Why Are a High Overdiagnosis Probability and a Long Lead Time for Prostate Cancer Screening So Important?

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In this issue of the Journal, Draisma et al. (1) thoughtfully and carefully estimate the proportion of prostate cancers overdiagnosed in the United States from 1985 through 2000, the early prostate-specific antigen (PSA) era in the United States. They also examine the lead time of PSA screening in that era, using several different definitions of lead time. They use three different independently developed models to estimate these parameters, calibrating each of the models to the observed incidence of prostate cancer in the United States over this time interval. They estimate an overdiagnosis probability, which is defined as the percentage of prostate cancers diagnosed by screening that would not have been diagnosed before death, from 23% to 42%, depending on the model. The estimated lead time for those prostate cancers not overdiagnosed, that is, cancers destined to be diagnosed clinically in the absence of screening, is 5.4–6.9 years. As the authors clearly point out, their results are dependent on how PSA screening was being implemented by clinicians in the United States at that time. In fact, these estimates are very likely too low for cancers diagnosed in the United States from 2000 to 2009 because the trend to perform biopsies at lower PSA levels, to take more biopsy cores, and to repeat biopsies when previous biopsies are negative will have increased both overdiagnosis and lead time.

That the estimates of overdiagnosis from this earlier era may now be too low is reflected in early results from the Göteborg branch of the European Randomized Study for Prostate Cancer Screening (ERSPC) (2). In that trial, men aged 50–66 years who were screened regularly with PSA had an 80% higher risk of a prostate cancer diagnosis for a period of 10 years than men in the control group, suggesting an overdiagnosis probability closer to 45%. Moreover, the estimate of the lifetime risk of a prostate cancer diagnosis for men in the United States has risen from about 9% in 1985 before PSA testing to about 17% in 2003–2005, suggesting an overdiagnosis probability approaching 50% (3,4).

Nevertheless, it seems clear that both the probability of overdiagnosis and the lead time for prostate cancer screening with the PSA test are substantial and higher than for other cancers for which screening is commonly undertaken. For example, for breast cancer screening, the overdiagnosis probability is estimated to be about 10%–25%, with a lead time of about 2 years (5–7). It is important to understand the implications of these estimates in anticipation of the results of ongoing prostate cancer screening trials.

Whether any medical intervention should be undertaken depends not just on whether there is any demonstrated benefit but whether the demonstrated benefits exceed the harms. The high probability of overdiagnosis and the long lead time of PSA screening suggest that the potential for harm is relatively high and the benefits, in terms of reductions in prostate cancer morbidity and mortality, will need to be large indeed to make screening worthwhile. Some reflection on which men stand to benefit from prostate cancer screening may help explain the relationship between overdiagnosis and lead time and screening harms.

First, men who are overdiagnosed, that is, men who would never have known about having prostate cancer until their death from another cause in the absence of screening, cannot possibly benefit from screening and can only be harmed. Unfortunately, it is impossible to know at the individual level which men have been overdiagnosed and require no treatment, so most of these men will experience not only the morbidity of dealing with a cancer diagnosis but also the potential harms of prostate cancer therapy, such as incontinence and erectile dysfunction. In the publication from the ERSPC trial (2), screening increased prostate cancer incidence approximately 80% through the effect of overdiagnosis. At the same time, the risk of undergoing radical prostatectomy or radiation therapy was more than twice as high in the screened group than in the control group (2). Because the mortality risk of these treatments is small but finite, these men can only lose life expectancy through screening.

Men whose cancers were destined to be diagnosed during their lives but who were not destined to die of prostate cancer, that is, those men destined to die with and not of prostate cancer, also have little to gain from screening. Some of these men might be able to avoid cancer morbidity through early detection, but they cannot gain a longer life expectancy. Instead, given an estimated lead time of 6 or 7 years, they must deal with a cancer diagnosis much earlier than they would have otherwise, experience any treatment-related morbidity that much longer, and again, can lose life expectancy only through any treatment-related mortality.

The men who stand to gain from screening are the approximately 3% who are destined to be diagnosed with and eventually die of prostate cancer, for whom earlier detection and attempted curative therapy may prevent their eventual death from prostate cancer. Of course, prevention of a prostate cancer death does not confer immortality; rather, other causes of mortality will eventually catch up with the man who dodges this fate through screening, and given that the median age of prostate cancer death is 80 years.

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in the United States, these other forces of mortality would likely catch up rather quickly (4).

Imagine a thought experiment in which ongoing randomized trials eventually demonstrate a one-third reduction in prostate cancer–specific mortality with regular PSA screening (a relative benefit somewhat larger than for mammographic or colonoscopic screening) (7–9). We can then consider the effects of overdiagnosis and lead time to weigh this hypothetical benefit against the potential risks. Taking as a starting point the current lifetime risk of a prostate cancer diagnosis of about 17%, about 8% of all men would contribute to this cumulative incidence as a result of overdiagnosis. Any morbidity or mortality they would suffer as a result of this diagnosis would lead to absolutely no benefit. Another 6% (the 9% of men destined to be diagnosed with prostate cancer before the advent of PSA screening minus the 3% of men destined to die of prostate cancer) of all men, who were destined eventually to be diagnosed with but not die of prostate cancer, would achieve no mortality benefit and would suffer any diagnosis- or treatment-related morbidity an average of about 6 years earlier. Of the 3% of all men destined to eventually die of prostate cancer (4), 2% of all men would not have their prostate cancer death averted but would again have to deal with prostate cancer and its consequences much earlier in their lives. Finally, about 1% of all men would have their prostate cancer deaths averted and instead die of something else at a later date. That is, about 16 men diagnosed with prostate cancer would suffer net harm for every one man who dies of something other than prostate cancer.

For most cancers without these high overdiagnosis probabilities and long lead times, demonstration of such a large relative mortality benefit from screening would likely overwhelm the harm done by diagnosis- and treatment-related morbidity and mortality. But with prostate cancer screening, the fact that so many more men are diagnosed so much earlier with PSA testing will make the calculation of net benefit more challenging when randomized trial results become available. In all likelihood, at the individual level, a shared decision-making approach to prostate cancer screening including discussion of the trade-offs between benefits and harms may still be the optimal strategy.

References


Notes

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