstruction, and in some cases the disease can present as acute retention of urine. Other features may include ureteric obstruction, hydronephrosis, or bone pain due to metastases. Depending on the tumor stage, management steps and options include repeated digital rectal exam and prostate specific antigen(PSA) measurements, prostatectomy, radiotherapy, orchidectomy and anti-androgens. Localized tumors have an 80% 5-year survival rate, local spread, 40%, and patients with metastases have a 20% rate of survival after 5 years.

The American Cancer Society predicts that 234,460 new cases of prostate cancer will be diagnosed in the United States in 2006. A recent study by the International Agency for Research on Cancer in Lyon, France, has reported an incidence of 2,060,400 cancer cases in the European Union for 2004(1). Prostate cancer accounted for 18.1% of these new cases, at an incidence of 202,100 cases, and was the most common cancer reported in men for that year. Such statistics have in recent years sparked increasing interest in prostate cancer and pushed for deeper investigation into its etiology and pathogenesis. This paper aims to review some of the risk factors currently being studied for prostate cancer, as a clear etiology has not been found and in some areas, data and reports have been conflicting.

FAMILY HISTORY

One non-disputed risk factor for developing prostate cancer is positive family history. This area continues to receive attention because of its implications for genetics counseling, screening, and experimental studies in chemoprevention. The literature on this topic goes back many years, and a more recent review by Johns & Houlston(6) attempts to make a more accurate assessment of familial risk by utilizing meta-analysis of previously reported data. They looked at twenty-two publications studying risk in first-degree relatives of established cases and based on their meta-analysis concluded that men with a positive family history do have a significantly greater risk of developing prostate cancer themselves. Furthermore, they found that relatives of those diagnosed at a young age and those with greater than one affected relative are at the most risk.

The importance of a positive family history in prostate cancer risk is therefore well-established, and provides a good foundation for moving forward in two main areas. Firstly, such a consensus can play a role in establishing criteria for screening programs. Secondly, the acceptance of the significance of family history has raised a whole new set of questions regarding the possible etiological factors behind this disease. Indeed, the recognition of the risk that comes with a positive family history points to genetics as well as certain environmental factors, and has therefore directed researchers to delve further into these areas in hope of finding more answers.

RACIAL DIFFRENCES

Race is a factor that has been looked at in many studies, and with rather consistent results. Interest in this area continues because the mechanisms behind

racial differences in prostate cancer incidence are poorly understood. Prostate cancer occurs about 60% more often in African American men than in white American men. However, Japanese and African men who live in their native countries have a low incidence of prostate cancer. However, these groups display a sharp increase in incidence when they immigrate to the United States, suggesting an environmental connection, possibly diet, smoking, less sun exposure, or infectious agents.

A recent publication from Brazil(5) resulted in findings that support the racial differences mentioned above. The study looked at 1,773 volunteer men in that country, and divided them into groups based on race as being black, white, or yellow. The volunteers underwent digital rectal exams and prostate specific antigen(PSA) measurements between 1992 and 1997, and those with abnormalities in either of these underwent transrectal ultrasound-directed prostate biopsy. Six hundred and eighty patients were indicated for biopsy, and of these, fifty-one were diagnosed with cancer. Blacks showed a prostate cancer prevalence of 5.5%, and whites 2.4%.

This recent article supports existing data on racial differences in prostate cancer, but as mentioned by its authors, fails to provide an explanation for these differences. Several hypotheses exist on this matter, for example the possible importance of social and economic factors. Clearly it would be of benefit to continue looking into the race factor, and while doing so begin taking into account other variables related to race in future studies. This would help to ascertain the existence of any environmental influences that may be masked by simply looking at race alone, and more importantly may help to uncover a risk or etiologic factor for prostate cancer that has yet to be considered.

GENETICS & HORMONES

The evidence supporting the notion that family history and race are risk factors for developing prostate cancer suggests that a genetic component exists behind them. This genetic factor may be related to two steroid hormones involved in prostate cell division, and which are needed for normal prostate epithelium to grow, testosterone and Vitamin D. There are several mechanisms by which increased hormone secretion may promote cancer development. For example, obesity leads to increased production of growth-promoting steroid hormones that can bind to receptors in hormone-dependent tumor cells. Also, steroid hormones can promote increased cell proliferation and DNA damage. Androgens have been demonstrated to increase oxidant stress in prostate cancer cells, and defense mechanisms against oxidants have been shown to be defective in early cancer.

Increased levels of testosterone have not been reliably observed in prostate cancer patients, but it is known that low levels, for example in castrated men, are associated with reduced incidence. In addition, interest in vasectomy as a potential risk factor sparked studies into this group. This is because it has been observed that men who have undergone vasectomy have increased levels of circulating testosterone, and the data does seem to show an association with vasectomy and increased prostate cancer risk. Furthermore, anti-androgens did find a place as a major part of therapy for metastatic prostate cancer[7].

A study by Ingles et al[4] looked at genetic polymorphisms in both the androgen receptor and vitamin D receptor, as these receptors are responsible for regulating the action of their respective hormones. This was done with the aim of identifying genes for a multigenic model for prostate cancer susceptibility. Indeed,

polymorphisms in both receptors were found to be associated with prostate cancer. Furthermore, the genes they looked at specifically, microsatellites of the individual receptors, also showed a significant association with advanced disease.

Despite these and similar findings, concrete evidence that androgens and/or their receptors have a major causative role in prostate cancer has not been elicited. In the year 2000, Shaneyfelt et al(8) conducted a meta-analysis based on the inconsistencies regarding this issue, by looking at all previous studies on hormonal factors that may predict prostate cancer development. After excluding some studies based on certain criteria, they found 28 studies on sex hormones, and three on insulin growth factor-1(IGF-1) and their respective roles in prostate cancer. Here, the authors looked for significant results in levels of total testosterone, DHT, and estradiol in prostate cancer patients compared with control groups. All the studies looked at testosterone levels, with fewer looking at DHT and estradiol. Interestingly, most of the studies found no significant differences in hormone levels between the cases and control groups. For example, of the studies that analyzed testosterone levels, fifty-seven percent showed no differences in serum testosterone levels between cases and controls, twenty-three percent showed lower levels for cases, and just twenty percent demonstrated higher levels.

On the other hand, the studies looking at the possible role of IGF-1 in prostate cancer consistently showed a significant, positive association with risk for prostate cancer. One of the studies they looked at in their meta-analysis focused on IGF-1 because of previous evidence of its mitogenic and anti-apoptotic effects on prostate epithelial cells. The study, done by Wolk et al., 1998(10) aimed to see whether elevated serum levels of IGF-1 correlated with an increase in risk for developing

prostate cancer by using immunoradiometric assay. Their study involved 210 newly diagnosed prostate cancer patients and 224 controls, and found a moderately strong, significant association between inceased serum IGF-1 levels and prostate cancer risk. The IGF-1 levels were higher among men below the age of 70, but they explain this with the fact that IGF-1 production declines with age. These results, along with those of the other two studies on IGF-1 reviewed in the meta-analysis, indicate a 2-fold higher risk for prostate cancer in patients with higher levels, and as the authors point out, this is comparable with the risk in men with a first-degree relative positive family history.

INFECTIOUS AGENTS

A very interesting area of research into prostate cancer etiology and risk is the potential role of infections. Young men who are sexually active with multiple partners face an increased risk of prostate cancer. Sexual promiscuity is a leading risk factor in contracting human papilloma virus (HPV), which is already linked to cervical cancer in women. HPV may be the reason why there has been a recent increased incidence of prostate cancer in men. Most likely, once young men are exposed to HPV it starts a series of genetic mutations that can eventually lead to cancer later in life. In addition to HPV, several other infectious agents have been suggested as having roles in the development of prostate cancer, including herpesvirus and cytomegalovirus. Overall this area is still inconclusive, as discussed by Pienta & Esper in their 1993 review on risk factors for prostate cancer(7). They highlight the incongruities in this area of research by mentioning that three studies have shown no link between sexually transmitted diseases and prostate cancer, while three others do provide evidence for a link.

Looking at a more recent publication, Cohen et al(2) looked at

propionibacterium acnes as a possible factor in prostate cancer evolution. Their 2005

study aimed to detect the presence of bacterial agents in prostatic tissue samples from

34 patients undergoing radical prostatectomy. Their results included two important

findings. Firstly, *Propionibacterium acnes* was both isolated from the samples, and

shown to be involved in prostatic inflammation. Secondly, there were genetic and

phenotypic differences between the *P. acnes* species they cultured and the common

strains normally isolated from skin. This implies that there may be subtypes of the

organism that are specifically involved in inflammatory processes linked to prostate

cancer development.

CARCINOGENS

Cadmium is a trace mineral and carcinogen found in cigarette smoke and

alkaline batteries, and high exposure can occur in people whose occupation involves

welding, metal work, or production of batteries and plastics. Also, the intake of

cadmium in heavy smokers can be twice that of nonsmokers. Cadmium has been

studied as a risk factor for prostate cancer due to its interactions with zinc. The

mechanisms by which this happens is still unclear, but zinc is a necessary cofactor for

several enzymes which have roles in DNA repair and it is found in relatively high

amounts in the prostate gland(7). Cigarette smoking is often cited as a risk factor for

prostate cancer, but in reality the data are not very clear. While the combination of

occupational cadmium exposure and cigarette smoking do seem to increase risk

significantly, the evidence for smoking as a major risk factor in of itself has not been

adequately presented.

DIET & OBESITY

There are several possible ways in which obesity could increase the risk of developing prostate cancer. Although there are no major studies proving that dietary changes can reduce the incidence of cancer, evidence does exist suggesting that maintaining a healthy body weight by reducing fat intake and eating more fruits, vegetables, and whole grains can be of benefit. Common forms of cancer including prostate cancer in those countries eating a western diet are showing relatively high incidence when compared with countries eating different diets. This western diet is rich in fat, sugar, and red meat, and poor in fiber, fruits and vegetables. In addition, individuals migrating from low risk to high-risk countries increase their risk of cancer significantly within one generation. Obesity is also associated with a number of common forms of cancer.

A population-based case-control study of prostate cancer involving blacks, whites, and Asian-Americans in the United States and Canada(9) looked at the roles of diet, physical activity patterns, body size, and migration on prostate cancer risk. The study looked at patients diagnosed with prostate cancer between 1897 and 1991 and compared them to controls matched by age, ethnicity, and region of residence. By using questionnaires, and prostate-specific antigen(PSA) measurements to compare with controls, the study showed a significant association of prostate cancer risk and total fat intake for the groups combined. This association was attributable to energy from saturated fats, and was unrelated to protein, carbohydrate, polyunsaturated fat, and total food energy. Furthermore, saturated fat intake was associated with higher risk for Asian-Americans than for blacks and whites. This suggests that saturated fat may be an etiologic factor in prostate cancer, but also indicates that other factors are

largely responsible for differences in risk between racial groups. Obesity is discussed further in the following section.

DISCUSSION

Every man over the age of 45 is at risk for prostate cancer, and age is generally considered to be the most important risk factor. Due to the vast number of studies on prostate cancer and its risk factors, it is well accepted that this disease is of multi-factorial etiology. The pathology of prostate cancer is complex, and the large amount of research on this subject suggests that many genes are involved as well as additional environmental factors such as diet and inflammation. With the development of new research tools such as DNA technology, knowledge about the mechanisms behind this disease are likely to become more clear, and better methods for prevention and treatment hopefully will emerge. To date, the most consistent findings regarding risk factors for prostate cancer are for factors that are the least controllable, namely age and race. Accordingly, the only preventive measures that are really under consensus are screening by digital rectal exam and PSA measurements. The American Cancer Society and the American Urological Society recommend these tests beginning at 50 years of age, and in the case of increased risk such as a positive family history or African-American race, screening from the age of forty-five is recommended.

Clearly, the high incidence of this disease demands the maximum amount of research into its risk factors and possibilities for prevention, and a literature search will show that such efforts are and have been underway for quite some time. The vast amount of data collected over the years has helped prompt several working theories

regarding etiological factors for prostate cancer and the risk for the disease they

impose. However, to date very few risk factors have been demonstrated on a

consistent basis and much of the evidence gathered in research studies is conflicting.

A good example of this is the possible risk factor of obesity. As previously

mentioned, there are several reasons to hypothesize that obesity is a risk factor for

prostate cancer. However, a recent 17-year follow-up to a previous study conducted

in Basel, Switzerland, seems to indicate otherwise. The 2005 publication(3) looked at

the association between body mass index(BMI) and lung, prostate, and colon cancer

mortality. The subjects were 2974 men between the ages of 29 and 70 and were

recruited as healthy volunteers between 1971 and 1973. This was a relatively

homogenous group with regard to socioeconomic status. They were weighed, their

heights measured, and they underwent laboratory investigations and filled out

questionnaires. The data was adjusted for age and smoking, and their status was

updated in 1990. The follow-up study concluded that there were no associations

between BMI and any of the three cancers mentioned, including that of the prostate.

Nevertheless, obesity is widely considered to be associated with several forms

of cancer, including that of the prostate. This example illustrates the discrepancies

that exist between the many studies looking at the risk factors for prostate cancer, and

therefore emphasizes both the complexities of its etiology and the need for much

more research. With regard to diet, most of the evidence indicates that high fat intake

increases risk, with some studies suggesting that a diet low in vegetables can do so

as well.

Perhaps the most significant future findings will be in the realm of genetics,

as a variety of different genetic factors are currently being researched and much of the

evidence thus far points in this direction. Variations in certain genes could be responsible for increases in prostate cancer rates in patients with positive family histories. The aim of this paper was to review the status of research into the risk factors for prostate cancer, a disease whose high incidence alone is grounds for an intensive effort. This undertaking has not found any new consensus about a particular risk factor, and the older agreed upon factors of race and family history continue to be supported. However, as advances have been and continue to be made in fields such as endocrinology and genetics, as well as in investigative techniques, more possibilities and tools are presenting themselves that will hopefully prove to be complex enough to deal with the complicated mechanisms that seem to lie behind prostate cancer.

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