Is a Screening Interval of Every 4 Years for Prostate Cancer Acceptable?

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In this issue of the Journal, Roobol et al. (1) report an analysis of two different screening intervals in the large European Randomized study of Screening for Prostate Cancer (ERSPC) to defend a screening interval of every 4 years. In contrast to the yearly screening for prostate cancer in the United States, most centers in the ERSPC trial chose to screen men every 4 years. Critics of the 4-year screening interval have voiced concerns that clinically significant cancers could be missed by such an extended interval. The authors attempted to soothe these concerns by comparing two screening intervals (2-year versus 4-year) within the ERSPC trial. Although they found that the incidence of interval cancers did not differ by screening interval, I am not convinced that their analysis has allayed these fears.

Why screen for prostate cancer? In 1989, prostate cancer became the most common cancer diagnosed in American men and the second leading cause of death (2). The majority of prostate cancers were either locally advanced or metastatic when diagnosed. The impact of prostate cancer on the male population is large—17% of men will develop it and approximately 3% will die from the disease (3). Three possible approaches exist to deal with this common neoplasm. The first is to develop a cure for advanced prostate cancer, but this has not yet been achieved. The second is to try to prevent the disease. An effective preventive agent was recently identified: finasteride, which reduced the 7-year period prevalence of prostate cancer by 25% (4). However, because of the initial concern that the drug could induce high-grade tumors in treated men, this approach to prevention was not embraced. Recent analysis would suggest that this high-grade cancer phenomenon may have been an artifact (5). A third approach is to find the disease early, treat it, and cure it; this approach is known as screening or early detection.

Screening for prostate cancer is controversial—some medical organizations support it, and others are skeptical. These controversies led to the development of a large randomized clinical trial in the United States to determine the value, if any, of early detection of prostate cancer: the Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) trial. This very important randomized trial began in 1992 (6). In this trial, a yearly screening interval for prostate cancer was chosen, and screening consisted of a serum prostate-specific antigen (PSA) test and digital rectal examination (DRE). To date, more than 154 000 men and women aged 55–74 years have enrolled in this trial. As yet we have no definitive answer as to the value of screening for prostate cancer.

As mentioned, in contrast to the yearly screening for prostate cancer in the PLCO, most centers in the ERSPC trial chose to screen men on an every-4-year basis. However, several centers chose to screen the participants every 2 years. Roobol et al. (1) compared the incidence of interval cancers between the Swedish center (Gothenburg, 2-year screening interval) and the Dutch center (Rotterdam, 4-year screening interval). The challenge with this analysis is that this is not randomization between 2- and 4-year screening intervals. The authors attempt to show balance; however, there are differences. The consent processes, indications for biopsy, follow-up, and age at entry are different. There are cultural differences as well. Therefore, many variables could affect the conclusion that there are no differences in the aggressive interval cancers between 2 and 4 years of screening. A potentially life-threatening interval cancer or aggressive interval cancer was defined as an interval cancer that had at least one of the following characteristics at diagnosis: stage M1 or N1, plasma PSA concentration greater than 20.0 ng/mL, or a Gleason score greater than 7. Cancers with these characteristics are often incurable. The 10-year cumulative incidence of all prostate cancers found in Rotterdam versus Gothenburg was 1118 (8.40%) versus 552 (13.14%) (P < .001), the cumulative incidence of interval cancers was 57 (0.43%) versus 31 (0.74%) (P = .51), and the cumulative incidence of aggressive interval cancers was 15 (0.11%) versus 5 (0.12%) (P = .72).

The authors do not relate the risk of an aggressive interval cancer to the initial PSA level. We were the first to point out that the risk of conversion to an abnormal PSA level is directly related to the initial PSA level. This was first reported from the Prostate Cancer Awareness Week data and later from the PLCO data (2, 7). In fact, if the initial PSA value is less than 1 ng/mL, then a screening interval of 5 years may be appropriate.

Numerous publications are arising from both the PLCO and ERSPC. The ultimate publications from these trials will be to define the value of early detection. Although many of us believe that early detection is saving lives, definitive evidence is lacking. When results of these trials are reported, there will be many criticisms of the design, the screening tools, the contamination, and the lack of standard treatment, depending on the results. The use of PSA and DRE as screening tools will change to more sensitive and specific methods. Because a low PSA level does not rule out prostate cancer, perhaps the only certain method would be a prostate biopsy. Men aged 50 years could combine a routine colonoscopy and prostate biopsy!

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