The Prostate Cancer Conundrum

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In 2003, the American Cancer Society estimates that 220,900 men will be diagnosed with prostate cancer and that 28,900 will die from this disease (1). Since the introduction of testing for prostate-specific antigen (PSA), the incidence of prostate cancer has increased, whereas the mortality from this disease has decreased. During the early 1990s, mortality from prostate cancer peaked in the United States at a rate of 26.4 prostate cancer deaths per 100,000 men at risk. By 1998, this rate had fallen to 21.5 per 100,000 men at risk, a decline of 2.6% per year (2). The drop in prostate cancer mortality has continued, and the rate in 2003 is now similar to levels seen during the 1950s, 1960s, and early 1970s, the years preceding the widespread use of transurethral prostate surgery (1,3).

What is happening? Many researchers attribute these dramatic changes to the pervasive use of PSA testing. Most epidemiologists would agree that the sharp rise and subsequent fall in incidence rates for prostate cancer during the early 1990s were direct results of the introduction of PSA testing. An explanation for the decline in prostate cancer mortality is more complex. Some have speculated that the introduction of PSA testing followed by the aggressive use of surgery or radiation therapy is the primary reason (4). Others are more skeptical. Researchers in the U.K., Canada, and the United States point to conflicting data concerning prostate cancer mortality that do not appear to support a direct link between PSA testing, aggressive intervention, and a subsequent decline in prostate cancer mortality (5–7). What might be another plausible explanation?

The article by Cooperberg et al. (8) appearing in this issue of the Journal suggests one intriguing possibility. The authors documented a dramatic increase in the use of androgen withdrawal therapy during the past decade. They note statistically significant increases in the use of primary androgen withdrawal therapy among men at low, intermediate, and high risk for developing prostate cancer metastases. In their discussion, they review several papers that appear to show a survival advantage for men who were placed on androgen withdrawal therapy early in the course of their disease. Bolla et al. (9), for example, showed a survival advantage for men with high-risk prostate cancer who received neoadjuvant androgen withdrawal therapy in conjunction with radiation therapy compared with those who did not. Messing et al. (10) showed that men undergoing radical prostate surgery who were found to have lymph node metastases appear to benefit from the early use of androgen withdrawal therapy. Results from the Medical Research Council trial (11) conducted in the U.K. also appeared to suggest a survival advantage among men who received androgen withdrawal therapy early in the course of their disease. Because prostate cancer is most prevalent among elderly men who have multiple competing medical conditions, a small improvement in survival increases the chance that men will die from a cause other than prostate cancer. As a consequence, the cancer-specific mortality rate will decline.

What does this imply about the efficacy of PSA testing and subsequent treatment with either surgery or radiation? These are important, but separate and independent, questions. Epidemiologists frequently cite declines in disease-specific mortality rates as proof of the efficacy of screening; however, two conditions must be satisfied. First, the screening test must identify disease sufficiently early in its natural history when it can be treated effectively. PSA testing appears to achieve this goal. Second, effective treatments must be available that can alter the natural outcome of the disease. The decline in prostate cancer mortality appears to support this condition, but which treatment is producing the effect?

The recently published data (12) from a randomized trial in Sweden comparing radical prostatectomy with watchful waiting suggests that radical surgery in the treatment of prostate cancer can have a modest impact on disease-specific survival. The treatment effect in relative terms is substantial: a decrease in disease-specific mortality of approximately 50%. In absolute terms, however, the impact is more modest: a decrease in disease-specific mortality rates from 13.6% to 7.1%. For younger men, this probably translates into a true survival benefit. For older men, however, surgery and, by inference, radiation therapy, may not be beneficial. In the Swedish study after 8 years of follow-up, all-cause survival was not statistically significantly different between the men undergoing surgery and the men who were followed conservatively. Furthermore, in the Swedish study, men were recruited before the advent of widespread PSA testing. The lead time introduced by PSA testing suggests that substantial survival benefits from surgery or radiation therapy are unlikely to occur for men with a life expectancy of less than 10 years. For these men, observation followed by the early initiation of androgen withdrawal therapy may be the preferred approach.

The recent decline in prostate cancer mortality rates suggests that some treatment is having an impact. Whether this is the result of the early use of androgen withdrawal therapy or whether this is the result of widespread use of surgery or radiation remains to be determined. Ultimately, randomized trials are needed to resolve these issues. In the United States, the Prostate Cancer Intervention Versus Observation Trial (PIVOT), designed to determine the relative efficacy of radical prostatectomy versus watchful waiting, continues to follow patients (13). Results should become available within the next decade. The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), designed to determine the relative efficacy of prostate cancer screening with PSA testing, also continues to monitor patient outcomes (14). This study, along with the European Randomized Study of Screening for Prostate Cancer, should provide important insights concerning the efficacy of PSA testing (15). With the growing enthusiasm for the early use of androgen withdrawal therapy, perhaps it is also time to initiate a trial of early versus delayed androgen withdrawal therapy to determine

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the relative survival benefit and costs in terms of health-related quality of life. Something good is happening in the world of prostate cancer management. Our next task is to determine which treatments are providing clinically meaningful survival advantages and which interventions expose patients to harms but little benefit.

**REFERENCES**