Benign Prostatic Hyperplasia and Prostate Cancer

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INTRODUCTION

Benign prostatic hyperplasia refers to an anatomic diagnosis, yet in practice it is typically diagnosed clinically on the basis of lower urinary tract symptoms and prostatic enlargement detected on manual rectal examination or transrectal ultrasonography (1). Over the past decade, since benign prostatic hyperplasia (2) and prostate cancer (3) were reviewed in this Journal, there has been a proliferation of research in the basic biology, genetics, and epidemiology of both disorders, and a number of reviews have been published (4–8). During this same time period, considerable change has taken place in the screening and diagnosis of prostate cancer. In the United States and, to a lesser extent, in other countries, the widespread use of prostate-specific antigen (PSA) testing has dramatically influenced the detection, diagnosis, treatment, epidemiology, and natural history of clinically diagnosed prostate cancer and its relation to clinically diagnosed benign prostatic hyperplasia. In the following presentation, the published epidemiologic studies of benign prostatic hyperplasia and prostate cancer will be reviewed, recent findings on the biology of prostatic growth will be summarized, how prostate size and urinary symptoms can increase the rate of detection of prostate cancer will be discussed, and, in conclusion, the implications of these findings for the design of future epidemiologic studies of prostate cancer will be presented. For a more comprehensive discussion of the epidemiology and natural history of benign prostatic hyperplasia and urinary symptoms the reader is referred to recent reviews (5–7).

PREVIOUS EPIDEMIOLOGIC STUDIES OF BENIGN PROSTATIC HYPERPLASIA IN RELATION TO PROSTATE CANCER

The relation between benign prostatic hyperplasia and prostate cancer was investigated nearly 30 years ago in two conflicting studies (9, 10); these studies have been reviewed previously (2–4). The study in which no elevation in risk was found compared prostate cancer incidence among men who had undergone transurethral prostatectomies for benign prostatic hyperplasia with age-matched controls (9). The author justified use of benign prostatic hyperplasia patients who had undergone transurethral prostatectomy by noting that prostatic cancer typically involves a part of the prostate not removed by the surgical procedure. However, the exclusion of men with previously unsuspected prostate cancer found at transurethral prostatectomy from the benign prostatic hyperplasia cases may have created a bias, since no similar exclusion could be made for controls.

The study which found a positive association consisted of two substudies, a follow-up study of men hospitalized for benign prostatic hyperplasia and a case-control study of prostate cancer and clinically diagnosed benign prostatic hyperplasia (10). The two substudies yielded similar results. Both benign prostatic hyperplasia patients and controls were considered by the authors to have had similar diagnostic scrutiny for prostate cancer. Nearly all the controls had received rectal examinations, and potential controls found to have had prostatic enlargement were eliminated. The authors concluded that the positive association that they found between benign prostatic hyperplasia and prostate cancer could be due either to a third factor being causally related both to benign prostatic hyperplasia and prostate cancer or to a direct association in which benign prostatic hyperplasia either predisposed to prostate cancer or was an intermediate stage in the causal pathway between some other factor and prostate cancer. One limitation of both substudies is the lack of a tissue diagnosis of benign prostatic hyperplasia. Some of the men with clinically diagnosed benign prostatic hyperplasia may also have had prostate cancer. Another limitation is the difficulty in assuring that the diagnostic scrutiny for prostate cancer was truly equal in benign prostatic hyperplasia patients and controls. Symptoms of benign prostatic hyperplasia can increase the detection rate of prostate cancer by increasing the number and extent of urologic examinations (11).

More recently, Simons et al. (12) conducted a follow-up study to compare prostate cancer mortality among Rhode Island men with surgically treated benign prostatic hyperplasia with that expected from population statistics (12). The authors reported an age- and time-standardized prostate cancer mortality of 1.14 (95 percent confidence interval: 0.96, 1.33) times the rate in the general population of Rhode Island men. They concluded that surgically treated benign prostatic hyperplasia does not appear to be an important determinant of prostate cancer mortality. The choice of prostate cancer mortality as an endpoint should greatly reduce detection bias. However, the exclusion of men in
whom prostate cancer was discovered at surgery may have created a bias in this study, as in the earlier study of surgically treated benign prostatic hyperplasia (9). None of the epidemiologic studies published to date have provided clear evidence suggesting an etiologic role for benign prostatic hyperplasia in the development of prostate cancer. For a more comprehensive understanding of benign prostatic hyperplasia in relation to prostate cancer, it is important to consider prostate biology and the way in which prostate cancer is diagnosed clinically.

ANATOMIC RELATION BETWEEN BENIGN PROSTATIC HYPERPLASIA AND PROSTATE CANCER

Readers unfamiliar with the terminology used in describing prostatic zonal anatomy will find a brief summary in a previous review (2) and a more comprehensive discussion in the medical literature (13–17). Nearly all benign prostatic hyperplasia arises in the transition zone of the prostate (16–18), although benign prostatic hyperplasia nodules may sometimes protrude into the peripheral zone and, rarely, may originate in the peripheral zone (16). About two thirds of all prostate cancers arise in the peripheral zone, one fourth in the transition zone, and the remainder in the central zone (19). Peripheral zone cancers do not occur in or near benign prostatic hyperplasia nodules but often are found in close proximity to lesions of high-grade prostatic intraepithelial neoplasia, which is considered to represent a premalignant lesion (20–26). Peripheral zone cancers are typically diagnosed by needle biopsy (16). Needle biopsies typically do not extend into the transition zone (16) and, hence, transition zone cancers are most commonly diagnosed on pathologic evaluation of tissue from a transurethral resection of the prostate (transurethral prostatectomy) performed to treat benign prostatic hyperplasia. Approximately 10–20 percent of transurethral resections of the prostate result in the detection of prostate cancer (27). Transition zone cancers are typically more well-differentiated, smaller, less aneuploid, and less likely to have extracapsular spread than are peripheral zone cancers. Approximately one third of transition zone prostate cancers are found within benign prostatic hyperplasia nodules (20).

Atypical adenomatous hyperplasia is a glandular lesion the histopathologic appearance of which closely resembles low-grade adenocarcinoma (28). In a pathologic examination of 217 radical prostatectomy specimens with prostate cancer, Bostwick and Qian (28) found atypical adenomatous hyperplasia to be spatially associated with prostate cancer but without morphologic features suggesting a transition. Atypical adenomatous hyperplasia was more common in older patients and in those individuals with greater prostate weight, greater percentage of nodular hyperplasia (benign prostatic hyperplasia), and greater volume of cancer. They concluded that atypical adenomatous hyperplasia may represent a precursor of prostate cancer, possibly related to cancers arising in the transition zone in association with benign prostatic hyperplasia, but it is also possible that the link between cancer and atypical adenomatous hyperplasia is an epiphenomenon. Epstein (29) reviewed the histopathology of atypical adenomatous hyperplasia in relation to prostate cancer and noted that there is very little data supporting a relation. He concluded that until long-term follow-up studies have been conducted to assess atypical adenomatous hyperplasia as a risk factor for prostate cancer, it should not be classified as a premalignant lesion.

Cheng et al. (31) showed that genetic changes commonly occurring in prostate cancer are also found in some atypical adenomatous hyperplasia lesions. These results have been interpreted as evidence suggesting that at least some atypical adenomatous hyperplasia lesions may be preneoplastic (32). Haeussler et al. (33) found that while atypical adenomatous hyperplasia had a higher rate of cell proliferation compared with benign prostatic hyperplasia, it was markedly lower than in low-grade prostatic intraepithelial neoplasia, high-grade prostatic intraepithelial neoplasia, and prostate cancer (33). In summary, evidence implicating atypical adenomatous hyperplasia in the pathogenesis of prostate cancer remains much less convincing than that supporting such a role for prostatic intraepithelial neoplasia.

ENDOCRINE FACTORS IN THE DEVELOPMENT AND PROGRESSION OF BENIGN PROSTATIC HYPERPLASIA

A number of theories have been proposed to explain the pathogenesis of benign prostatic hyperplasia (5, 16, 34) with all of them incorporating factors related to aging and circulating androgens. Anecdotal evidence suggests that men castrated prior to puberty do not develop either prostate cancer or benign prostatic hyperplasia (34). Within the prostate, testosterone is converted to dihydrotestosterone by the enzyme 5α-reductase type 2 (35), with the result that 90 percent of total prostate androgen is in the form of dihydrotestosterone. Randomized double-blind placebo-controlled clinical trials of a specific 5α-reductase inhibitor showed that pharmacologic inhibition of dihydrotestosterone is associated with a statistically significant reduction in prostate size, urinary symptoms, and surgery for benign prostatic hyperplasia in the treated group, as compared with the placebo group (36, 37). A randomized double-blind placebo-controlled clinical trial of the same 5α-reductase inhibitor is ongoing to examine whether pharmacologic suppression of dihydrotestosterone can decrease the incidence of prostate cancer (38).

As testicular function declines with increasing age, serum levels of estradiol rise in relation to those of testosterone (39). In the dog it has been shown that benign prostatic hyperplasia is increased by an imbalance between estrogen and androgen (40). In humans the role of estrogen in the development of benign prostatic hyperplasia is less clear (35, 41). Griffiths and Coffey (42) have postulated that factors in Asian diets may act as anti-estrogens to inhibit prostate growth. Geller et al. (43) showed that genistein, a phytoestrogen which is a major ingredient in tofu, inhibits growth of human benign prostatic hyperplasia and prostate cancer in histoculture. Recent evidence has implicated compounds found in green tea as having an inhibitory effect on abnormal prostate growth (44, 45). Griffiths (46) recently provided a comprehensive review of the roles of androgens, estrogens, growth factors, and phytoestrogens in the molecular control of prostate growth.

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The finding that constituents of Asian diets inhibit both benign prostatic hyperplasia and prostate cancer growth in cell cultures is consistent with the lower incidence of prostate cancer in Japanese men than in American men. It is also consistent with recent findings concerning prostate sizes in Japanese and American men. In population-based cross-sectional studies conducted in Japan and Olmsted County, Minnesota, using a common measurement protocol and standardization of the measurement techniques, Masumori et al. (47) found that the age-related increase in prostate size by transrectal ultrasound in Caucasian American men was much higher than in Japanese men, and the median prostate size at each age was also larger in American men than in Japanese men, even after adjusting for height, weight, and voided volume. In summary, similar endocrine and dietary factors appear related to both benign prostatic hyperplasia and prostate cancer.

**STROMAL-EPITHELIAL INTERACTIONS IN THE CONTROL OF PROSTATE GROWTH**

Biochemical mediators found in prostatic fibromuscular stroma have been shown to play a role in normal prostate development and in both benign prostatic hyperplasia and prostate cancer. Keratinocyte growth factor, a member of the fibroblast growth factor family, is produced within the stroma and stimulates prostatic epithelial cells (48). Similarly, insulin-like growth factor-1, a member of the insulin-like growth factor family, is produced mainly within the stroma and stimulates prostatic epithelial cells (49). The epidermal growth factor family has a growth stimulatory effect. The ErbB-2/Neu oncoprotein, which is structurally related to epidermal growth factor receptor, has been identified in human benign prostatic hyperplasia and prostate cancer tissue (50). Transforming growth factor-β inhibits proliferation and induces apoptosis in benign prostatic epithelial cells; however, as prostate cancer develops, transforming growth factor-β has tumor promoting effects (51, 52). While it is clear that stromal-epithelial interactions are important in both normal and abnormal prostatic growth, the specific mechanisms by which these cell-signaling interactions affect development of benign prostatic hyperplasia and prostate cancer have not yet been fully elucidated.

**BIOCHEMICAL AND GENETIC ALTERATIONS IN BENIGN PROSTATIC HYPERPLASIA AND PROSTATE CANCER**

Recent studies have shown apoptosis is inhibited in benign prostatic hyperplasia (53–55). A recent study involving multivariate analysis of DNA structures in normal prostatic tissue, benign prostatic hyperplasia tissue, and prostate cancer from human specimens suggests that the progression of normal tissue to benign prostatic hyperplasia and to prostate cancer involves structural alterations in DNA that are distinctly different (56). Malins et al. (56) concluded that their findings do not support a concept of benign prostatic hyperplasia as a precursor of prostate cancer. Another approach that has shown near perfect sensitivity and specificity in separating benign prostatic hyperplasia from prostate cancer involves H magnetic resonance spectroscopy (57).

De Marzo and colleagues (32, 58) reviewed evidence on cell proliferation in benign prostatic hyperplasia, prostatic intraepithelial neoplasia, and prostate cancer, and proposed an hypothesis suggesting that the difference in malignant potential of benign prostatic hyperplasia and prostate cancer may be explained by distinct alterations in stem cell-like properties. Specifically, they noted that in benign prostatic hyperplasia, most replicating epithelial cells are basal cells expressing the pi class glutathione S-transferase, which has been proposed to protect against DNA oxidative damage from environmental and endogenous carcinogens. In most prostatic adenocarcinomas and in high-grade prostatic intraepithelial neoplasia, hypermethylation of the promoter results in glutathione S-transferase not being expressed. In related studies, De Marzo et al. (59) also reported that the cyclin-dependent kinase inhibitor p27Kip1 was down regulated in high-grade prostatic intraepithelial neoplasia and prostate adenocarcinoma, leading to increased epithelial cell proliferation. In addition, Sommerfeld et al. (60) found telomerase activity was not present in normal prostate tissue and was much more strongly associated with prostate cancers than with benign prostatic hyperplasia tissue from the same patients. Telomerase activity was not found at all in benign prostatic hyperplasia tissue from patients who underwent surgery for benign prostatic hyperplasia and did not have any evidence of prostate cancer. These findings were discussed in the context of a stem cell theory of prostate carcinogenesis proposed by Isaacs and Coffey (61) and others (62). De Marzo et al. (59) concluded that while high-grade prostatic intraepithelial neoplasia is a likely precursor of many prostatic adenocarcinomas, benign prostatic hyperplasia rarely if ever progresses directly to carcinoma.

**PSA IN BENIGN PROSTATIC HYPERPLASIA AND PROSTATE CANCER**

PSA is a serine protease which mediates liquefaction of the seminal coagulum formed at ejaculation (63). It has been estimated that each gram of prostate cancer tissue elevates serum PSA by about 3.5 ng/ml, while each gram of benign prostatic hyperplasia tissue elevates serum PSA by about 0.3 ng/ml (64). Since benign prostatic hyperplasia often contributes 10–20 g of additional tissue to the prostate, while organ-confined prostate cancer typically comprises a far smaller amount of tissue mass, it is not surprising that the distribution of serum PSA levels in men with benign prostatic hyperplasia is similar to the distribution in men with organ-confined prostate cancer (65). Serum PSA levels in excess of the commonly accepted upper limit of normal (4.0 ng/ml) are found in 8–13 percent of men without benign prostatic hyperplasia or detectable prostate cancer, and in more than 30 percent of men with benign prostatic hyperplasia but no detectable prostate cancer (66, 67). For reasons which are not entirely understood, the ratio of non-protein-bound (free) PSA to total PSA is higher in benign prostatic hyperplasia than in prostate cancer (68). Using the ratio of free PSA to total
PSA modestly improves the ability to differentiate between benign prostatic hyperplasia and prostate cancer on the basis of PSA testing of men with total serum PSA levels in the range 4.0–10.0 ng/ml (69). However, the specificity of PSA testing continues to be low in men with benign prostatic hyperplasia (66, 67, 70). Another approach which has been shown to improve the ability to distinguish between benign prostatic hyperplasia and prostate cancer in men with total serum PSA levels in the range 4.0–10.0 ng/ml is to use transition zone PSA density, which is the ratio of serum PSA to the volume of the prostatic transition zone measured on transrectal ultrasound (71, 72).

PROSTATE SIZE, URINARY SYMPTOMS, AND PROPENSITY FOR PROSTATE CANCER DETECTION

In large prostate cancer screening studies, urinary symptoms have not been found to be predictive of prostate cancer (73–75). Furthermore, urinary symptoms are only modestly related to prostate size (7), do not appear to be any less common in Japanese men than in American men (76), and can be improved by pharmacologic treatments that do not decrease prostate size (77). However, in epidemiologic studies, urinary symptoms and prostate size have been associated with an increased likelihood of physician evaluation for urinary symptoms (11, 78) and increased likelihood of PSA testing (65). In the Health Professionals Follow-Up Study, Meigs et al. (65) found in age-adjusted analyses that men were more likely to undergo PSA testing if they had any urinary symptoms characteristic of benign prostatic hyperplasia, a prior history of prostatectomy, or a physician diagnosis of benign prostatic hyperplasia. McNaughton Collins et al. (79) estimated that, in published prostate cancer detection studies, up to one quarter of PSA-detected prostate cancers appear to have been chance findings secondary to an evaluation of a serum PSA level whose elevation was unlikely to have been accounted for by the cancer itself, because it was so small (<1.0 ml).

Together, these results suggest that factors such as urinary symptoms or prostatic enlargement which increase either the likelihood of PSA testing or the likelihood of an elevated PSA may also increase the chances that a prostate cancer may be detected which otherwise could have gone undetected. Further evidence of this is provided by a recent study of 720 men who had undergone radical prostatectomy at Johns Hopkins for stage T1c or stage T2 prostate cancer (80). Clinically unapparent tumors which are not palpable nor visible by imaging and are identified on needle biopsy (e.g., because of elevated serum PSA) are classified as T1c, while palpable or visible organ-confined prostate cancers are classified as T2 (81). Prostate volume in men with T1c cancer was statistically significantly greater than in men with stage T2 cancer diagnosed in the pre-PSA era, and statistically significantly greater than in men of similar age without known prostate cancer. Prostate volumes in men with stage T2 cancer diagnosed in the pre-PSA era and in men without cancer were not statistically significantly different (80). The authors concluded that the higher volume in men with T1c prostate cancer may result from benign prostatic hyperplasia-associated elevations in PSA, increasing the likelihood of prostate cancer diagnosis in men with larger prostates.

Autopsy studies have shown that the percentage of men with undiagnosed prostate cancer extensive enough to be considered clinically important were it to be detected (i.e., extracapsular or >0.5 cc intracapsular) is about 6.0, 8.8, and 15.6 percent for men in their 50s, 60s, and 70s, respectively (82). Because of the high prevalence of undiagnosed prostate cancer, any condition that increases the rate of urologic evaluation or PSA testing is likely to increase the detection rate of prostate cancer that may otherwise have gone undetected. While the data documenting this are from the United States where PSA testing is more common than elsewhere, it is likely to apply to some extent elsewhere since small palpable prostate tumors detectable through careful urologic examination may otherwise go undetected. Evidence in support of this comes from the high prevalence at autopsy of large (83) and poorly differentiated (84) prostate cancers in many countries in autopsy studies conducted prior to the introduction of PSA testing. These studies show that prostate cancers large enough to be considered clinically important are prevalent enough throughout the world, that whatever increases diagnostic intensity is likely to increase incidence.

IMPLICATIONS FOR THE DESIGN OF FUTURE EPIDEMIOLOGIC STUDIES OF PROSTATE CANCER

On the basis of available biologic evidence, benign prostatic hyperplasia appears to be etiologically unrelated to prostatic adenocarcinomas arising in the peripheral zone. Even for prostatic adenocarcinomas originating in the transition zone, the evidence suggesting a possible precursor role for benign prostatic hyperplasia either directly or through atypical adenomatous hyperplasia appears weak. However, as discussed above, there is evidence suggesting that benign prostatic hyperplasia and prostatic adenocarcinoma share common predisposing factors. Future epidemiologic studies examining the association between clinically diagnosed benign prostatic hyperplasia and incident prostate cancer do not appear likely to add meaningful new information on the etiology of prostate cancer, in part because the exposure itself is too heterogeneous to be meaningful in light of what is known of the biology and clinical presentation of both benign prostatic hyperplasia and prostate cancer and in part because symptoms of benign prostatic hyperplasia increase the likelihood of diagnosing prostate cancer that might otherwise have gone undetected. Further studies of surgically treated benign prostatic hyperplasia in relation to subsequent prostate cancer also do not appear likely to add to what has been learned from the two previous such studies (9, 12). It would seem more productive to target the epidemiologic effort toward helping to define processes controlling prostate growth.

Prospective longitudinal studies with prostate size measured by transrectal ultrasound and with banked serum and DNA can help identify determinants of normal and abnor-
mal prostate growth. One such study, the Olmsted County Study of Urinary Symptoms and Health Status Among Men (85), has been ongoing for more than 10 years. This study has followed 2,000 randomly chosen Caucasian male residents of Olmsted County, Minnesota, with questionnaires and uroflow measurements, and has followed a subset of approximately 500 men with periodic serum PSA measurements (86) and transrectal ultrasound measurements of prostate size (87). Similar studies including African-American men would provide an opportunity to examine determinants of normal and abnormal prostate growth in African-American men. Longitudinal studies of prostate growth in Chinese or Japanese men living in their country of origin and Chinese or Japanese men living in the United States could help identify how dietary, genetic, and environmental factors may affect both benign prostate growth and the development of prostate cancer. In such studies information on symptoms could be collected in a uniform way using the International Prostate Symptom Score, whose American version is known as the American Urological Association Symptom Index (88, 89). Culturally adapted translations of this questionnaire into a number of different languages are available. Some have been published in the Proceedings of the International Consultations on Benign Prostatic Hyperplasia (90).

Since benign prostatic hyperplasia and prostate cancer may share a number of determinants, a problem in any epidemiologic study of prostate cancer is whether to consider benign prostatic hyperplasia as a potential confounder. Weinberg (91) has shown that bias can result when factors are adjusted for that are at least partly caused by the exposure under study and are also associated with the outcome. For this reason researchers need to think carefully about whether adjustment for benign prostate hyperplasia would be appropriate in any given study and not simply make the decision on data-analytical criteria alone.

Another problem likely to arise in any epidemiologic study of prostate cancer in relation to determinants of benign prostatic hyperplasia is that of detection bias. This can occur whenever the exposure is likely to have an effect on either prostate size or urinary tract symptoms, since each can affect prostate cancer detection. Use of prostate cancer mortality as an endpoint should reduce, though probably not eliminate, detection bias. Epidemiologic studies conducted in the United States before the era of PSA testing have shown that prostate cancer as a cause of death was sometimes established only at autopsy (92), and that prostate cancer mortality rates may be affected by nonresponse bias in a longitudinal study (93). A way to further reduce detection bias would be to study a population whose members all receive periodic standardized urologic examinations including PSA testing. One such population would be the screening arm of a large randomized prostate cancer screening trial (94). By also including the nonscreening arm in the study, one could determine whether the exposure-disease relations were affected by the standardized screening regimen. Thus, the ongoing randomized prostate cancer screening trials should provide a good setting for nested case-control studies of prostate cancer mortality.

REFERENCES


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