Temporal Changes in the Clinical Approach to Diagnosing Prostate Cancer

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The diagnosis and detection of prostate cancer has undergone profound changes over the past three decades, due primarily to the development and widespread clinical use of prostate-specific antigen (PSA) testing. These changes have led to substantial differences in the prostate cancer phenotype. It is important to understand these changes to develop appropriate treatment options for contemporarily diagnosed prostate cancer. We explored a group of four temporal changes in prostate cancer detection that occurred after the advent of PSA testing. Through changes in the use of PSA testing, performance of prostate biopsy, application of PSA testing in different age groups, and pathologic tumor grading, a significant increase in detection of potentially inconsequential prostate cancers has occurred. The prostate cancer of 2011 is generally a smaller, lower-grade tumor and more often observed in younger men. These changes in detection will allow for increased use of active surveillance for prostate cancer.

Prostate cancer has become an extremely important public health problem in the United States. The disease is the second leading cause of cancer-related death among US men; in 2010, an estimated 217,030 new cases of prostate cancer in the United States were diagnosed, and 32,050 died as a direct result of the disease (1). The cost of treating prostate cancer has been estimated to rise to $16.85 billion in 2020, representing a 28% increase in expenditures from today’s cost of $11.85 billion (2). Despite these sobering statistics, a majority of prostate cancers currently diagnosed would never have been diagnosed were it not for the introduction of prostate-specific antigen (PSA)-based prostate cancer screening. A fundamental challenge of PSA-based prostate cancer screening is that many of the cancers diagnosed are destined to never cause harm or death to the patient. If these indolent tumors are treated, there is no health benefit, but the associated costs and morbidity are substantial.

In this chapter, we review the temporal changes in clinical and in other practices that have contributed to a previously unseen major migration in the type of prostate cancer diagnosed over the past several decades, including the impact of PSA testing and other techniques of diagnosis and staging. It is these changes that have led to the current situation in which a large number of men with prostate cancer at very low risk of progression, morbidity, and mortality are diagnosed.

Prostate Cancer Detection and Diagnosis in the Pre–PSA Era

Screening for prostate cancer has a relatively long history compared with many other cancers. Hugh Hampton Young is credited with being the first to advocate prostate cancer screening with routine digital rectal examination (DRE). In 1926, Young and Davis wrote, “The principal resource in the diagnosis of prostatic carcinoma is the rectal examination . . . every male above the age of fifty, without any symptoms, may have prostatic carcinoma, and every physical examination made above this age should include a rectal examination” (3). DRE remained the standard screening tool for prostate cancer for decades.

Prior to the 1980s, prostate cancer typically presented predominantly with lower urinary tract symptoms, consisting of dysuria, slow stream, urinary frequency, retention, back or hip pain, dribbling of urine, hematuria, bladder pain, constipation, and rectal or perineal pain (4). In the pre–PSA era, DRE was accurate for diagnosing prostate cancer in 50%–75% of cases (5–7). Upon presentation with these symptoms and in the care of an attentive physician (who would perform a DRE), an abnormal DRE would warrant referral for possible biopsy. Prostate biopsy at that time was often performed with general anesthesia and transperineally using a biopsy needle such as a Vim-Silverman needle (8). The quality of tissue obtained was often poor, and it was not uncommon for only two or four biopsy cores to be taken, often just of the nodule.

The net effect of these “prompts” made diagnosing prostate cancer in the pre–PSA era challenging. Often only those men with advanced local disease underwent biopsy; and biopsy only minimally sampled the prostate. As a result, generally only those men with extensive disease were identified. It is not surprising then that as a result of the small fraction of tumors clinically felt to be organ-confined at the time, about two-thirds were subsequently proven to be extraprostatic at the time of radical prostatectomy (9).

Staging of prostate cancer was also problematic in the pre–PSA era. At that time, the most important biochemical test for determining the diagnosis of disseminated prostate cancer was serum acid phosphatase. It was only recognized much later that serum acid phosphatase was a poor choice for screening for prostate cancer because it was elevated only in men with far-advanced
Prostate Cancer Detection and Diagnosis in the Post–PSA Era

Although PSA was described in the 1970s and was first used clinically in the 1980s, PSA testing was not approved by the Food and Drug Administration for monitoring prostate cancer progression until 1986 and for screening for prostate cancer until 1992 (14). FDA approval of PSA for prostate cancer screening subsequently led to widespread dissemination of PSA testing; however, data on the rate of PSA testing during its first decade of use for screening are largely unavailable. In the United States, PSA-based prostate cancer screening spread quickly. Perhaps the greatest evidence of the use of PSA screening was the rapid increase in prostate cancer detection seen in the mid to late 1980s (Figure 1).

Recent data would suggest that a majority of at-risk men in the United States have undergone PSA testing. Sirovich et al. reviewed data from the 2001 Behavioral Risk Factor Surveillance System, a telephone survey of US adults conducted by the Centers for Disease Control and Prevention, on 49,315 men aged 40 or older and concluded that 75% of men older than 50 years of age had undergone a PSA test (15). Catalona et al. were the first investigators to observe a stage migration from metastatic to organ-confined disease following the advent of PSA-based screening (16).

Although the introduction of PSA screening led to a profound change in prostate cancer detection, concurrent changes in practice and in technology, as well as a better understanding of the applica
tion of PSA, have led to a clinical prostate cancer today that is profoundly different from the prostate cancer of the pre–PSA era or even the tumor of the early PSA era. Here, we explore the temporal changes in a number of these arenas.

Change No. 1: What Is an Abnormal PSA? The Threshold at Which Biopsy Is Performed

Changes in PSA are generally seen long before a palpable change in the prostate is noted that is due to cancer; thus with the introduction of PSA for prostate cancer screening, elevated serum PSA levels became the most common reason for a prostate biopsy. With current common screening practices, most prostate cancers are nonpalpable by DRE and, if screening is performed regularly, PSA level at diagnosis is between 2.5 and 10.0 ng/mL (17,18). At the early outset of PSA-based prostate cancer screening, initial reports, concerned about the specificity of the test, recommended that an abnormal PSA should be higher than 4.0 ng/mL, between 7.5 and 10.0 ng/mL (19,20). In 1991, Catalona et al. measured PSA levels in 1,653 men older than 50 years and performed a prostate biopsy in men with a PSA greater than 4.0 ng/mL or with abnormal findings on DRE or ultrasound. Based on the results of this series, he concluded that the combination of PSA greater than 4.0 ng/mL and DRE resulted in improved screening for prostate cancer. Additionally, after reviewing 6,630 patients, Catalona and colleagues recommended an upper limit of 4.0 ng/mL for a normal PSA (21). Eventually, consensus in the urologic community resulted in recommendation of a prostate biopsy for any man with a PSA more than 4.0 ng/mL. Perhaps serendipitously, selection of a threshold for abnormal PSA of 4.0 ng/mL coincided with the perceived prevalence of prostate cancer at that time: About 8% of the general population harbors a PSA above 4.0 and, in the mid-1980s, the lifetime risk of a prostate cancer diagnosis was about 8%. In 1997, Catalona et al. suggested lowering the cutoff of PSA after screening 914 men with a PSA of 2.6–4.0 ng/mL (22). This study concluded that the majority of tumors identified in this cohort were medically significant and implied that the threshold for abnormal PSA should be 2.5 ng/mL.

In 2003, results of the Prostate Cancer Prevention Trial (PCPT), a study designed to compare finasteride to placebo for prostate cancer prevention, were made available (23). During the seven annual study visits, a prostate biopsy was recommended if the patient’s PSA exceeded 4.0 ng/mL or if his DRE was abnormal. Importantly, at the conclusion of the study, men without prostate cancer were recommended to undergo an end-of-study prostate biopsy. The results were very surprising, with 15% of men with a PSA less than 4.0 ng/mL and with a normal DRE for each of seven annual visits during the study proving to have prostate cancer and another 15% of these having high-grade (Gleason grade ≥ 7) prostate cancer (24). With this finding, PSA gradually changed from a dichotomous test (“elevated” vs “normal”) to a test reflecting a continuous risk of prostate cancer and of high-grade prostate cancer.

Following the observations of the PCPT, clinical practice in the United States changed toward the adoption of lower thresholds of PSA to prompt biopsy. This change has had a profound effect on the type of tumors detected. Because the level of PSA is directly related to both tumor grade and volume, the use of lower levels of PSA to prompt biopsy has resulted in an increase in the detection of low-grade and low-volume disease (Figures 2 and 3) (25,26). Concurrently, men began entering screening programs for prostate cancer in their physician’s office at a younger age. The resulting repeated PSA testing in these men generally led to an earlier detection of prostate cancer and lower PSA levels prompting biopsy and an increase in the proportion of low-grade and low-volume tumors among all cancers detected. A more recent advance in prostate cancer early detection has occurred since the recognition that other biomarkers and biomeasures may influence a man’s risk of cancer or of high-grade disease. This was first developed based on the Prostate Cancer Prevention Trial in which systematic biopsy was performed on all men, regardless of PSA; this analysis demonstrated that PSA, DRE findings, age, race/ethnicity, family history of prostate cancer, and prior negative biopsy independently contributed to the risk of cancer or high-grade cancer on biopsy (27). Subsequently, the
Figure 1. Incidence of prostate cancer from 1975 to 2008. The introduction of PSA-based prostate cancer screening resulted in a marked increase in cases beginning in 1988.

Figure 2. Decreasing grade of prostate cancer. After prostate-specific antigen (PSA) was introduced, a dramatic decrease in Gleason grade was observed. Reproduced from Newcomer et al. (25) with permission from Elsevier.
PCPT Risk Calculator has been validated in other populations and has been followed by other calculators including one based on the European Randomized Study of Screening for Prostate Cancer (ERSPC) (28). These tools have been very helpful in allowing physicians to fully understand both a patient’s risk of cancer and his risk of high-grade cancer, the latter of which is likely to be far more important than the former.

A final change that has had the effect of an even greater reduction in the level of PSA that has prompted biopsy and the increase of low-grade and low-volume tumors has been the widespread use of increases in PSA (commonly referred to as “PSA velocity”) to prompt biopsy. Initially pegged at 0.75 ng/mL-year as a threshold for biopsy based on data from a small number of subjects from the Baltimore Longitudinal Study of Aging, many subsequent studies demonstrated that increases in PSA above some threshold were associated with a risk of prostate cancer and that these cancers were likely to be organ-confined, at that time, thought to be a salutary effect (29). Subsequently, we and others have demonstrated that PSA velocity adds no independent predictive value to PSA alone for the diagnosis of prostate cancer or for the risk of high-grade disease (27,30). Because of the day-to-day and year-to-year variability of PSA in the general population, it is especially problematic that small changes in PSA at low levels are often used to prompt biopsy. In this population, as illustrated in the PCPT’s experience, the majority of tumors detected are low-grade and also low-volume tumors of low biologic potential.

**Change No. 2: Technique of Prostate Biopsy**

Ferguson is credited with performing the first prostate needle biopsy in 1930, whereas Astraldi was the first to perform prostate biopsy transrectally (31,32). Since then the technique of prostate biopsy has evolved markedly. Before the 1980s, prostate biopsy techniques varied widely and often obtained no more than two biopsy cores (33). The technique was not standardized, used large-gauge biopsy needles, and was often unreliable. Lee and colleagues reviewed results with transrectal ultrasound-guided prostate biopsy and concluded that use of ultrasound significantly improved safety and diagnostic accuracy (34). In 1988, Radge and colleagues reported results using an 18-gauge spring-loaded biopsy gun and reported a significant improvement in specimen quality and diagnostic accuracy (35). Perhaps the most profound effect of the development of this biopsy device was that a reliable core of tissue could be obtained quickly, and an increased number of cores could be obtained with minimal additional effort. Soon thereafter, Hodge described the ultrasound-guided “sextant” (six-core) biopsy in 1989 (36). In the late 1990s, several studies observed high false-negative rates with the sextant biopsy, recommending even more cores during prostate biopsy (37–39). Currently, the most common biopsy scheme is at least 10–12 cores of tissue specifically targeting the peripheral zone of the prostate at the apex, midgland, and base (40).

Prostate biopsy has even progressed to a greater sampling of the prostate in two manners. First, in a man in whom prostate cancer is suspected it is not unusual for repeated biopsies to be performed over several years. As prostate cancer is usually a slow-growing disease and as there is a low likelihood of significant change during such a timeframe, these repeated biopsies are similar to doubling (with the second biopsy) or tripling (with the third) the number of cores obtained. Taking this even further, for the man in whom cancer cannot be identified on the first or second biopsy, it is not unusual for a “saturation” biopsy to be performed, which may have 30–60 cores. When this is done, even with a perineal brachytherapy template in which every one cubic centimeter is sampled, one would anticipate that the risk of diagnosis rates of prostate cancer approaching those of autopsy series is great (41).

**Change No. 3: Age and Prostate Cancer Screening**

The strongest risk factor for the development of prostate cancer is age. Patients more than 75 years old are at an increased risk...
of having locally advanced or metastatic prostate cancer at the time of diagnosis and have lower overall survival when compared with younger men. Bechis et al. examined 11,970 men from the CaPSURE database and concluded that age at diagnosis accurately predicted both overall and cancer-specific survival on univariate analysis (42). In a review of the Center for Prostate Cancer database, Brassell and colleagues observed that older patients had a higher clinical stage, biopsy grade, and PSA velocity prior to diagnosis (43). These investigators also concluded that prostate cancer–specific and overall survival was lower in older patients. In a recent study, Scosyrev et al. examined the records of 464,918 men from the Surveillance, Epidemiology, and End Results database according to age groups and found that the incidence of metastatic prostate cancer increased dramatically by age group. In patients younger than age 75 years, the incidence of metastatic prostate cancer was 3%, and it increased as a function of age (44). These investigators observed that in men older than 90, the rate of metastatic prostate cancer at diagnosis increased to 30%. Additionally, although men older than 75 years old only contributed 26% of all prostate cancer diagnoses, this group harbored a disproportional amount of metastatic prostate cancer at diagnosis (48%) and accounted for 53% of all deaths from prostate cancer. Clearly, these studies highlight the fact that older age confers a significantly higher morbidity and mortality from prostate cancer. As life expectancy of the American population increases, we may expect to see more advanced prostate cancers.

In our study of 5519 subjects from the PCPT, we examined the independent predictive value of a group of variables and prostate cancer risk (27). In this study, highly significant values for correlation with prostate cancer risk and high-grade disease were achieved by PSA, age, race, DRE, and family history of prostate cancer. Important, and an item that is often overlooked by many practicing physicians, was that age and PSA were independently associated with the risk of high-grade disease. As such, the same PSA value in an older man was significantly more likely to be due to a high-grade tumor than in a younger man.

These two observations may help explain one of the most interesting observations regarding the current era in PSA testing. Many organizations recommend beginning prostate cancer screening in younger men, especially if the man has other risk factors such as African American race or a family history of prostate cancer. Additionally, because of the concern of a longer risk period in younger men, lower PSA levels often used to prompt biopsies in younger men. Concurrently, these organizations increasingly recommend a more “hands-off” approach to older men, often only paying attention to very high levels of PSA because of the perception that there is a greater risk of overtreatment in these men. Using these two decisions, tumors diagnosed in young men are more often low-grade, low-volume (potentially indolent) tumors, whereas late diagnosis of high-grade, potentially lethal cancer is more common in older men (45). This phenomenon can be easily illustrated using the Prostate Cancer Prevention Trial risk calculator (http://depts.washington.edu/prostatecalc/) examining two men: both Caucasian with negative family histories of prostate cancer and a normal DRE. The only difference is that Man A is 55 and Man B is 75. If a lower PSA of 3.0 is used to prompt biopsy in Man A and a level of 6.0 prompts biopsy in Man B, the following are the results. Man A has a 25.5% risk of low-grade prostate cancer and a 4.1% risk of high-grade cancer; Man B has a 26.8% risk of low-grade prostate cancer and a 16.3% risk of high-grade cancer. Interestingly, one can see that their risk of indolent cancer is essentially the same, but the older man’s risk of potentially lethal cancer is fourfold greater. Given general perceptions of how PSA should be used in men of different ages and this relationship of age and prostate cancer risk, it is not surprising that the burden of mortality from prostate cancer disproportionately affects older men, whereas the burden of overtreatment of indolent disease is primarily an occurrence in younger men.

Change No. 4: Grade Inflation

A fascinating phenomenon in prostate cancer has developed over the past two decades because pathologic interpretation of prostate biopsies has changed over time. Known as either the Will Rogers Phenomenon or as “grade inflation,” this has had a major influence on practices of treatment of prostate cancer.

Now documented on several occasions, perhaps the largest and most valid study was conducted by Albertsen using the Connecticut Tumor Registry (46). In this study, the authors reviewed a population-based cohort of 1858 men who had diagnostic tissue available from initial prostate cancer diagnosis made between 1990 and 1992. They had the original diagnostic material reexamined between 2002 and 2004 by a pathologist using contemporary diagnostic criteria, blinded to the original tumor-grade assignment. The results were stunning: Upgrading of prostate cancer occurred in 55% of specimens, with the average Gleason score increasing nearly a full point—from 6 to 6.8. As an illustration, of the 366 subjects originally assigned a Gleason 5 score, only 25 remained Gleason 5 with 205 being reassigned to a Gleason 6, 100 to a Gleason 7, 17 to a Gleason 8, 8 to a Gleason 9, and 2 to a Gleason 10. The impact of these results was substantial as illustrated by the authors. By simply using the reassigned Gleason scores, grade-standardized prostate cancer mortality rates were improved by 28%.

The implications on current treatment options by this phenomenon are extremely important, and we pointed these out in an editorial accompanying the Albertsen article (47). Although it would rarely be disputed that Gleason 8–10 tumors are potentially lethal, it is common today for a clinician to recommend active treatment for a Gleason 3+4 tumor, calling it a high-grade tumor. This recommendation comes from many series including an older series from Albertsen in Connecticut in which prostate cancer–specific mortality was quite high for Gleason 7 tumors (48). Morbidity outcomes were distinctly less common in Gleason 6 tumors. From the recent studies demonstrating tumor upgrading in contemporary series, it is clear that most current Gleason 3+4 tumors would have actually been classified as a Gleason 3+3 tumor for which surveillance may have been a reasonable option.

Evidence confirming this observation could be found as well in the outcomes of the Prostate Cancer Prevention Trial in the end-of-study biopsies of men with a PSA less than 4.0 ng/mL and a normal DRE. Of 3820 men with these criteria in the placebo group of the study, 576 were found to have cancer. Of the 564 of these in whom grade was established, 399 had Gleason 6 disease, 81 had Gleason 7 disease, and 8 had Gleason 8–10 disease. With the knowledge that somewhat less than 3% of the US male population will be expected to die of prostate cancer, that fully 2% of a low-risk
population (normal DRE, PSA < 4.0 ng/mL) sampled at a single point in time would have Gleason 7 disease illustrates that many of these tumors will be biologically inconsequential (23). Additional evidence that Gleason 7 (especially Gleason 3+4) cancer may have a lower biological potential comes from the University of Toronto surveillance series in which 17% of 450 patients were Gleason 3+4; although there was a greater risk of definitive intervention in this group compared with patients with Gleason 6 disease, 10-year prostate cancer actuarial survival was 97.2% (49).

The Future of PSA Testing: Advent of Grade/Risk-Based Biomarkers

We have demonstrated that several other variables significantly impact on the risk of prostate cancer, including age, race, family history, history of prostate biopsy, and use of 5-alpha reductase inhibitors. Since the original publication of the findings that led to the PCPT Risk Calculator, additional biomarkers and biomarkers have been added to the tool including body mass index, urine PCA3 level, percent free PSA in serum, [-2]proPSA in serum, and combinations of these markers. Formal validation of [-2]proPSA as a biomarker that provides independent predictive value for prostate cancer has been accomplished by the Early Detection Research Network (EDRN) of the National Cancer Institute (50). A second prospective study to validate PCA3, a gene that is overexpressed in prostate cancer and has been correlated with tumor grade, has now been completed, and results will be available shortly (51). As PCA3 is measured in the urine after a DRE, a biobank was created of these specimens to allow testing of other markers measured with such specimens. Ongoing at this time, using this biorepository, is a formal validation of TMPRSS2:ERG fusion transcript, a marker that appears to improve detection of not just prostate cancer but of high-grade disease (52).

Current efforts in the EDRN are focusing on a new paradigm for prostate cancer detection in which men who are at a higher risk of high-grade disease are recommended for biopsy, whereas men in whom the primary risk is of low-grade disease will be offered the opportunity of surveillance without biopsy. This approach should ultimately target biopsy and detection for biologically consequential tumors while avoiding detection of tumors of low biologic potential in which the risk of overdetection and overtreatment is significant.

References

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