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Editorial

Prostate cancer screening practices and cancer control research (United States)

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Introduction

The diffusion and frequency of screening may confound demographic comparisons of incidence rates by age, race, ethnicity, socioeconomic status, geographic residence, and temporal trends. Prostate cancer encompasses a biologic spectrum ranging from the commonly prevalent, latent, microscopic, pre-invasive, or minimally invasive form of the disease, which is not apparent clinically, to the substantially diminished fraction, the 'tip of the iceberg', that is clinically manifested as invasive and potentially fatal prostate cancer [1]. The accelerated increases in prostate cancer incidence rates in the United States during the late 1980s and early 1990s have been attributed mainly to increased utilization of prostate-specific antigen (PSA)-based screening and the urologic practice of random sextant biopsies based on a PSA threshold in addition to biopsies in suspect areas of digital rectal examination and ultrasound abnormalities [2–5]. Incidence and mortality have decreased since the early 1990s [5]. The introduction of an innovative cancer screening method into the population is associated with enhanced lead-time in diagnosis and expansion of the prevalent pool of diagnosed cases. Alterations in incidence trends may be artifactual and transient, unless there are concurrent factors that are affecting risk in the target population. A challenging aspect of research will be to address whether there are common or contrasting causal factors in the pathogenesis of incipient, latent prostate cancer revealed through screening when compared with clinically apparent disease diagnosed in the absence of screening.

Spectrum of prostatic neoplasia

Autopsy studies in United States men over the age of 50 have demonstrated that the prevalence of undetected micro-invasive prostate carcinoma was about 30%. For a 50-year old man, the remaining average lifetime risk of developing clinically apparent prostate cancer has been projected to be 9.5%, and of dying of prostate cancer, 2.9%. Autopsy studies conducted in different countries or in different racial groups, at varying risks of symptomatic or fatal prostate cancer, have described a similar prevalence of clinically occult cancers in older men [6, 7].

Initially, there was concern that the majority of prostate cancers detected by PSA screening would be non-progressing, or tumors that would, in most instances, not require aggressive treatment. Assessment of the potential clinical significance of prostate carcinomas detected by serum PSA elevation has been based on the Gleason's grade, pathologic stage, and tumor volume. Clinical and pathological studies have estimated that more than 50% of the carcinomas detected by PSA are clinically significant. For example, the pathologic features of 100 prostate cancer patients who were enrolled in the Washington University PSA screening program revealed a median tumor volume of 1.0 cm^3, a median Gleason score of six, and a confinement of only 61% of tumors to the prostate gland. The clinical studies are compatible with SEER trends after 1985 that have described increased incidence rates for both localized and regional cancers of intermediate histologic grade [2, 8].

The search for the precursor of prostatic cancer has focused on the spectrum of histopathologic changes referred to as prostatic intraepithelial neoplasia (PIN). PIN is characterized by atypical or dysplastic cellular proliferation in ducts and acini occurring most commonly in the peripheral zone of the prostate (about 85%), in comparison with the central (< 15%) and transition (about 1%) zones. High-grade PIN, or moderate to severe dysplasia co-exists with prostate cancer in more than 80% of cases, and is significantly predictive of prostate cancer on subsequent follow-up and repeated biopsy. High-grade PIN on biopsy signals a 30–50% cumulative incidence of prostate cancer on subsequent biopsies. Thus, patients with multi-focal

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high-grade PIN are a strategic subgroup in the population suitable for studies of screening methods and chemoprevention trials [9, 10].

The morphologic continuum that proceeds from a subset of foci of PIN to invasive adenocarcinoma is characterized by progressive disruption of the basal cell layer, increasing nuclear and nucleolar alterations, increasing rates of cell proliferation, aberrant apoptosis, variation in DNA content, aneuploid nuclei, increasing microvessel density or neovascularity, and increasing genomic instability associated with cumulative chromosomal and allelic losses or gains. Dysregulation of genes in the pathogenesis of invasive prostate cancer include the overexpression of oncogenes (e.g., Ha-ras) and loss of expression of tumor suppressor genes (e.g. p53, Rb, chromosome 8p) associated with critical cell functions such as proliferation, differentiation, cell adhesion, DNA repair, and angiogenesis. Fluorescence *in situ* and comparative genomic hybridization studies have revealed similar chromosomal anomalies in PIN and invasive prostate cancer, although at a greater frequency in invasive tumors and in a subset of PIN lesions. Chromosomal aberrations in PIN lesions include losses on 8p and 13q and gains on 8q. In the morphogenesis of metastatic prostate carcinoma, losses on chromosomes 2, 5, 18 and X, and gains on 7, 9, 12q and 15q have been reported. The validation of molecular genetic events in the subset of PIN lesions that are predictive of tumor progression may serve to guide treatment planning and future molecular epidemiologic studies. Immunohistochemical expression studies and serum concentration levels of PSA are not yet elevated in patients with PIN in the absence of invasive prostate cancer [11, 12].

Prostate cancer mortality in African Americans

The average annual age-standardized prostate cancer mortality rate during 1990–1997 in US blacks was more than twice (2.32) of that in whites. The more than twofold higher prostate cancer mortality experienced by US blacks, when compared with US whites, has been attributed to a relatively higher frequency of poorly differentiated invasive tumors of larger volume, a more advanced stage at diagnosis that is predictive of a higher recurrence rate, and a higher prevalence of co-morbid diseases that may impact the outcome because of deaths due to other causes [2, 13, 14]. In an analysis of knowledge, attitudes, and screening practices among older men (50–74 years of age) regarding prostate cancer, which was based on a random digit-dialed telephone interview survey conducted in New York State, black men were 0.3 times as likely as non-Hispanic white men to report ever having had a PSA test [15]. Socioeconomic impediments and the omission of active interventions or recommendations for screening by physicians are correlated with lower utilization of early detection methods, but even after controlling for age, stage and tumor grade, US blacks at the time of diagnosis of prostate cancer are reported to have higher mean serum PSA levels and a subsequently higher risk of prostate cancer-specific mortality [16]. Based on a study of 584 decedent prostate cancer cases treated at the Kaiser Permanente Medical Care Program, approximately 54% (95% CI 50–58%) of deaths were certified as due to prostate cancer. When comparing prostate cancer subjects who were listed as dying of prostate cancer with those prostate cancer subjects who were certified as dying of other causes, decedents who were black were more likely to have died of prostate cancer, after controlling for age, stage, comorbidity (e.g., cardiovascular disease, diabetes) at diagnosis of prostate cancer, initial treatment, and time to death (OR = 1.59, 95% CI, 1.01–2.53) [17]. Incidence in Los Angeles County was not related to socioeconomic status prior to the PSA screening era, but now, is directly related to SES [18]. Recent data from the population-based prostate cancer outcomes study indicate that prostate cancer is more advanced at diagnosis among African American men even after adjusting for a broad set of socioeconomic and clinical factors [19]. These issues require further evaluation as they contribute only in part to the racial disparities.

Prostate cancer screening and epidemiologic inferences

As reported in SEER and Olmsted County, concurrently with the diffusion of PSA testing in medical practice, there has been enhancement of the clinical and pathological prognostic features of prostate cancer [2, 20]. The incidence rate of distant or metastatic prostate cancer at diagnosis decreased from 14.9 per 100,000 in 1985 to 6.6 per 100,000 in 1995, whereas there was a substantial relative and absolute increase in the incidence of localized, organ-confined prostate cancer, and of regional disease, namely disease that has extended through the prostatic 'capsule' [2]. Such changes are consistent with screening but fail to indicate whether it is effective as a public health strategy, which requires a mortality benefit [21].

The extent of disease at diagnosis is correlated with histologic grade of differentiation. Histologic grade, based on Gleason's scoring, may be classified as well-differentiated (scores of 2–4), moderately differentiated

(scores of 5–7), and poorly differentiated (scores of 8–10). These histologic patterns are categorized at low microscopic magnification according to the extent of glandular differentiation and the pattern of growth of the tumor within the prostatic stroma. Prostate cancers may contain dominant and secondary histological patterns in relationship to increasing tumor volume and multi-centric clonal foci of pathogenesis. Gleason assigned a primary grade score (1–5) to the dominant pattern, and a secondary pattern grade score (1–5), and then both scores were summed. More than 80% of prostate cancer cases with well-differentiated tumors (Gleason 2–4) are staged as localized disease. In contrast, only 42% of men with poorly differentiated cancers (Gleason 8–10) are staged as localized. The increase in prostate cancer incidence in the United States reported after 1985 consisted primarily of an increase in Gleason 5–7 moderately differentiated cancers. With respect to prostate cancer cases clinically staged as localized, both histologic grade and the concentration level of serum PSA at diagnosis are predictive of survival [22–25].

In the absence of uniform national or regional guidelines for prostate cancer screening practices, one must ask the question, are there distinguishing characteristics among men who were screened from those who were never screened? Selection bias would impact medical and epidemiologic studies when the characteristics of participating subjects would differ from the population that is the target for inferences drawn from the study data. To overcome such bias, community-based studies may offer new insights. One such study, a community-based epidemiologic study of prostate cancer and benign prostatic hyperplasia (BPH) in US black men of 40–79 years of age, is being conducted in Flint, Michigan. This study has investigated potential selection bias among participants when determining the age-specific distribution of serum concentration levels of prostate-specific antigen. A probability sample of 819 African American men completed an in-home epidemiologic interview, and among those without a history of prostate cancer or prostate surgery, blood was drawn for PSA testing. In addition, the control subjects without prostate cancer were examined clinically by a urologist for obstructive urinary tract symptoms, rate of urine flow, digital rectal examination and transrectal ultrasonography of the prostate.

While previous studies conducted among various racial and ethnic groups have emphasized that social, cultural, and economic factors affect cancer screening and preventive attitudes and practices, the Michigan study controlled for economic barriers, but underscored other important differences among participants from a high-risk minority group. Namely, younger men with current lower urinary tract symptoms, and a family history of prostate cancer were more likely to participate in a protocol of PSA testing and clinical urological examination. However, neither family history nor the number of obstructive or irritative lower urinary tract symptoms was a significant predictor of log PSA values in the black men [26, 27].

The concern for potential confounding and misclassification bias would arise when comparing screen-detected cases with unscreened controls. Confounding would occur when characteristics (positively or inversely) associated with screening are also predictive of stage-specific prostate cancer. For example, family history of prostate cancer appears to be positively correlated with the utilization of screening tests for prostate cancer, and prostate cancer screening 'exposures' may confound genetic anticipation studies of successive generations in family pedigrees. In genetic anticipation, age of onset (or diagnosis) of disease occurs earlier with greater severity over successive generations, and has been attributed to the variable number of tandem repeats (e.g., trinucleotide repeats) in an inherited susceptibility locus [28].

With the introduction of an innovative screening method, the enhanced sensitivity for early detection would tend to shift the stage distribution of prostate cancer cases in a population. Detection by screening would favor cancer cases that are less aggressive or with relatively longer average tumor doubling time when compared with clinically diagnosed symptomatic cases because of 'length-bias', and this phenomenon would be reflected in prolonged diagnostic 'lead-time'. Conversely, 'interval' cancers, diagnosed after prior negative screening examinations, may exhibit aggressive behavior and metastatic potential. Early molecular and morphologic events of carcinogenesis may be associated with a subset of environmental risk factors that are distinguished from risk factors impacting extracapsular extension and ultimately fatal prostate cancer.

For example, epidemiologic studies of cigarette smoking and the risk of metastatic or fatal prostate cancer has considered screening behavior in smokers and non-smokers. Cohort studies have reported modest associations, namely rate ratios < 2.0 in current smokers or smokers who stopped less than 10 years prior to diagnosis [29–31]. In the study of health professionals by Giovannucci *et al.*, the higher rate of fatal prostate cancer among smokers was inferred after controlling for other lifestyle risk factors, smoking-related co-morbidities, and frequency of screening examinations [32]. There was no indication of any delay in diagnosis and treatment as a result of lower frequency of prior screening exams at baseline among smokers compared

with never smokers. Assuming that uncontrolled residual confounding does not account for the association, pathogenic mechanisms have been hypothesized for systemic and intraprostatic effects of tobacco smoke. Namely, the putative mechanism may include effects on estrogen and androgen metabolism, perturbations in immune function, or gene–tobacco interactions. Most intriguing is the effect of cigarette smoking on increased serum levels of testosterone, dihydrotestosterone, and androgenic hormones formed by the adrenal gland [33, 34].

Future directions in research

Randomized screening trials are in progress in the United States and Europe to address the relationship between PSA and digital rectal examination screening strategies and prostate cancer mortality [35]. The results of these trials may ultimately influence global policies and practices, incidence, and mortality trends. We may anticipate, however, that access and utilization in a geographic area will continue to be uneven and correlated with sociocultural, economic and lifestyle risk factors, family history, urologic symptoms, and other comorbidity characteristics. Lack of standardization of assay methods and clinical examination procedures, threshold criteria for prostatic biopsy, age at initiation of screening, and recommended screening intervals, will confound the interpretation of demographic trends and impact the heterogeneous nature of diagnosed cases.

Either by design or analysis, discrepancies between study and control subjects in prior baseline or follow-up screening exposures should be considered as they may affect the magnitude or direction of putative causal associations. Stratification of cases by clinical staging, grade of differentiation, molecular tumor prognostic markers, and whether the cases were detected by screening will serve to sharpen the focus on the independent or interactive relationships of environmental risk factors, endogenous hormones, and peptide growth factors, as well as genetic susceptibility polymorphisms.

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