Perspectives on the epidemiology of prostate cancer

Prostate cancer is the most prevalent noncutaneous malignancy in men. The National Cancer Institute's Surveillance Epidemiology and End Results report estimates that an American man has an approximately 16% of chance of being diagnosed with prostate cancer in his lifetime.[1] The age-specific incidence of prostate cancer (prostate cancer detection) gradually increases as men are in their 40s, peaks when they are in their 70s, and then gradually decreases after this. The prevalence of prostate cancer in autopsy cases in men older than 80, however, is as high as 40%-64%.[2] Prevalence of prostate cancer at different ages is similar across various ethnic groups, even though incidence of this malignancy varies greatly among different ethnic groups.[2]

Two types of tumors are observed in the prostate: microfocal tumors with low Gleason scores (clinically insignificant cancer) and large tumors and high Gleason scores (clinically significant cancer). In younger men, incidence of insignificant cancer is greater than incidence of significant cancer, but this is reversed in older men. Small, insignificant cancer may develop into significant cancer, a process known as tumor progression. Although the time required for insignificant prostate cancer to progress to significant cancer is unknown, it may take longer than 10 years, since insignificant cancer is first observed in the 3rd decade of life and significant cancer is first observed in the 4th decade of life. The observations that incidence of prostate cancer is lower in elderly men than in younger men, and that elderly men are "resistant" to prostate cancer may be due to "under-screening" and "under-diagnosis" of this cancer in elderly men.[3] For example, the U.S. Preventive Services Task Force does not recommend performing PSA tests for men over age 75.[4]

Epidemiological studies have strongly suggested that environmental factors (such as diet and lifestyle) are involved in carcinogenesis of the prostate. Data also suggest that environmental factors are involved in the progression of clinically insignificant cancer to significant cancer. According to one study, while prevalence of prostate cancer in autopsies of Japanese men who had lived in Japan or Hawaii are very similar, incidence of prostate cancer among Japanese men living in Hawaii is much higher than among Japanese men living in Japan.[5] A study comparing monozyotic and dizygotic twins reports that genetic factors account for 42% of the risk of developing prostate cancer, while environmental factors account for 58% of the risk in these twins.[6]

A gene for prostate cancer might be expressed without any environmental influence or it might only be expressed when activated by environmental factors.[7] The fact that over the past few decades, incidence of overall prostate cancer has risen dramatically, while the rate of familial prostate cancer has remained constant at about 10%, suggests that environmental factors are playing a role. Otherwise, if men with a gene making them susceptible to prostate cancer were not also affected by environmental factors, the proportion of familial prostate cancer cases would have decreased as the number of cases of overall prostate cancer increased. Environmental factors likely affect a man's susceptibility to prostate cancer, whether or not he has genetic susceptibility to this cancer. The rising incidence of prostate cancer may be due to multiple factors including changes in environmental factors (such socio-cultural activities and lifestyle) and increased PSA screening.[7]

The onset of familial prostate cancer occurs earlier than the onset of sporadic prostate cancer. However, there is no difference in clinicopathological features and progression-free survival.[8] The stage and grade of prostate cancer at diagnosis changes only slightly with age, probably because of a lower intensity of screening and therefore diagnosis at a more advanced stage and grade in older men, rather than any change in prostate cancer biology with age.[9] This suggests that carcinogenic initiation produces similar biological prostate cancer in young or old men, and in men with or without a family history of this cancer.

The etiology of prostate cancer is multifactorial and complex. Intrinsic factors such as prostate cancer susceptibility genes and genes that activate testosterone in prostatic cells may contribute to the development of insignificant cancer.[10] However, the involvement of these genes does not preclude the possibility that exposure to exogenous carcinogens may result in tumor initiation. Further exposure to intrinsic or exogenous factors may enhance progression to significant cancer. The Prostate Cancer Prevention Trial showed that finasteride reduced the incidence of overall prostate cancer by 25%, and this reduction was mainly for cancers with a Gleason score of 4 to 7.

The incidences of prostate cancer with Gleason scores of 5, 6, and 7 were reduced by 58%, 52%, and 22%, respectively.[11] Since biopsy, which has a low sensitivity[12] was used for cancer detection in the study, it is unknown whether finasteride also reduced overall cancer burden. Nevertheless, the study strongly suggests that finasteride suppresses progression of prostate cancer.[11]

Manganese superoxide dismutase (MnSOD) polymorphism is associated with aggressive prostate cancer only in men whose diets include a high iron intake[13] or who have a low antioxidant status.[14] These findings suggest that oxidative stress is associated with progression of prostate cancer and may be a target for chemoprevention. Oxidative stress may also be involved in initiation of insignificant prostate cancer, since MnSOD polymorphism is also associated with prostate cancer in autopsy cases that include insignificant prostate cancer.[15]

Insignificant prostate cancer constitutes 70% of undetected prostate cancer in men who are 71 to 80 years old.[2] This suggests that measures to prevent prostate cancer progression may be effective for men even in their 70s.

Epidemiology studies that use clinical cases as the cancer group can be used to delineate factors that may contribute to tumor progression. However, conventional case control and cohort studies need to consider that (a) the rate of undetected insignificant and significant prostate cancer in the control group may be as high as 30%,[15] (b) depending on their age, prostate cancer free subjects in the control group may have up to a 16% chance of being diagnosed with prostate cancer in the rest of their lifetimes, and (c) with increasing, extensive PSA screening, more cases of prostate cancer in the cancer group are insignificant cancer.

A two stage model of the development of prostate cancer is attractive, since it offers an opportunity to intervene either during the initiation of insignificant cancer and/or the progression to significant cancer. Intervention that prevents progression of insignificant cancer appears to be an achievable chemoprevention goal.

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References

1. The National Cancer Institute. Surveillance Epidemiology and End Results. http://www.seer.cancer.gov/statfacts/html/prost.html. Accessed July 15, 2009.
2. Haas GP, Delongchamps N, Brawley OW, Wang CY, de la Roza G. The worldwide epidemiology of prostate cancer: perspectives from autopsy studies. *Can J Urol* 2008;15(1):3866-3871.
3. Harding C, Pompei F, Lee EE, Wilson R. Cancer suppression at old age. *Cancer Res* 2008;68(11):4465-4478.
4. U.S. Preventive Services Task Force. Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2008;149(3):185-191.
5. Stemmermann GN, Nomura AM, Chyou P-H, Yatani R. A prospective comparison of prostate cancer at autopsy and as a clinical event: the Hawaii Japanese experience. *Cancer Epidemiol Biomarkers Prev* 1992;1(3):189-193.
6. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med 2000;343(2):78-85*.
7. Pakkanen S, Baffoe-Bonnie AB, Matikainen MP, Koivisto PA, Tammela TL, Deshmukh S, Ou L, Bailey-Wilson JE, Schleutker J. Segregation analysis of 1,546 prostate cancer families in Finland shows recessive inheritance. *Hum Genet* 2007;121(2):257-267.
8. Roehl KA, Loeb S, Antenor JAV, Corbin N, Catalona WJ. Characteristics of patients with familial versus sporadic prostate cancer. *J Urol* 2006;176(6 part 1):2438-2442.
9. Alibhai SM, Krahn MD, Fleshner NE, Cohen MM, Tomlinson GA, Naglie G. The association between patient age and prostate cancer stage and grade at diagnosis. *BJU Int* 2004;94(3):303-306.
10. Crawford ED. Understanding the epidemiology, natural history, and key pathways involved in prostate cancer. *Urology* 2009;73(Suppl 5A);4-10.
11. Kaplan SA, Liu KS, Carides AD, Binkowitz BS, Heyden NL, Vaughan ED Jr. Evidence that finasteride reduces risk of most frequently detected intermediate- and high-grade (Gleason score 6 and 7) cancer. *Urology* 2009;73(5):935-939.
12. Haas GP, Delongchamps NB, Jones RF, Chandan V, Serio AM, Vickers AJ, Jumbelic M, Threatte G, Korets R, Lilja H, de la Roza G. Needle biopsies on autopsy prostates: sensitivity of cancer detection based on true prevalence. *J Natl Cancer Inst* 2007;99(19):1484-1489.
13. Choi J-Y, Neuhouser ML, Barnett MJ, Hong CC. Kristal AR. Thornquist MD. King IB. Goodman GE. Ambrosone CB. Iron intake, oxidative stress-related genes (MnSOD and MPO) and prostate cancer risk in CARET cohort. *Carcinogenesis* 2008;29(5):946-970.
14. Li H, Kantoff PW, Giovannucci E, Leitzmann MF, Gaziano JM, Stampfer MJ, Ma J. Manganese superoxide dismutase polymorphism, prediagnostic antioxidant status, and risk of clinical significant prostate cancer. *Cancer Res* 2005;65(6):2498-2504.
15. Iguchi T, Wang CY, Delongchamps NB, Sunheimer R, Nakatani T, de la Roza G, Haas GP. Association of prostate cancer and manganese superoxide dismutase AA genotype influenced by presence of occult cancer in control group. *Urology* 2008;72(2):238-242.