



## Tower Cancer Research Foundation

### Incidental Prostate Cancer

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More than 15 years ago the distinguished urologist Willet Whitmore acknowledged the problems created by overdiagnosis of prostate cancer during the height of the PSA screening era. His famous statement is just as accurate today as it was then: "the quandary in prostate cancer: is cure necessary in those for whom it is possible, and is cure possible in those for whom it is necessary?"<sup>2</sup> The first phrase questions the necessity of cure by implying that some cancers will not progress or cause death within the patient's lifetime. This is a concept which then and even now is difficult for some physicians and many patients to accept. For most cancers the cornerstone of cure is considered early detection and surgical intervention, which usually leads to improved outcome. Therefore, the observation that for many cases of prostate cancer, early diagnosis followed by early prostatectomy or radiation therapy may have no impact at all on survival, and possibly do more harm than good, tends to be counter-intuitive.

As a result of the introduction of the PSA test in 1987, the incidence of prostate cancer increased by 26% between 1986 and 2005. When compared to the pre-1986 baseline incidence, this translates into an estimated additional 1,000,000 men diagnosed and treated for prostate cancer. The authors of this statistical study described this phenomenon as "overdiagnosis", and believe that the vast majority of these additional cases did not benefit and were subjected to unnecessary treatment and complications<sup>1</sup>.

Many experts have adopted a contrary position and point to the 40% decline in prostate cancer mortality between 1993 and 2009. The precise reason for the decline is unknown, but could relate to PSA screening, better treatment of metastatic disease, unmasking and earlier treatment of occult aggressive disease, changes in the attribution of death, or other factors<sup>2</sup>.

Central to this debate is the answer to two questions:

1. Does prostate screening save lives?
2. How do physicians determine which cases need treatment and which do not?

#### Effect of Screening on Prostate Cancer Survival

Two very large randomized, controlled trials, one European, the other American, were published in March 2009. The goal of each was to determine if screening decreased the risk of death from prostate cancer. Each trial came to opposite conclusions. The European trial at 8.8 years follow-up found that screening reduced cancer deaths by a modest 20%. Expressed differently, 1410 men would have to be screened and 48 treated to prevent one death from prostate cancer<sup>3</sup>. At 7 years follow-up the U.S. trial concluded there was no benefit to PSA screening, and also determined that the rate of cancer death during the first decade after diagnosis was very low<sup>4</sup>. Despite flaws in both trials, the data is still the best available. Therefore, currently there is no incontrovertible evidence that screening saves lives. Without doubt, however, the PSA and digital rectal exam (DRE) are effective for uncovering prostate cancer, which then most often leads to either prostatectomy or radiation, possibly with associated complications.

Recognizing this uncertainty concerning the balance of benefits versus harmful effects from screening, relevant medical societies (Am. Cancer Society, Am. Urological Association, as well as the U.S. Preventive Services Task Force) currently do not support routine screening. Instead, these organizations suggest that patients make individual decisions about screening after a thorough educational discussion with their physicians regarding benefits and potential harms. If screening is performed and the PSA elevated, rather than proceeding to biopsy based on the PSA alone, computer-based tools that predict the estimated risk of detecting cancer, and more

importantly, high grade cancer requiring treatment, have proved useful to decide whether biopsy is imperative. The PCPT risk calculator is a good example (<http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp>)<sup>5</sup>.

#### Which Cases Need Treatment?

Incidental prostate cancer is exceedingly prevalent in the general population. The most recent autopsy study of individuals dying of traumatic and medical conditions uncovered silent prostate cancer in 12% overall. The incidence increased by the decade: in the fifth 30%, sixth 33%, seventh 46%, eighth 55%, and by the ninth almost 100%<sup>6</sup>. What would have been the natural history of these cancers had the individuals survived?

This question was addressed by the now famous Scandinavian Prostate Study Group. Men with localized prostate cancer were randomly assigned to prostatectomy or watchful waiting and followed for a median of 10.8 years. At 12 years, 12.5% of the surgery group and 17.9% of the watchful waiting group had died of prostate cancer; and metastases were present in 19% versus 26% respectively. The authors concluded that radical prostatectomy reduced prostate cancer mortality and the risk of metastases up to 10 years after diagnosis<sup>7</sup>. However, the study has been questioned because only 5 to 7% of the participants actually benefited from prostatectomy, and 75 to 85% of men could have avoided surgery and had the same outcome. Also, in most subjects the diagnosis was made by digital rectal exam, suggesting that these cases were more advanced at the outset than the typical cases diagnosed mainly by PSA in the U.S. Because of this important difference in case presentation, it is difficult to apply the Scandinavian data to the U.S. localized prostate cancer population<sup>5</sup>.

A recent observational study followed a population of men 65 or older (median age 78) with localized prostate cancer detected primarily by PSA and managed conservatively. Ten year disease specific mortality was only 8.3% for well-differentiated, and 9.1% for moderately differentiated, but 25.6% for poorly differentiated tumors<sup>8</sup>. This correlates with Gleason's seminal paper in 1998 reporting that patients either not treated or treated with androgen withdrawal only and Gleason scores of 2-4, and 5, face a 4% to 7%, and 6% to 11% chance of prostate cancer death within 15 years respectively, while scores of 8-10 face a 60% to 87% cancer-specific mortality<sup>9</sup>. Other similar studies support the observation that that men with Gleason low grade tumors rarely die from prostate cancer.

This data certifies watchful waiting as a legitimate therapeutic option for men with prostate cancer unlikely to become symptomatic or metastatic during their lifetime. It is impossible to make this prediction precisely, but physicians considering this option should weigh predictive risk factors as age, Gleason score, findings by DRE, comorbid conditions that might shorten lifespan to 10 years or less, PSA levels as well as PSA density and doubling time, and importantly, the probability of patient compliance with regular follow-up testing. Watchful waiting is not a likely option for men with high or perhaps intermediate grade tumors, or young age with a life expectancy of 20 to 30 years or so; in this situation, active intervention could be more appropriate<sup>10</sup>. Ultimately, this debate should be resolved by the ongoing PIVOT and PROTECT trials designed to answer the question of the optimal treatment for localized prostate cancer detected by PSA testing.

#### References

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