

Understanding and Appreciating Overdiagnosis in the PSA Era

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Screening, for any disease, is often mired in controversy. If there should be any doubts regarding this observation, one only needs to examine the recent uproar surrounding mammography. In that case, seemingly convincing evidence from randomized trials supporting the efficacy of mammography was brought into question decades after the test's widespread acceptance and large-scale implementation (1–4). Take that situation and magnify it by several orders of magnitude and you have the controversy associated with the use of prostate-specific antigen (PSA) screening for the detection of prostate cancer.

Since its introduction in 1987, the use of PSA screening among Medicare beneficiaries has increased substantially (5,6), despite the lack of any truly randomized evidence of its efficacy. Furthermore, the majority of primary care physicians in the United States reported that they performed routine PSA testing in men over 80 years of age, even though these men are unlikely to benefit from treatment (7). As a consequence, it should not be surprising that concerns regarding PSA testing have flourished and that overtly contradictory recommendations for the use of this test exist among professional societies (8).

Several factors contribute to the controversy in PSA screening. For example, consider the numerous requirements necessary for a screening test to be deemed effective. An effective test must a) identify a disease that profoundly impacts the patient's life, b) be acceptable to the patient and perform adequately, c) identify the disease at a point in time during which acceptable and adequate treatment exists, and d) use a reasonable amount of resources. Healthcare providers and consumers will immediately recognize that whether many of these conditions have been satisfied with PSA testing remains an open question. By using a computer simulation to determine the proportion of men overdiagnosed with prostate cancer through PSA testing, Etzioni and colleagues (9) further address the adequacy and performance characteristics of the PSA test.

In their study, the authors used data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER)¹ population-based cancer registry to estimate the potential extent of overdiagnosis associated with PSA screening. They approached this problem in an almost algebraic manner by recognizing that cancer incidence (after the introduction of a screening test) is the sum of two terms: the incidence rate in the absence of the test and the excess incidence attributable to the test. The second term is, additionally, a function of the test dissemination rate and the lead time due to the test (i.e., the amount of time that diagnosis is moved forward by the test). The authors found that among men aged 60–84 years, 18%–39% of Caucasian men and 20%–44% of African-American men may be overdiagnosed with PSA screening (9).

For the purposes of their study, however, the authors defined overdiagnosis as the proportion of patients whose cancer was

detected through PSA screening but who did not survive long enough to have their cancer *clinically diagnosed*. This definition is distinctly different from that most often cited in textbooks and in the literature where overdiagnosis is usually defined as the identification of disease that would not have produced *signs or symptoms* before death (10,11). These two definitions of overdiagnosis would be the same only if all clinically diagnosed cancers produced signs and/or symptoms.

In fact, we know that this situation probably is not the case, perhaps because most ($\approx 70\%$) prostate cancers reside in the peripheral zone of the prostate rather than next to the urethra (or other common symptom-producing structures) in the transition zone (12). As the authors noted, even in the pre-PSA era, transurethral resections of the prostate for benign prostatic hyperplasia were detecting cancers long before patients developed signs and/or symptoms of disease. Other common routine procedures and tests (13,14), such as digital rectal exam (15) or techniques used in the evaluation and treatment of comorbid conditions, are also known to detect even greater numbers of asymptomatic prostate cancers.

How do these factors affect our interpretation of the study by Etzioni et al. (9)? Because asymptomatic, localized, or even regional disease (i.e., incident disease) can precede symptomatic disease (12,16,17) by many years [the time from clinical diagnosis to just progressive disease can exceed 10 years in certain cohorts (18)], many more men will die of causes other than prostate cancer during the time interval from clinical diagnosis to the development of signs and/or symptoms. That is, the additional period of time required to experience symptomatic disease allows patients to die of alternative causes and thus be overdiagnosed. Hence, the use of incident, rather than symptomatic, disease by Etzioni et al. effectively decreases the opportunity to die of a competing cause, thereby decreasing the likelihood of overdiagnosis (Fig. 1).

Consistent with this possibility, estimates of overdiagnosis in prospective, randomized, screening studies (19–22) are much higher than those reported by Etzioni et al. As the authors note, the methods of analysis used in these other studies were different and may overestimate the rate of overdiagnosis, but the existing individual-level data from these studies should be sufficient to perform a more formal analysis of overdiagnosis that is subject to fewer assumptions than are required for simulations.

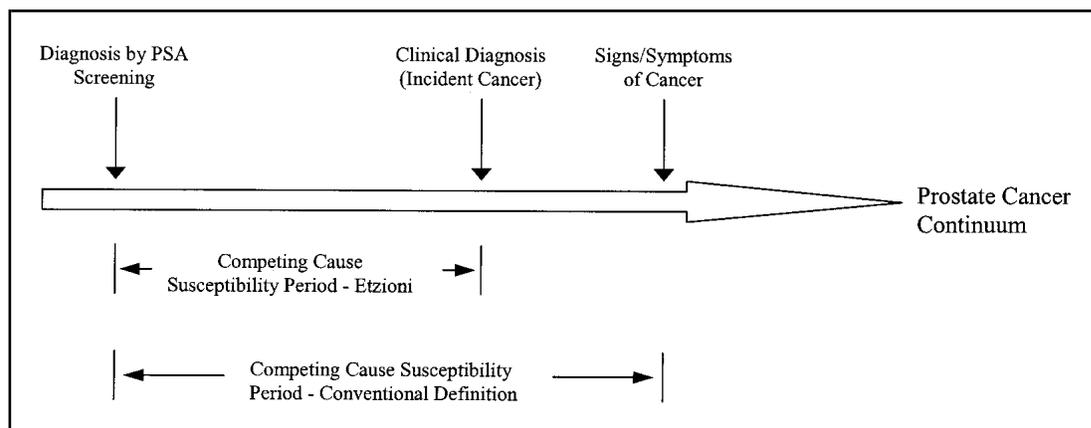
In addition to this difference, for the individual patient or

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Fig. 1. When signs/symptoms are used to calculate overdiagnosis, there is a longer period of time available for the patient to die of a competing cause and be overdiagnosed.



healthcare provider trying to understand the potential implications of being overdiagnosed, mortality might be a more important end point than disease incidence or signs/symptoms of disease, because the benefit of early treatment in many men with prostate cancer has not been clearly established (23,24). As a consequence, a man who is diagnosed by screening but whose life is not extended by screening might consider himself overdiagnosed. As the authors point out, the use of a mortality end point was the approach used by McGregor et al. (25), who found that 84% of screen-detected cancers would be overdiagnosed.

Irrespective of the variability in reported overdiagnosis rates, even the seemingly modest rates reported by Etzioni et al. (9) can be considerable from a patient's point of view. Assuming that PSA screening is effective, overdiagnosis might be acceptable (as it often is in other diseases) were it not for the fact that many of the 18%–44% (or more, considering data from the other aforementioned studies) of men diagnosed with prostate cancer by PSA testing would be subject to the substantial and sometimes uniquely enduring morbidities of treatment (26), even though they would not benefit from treatment. Therefore, in spite of the potentially conservative results of Etzioni et al. and their caution that their study is exploratory, the consequences of overdiagnosis for the individual patient may be formidable, and for those who choose to discuss the option of screening with their healthcare provider, the important possibility of overdiagnosis should not be underestimated or overlooked.

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NOTES

¹*Editor's note:* SEER is a set of geographically defined, population-based central cancer registries in the United States, operated by local nonprofit orga-

nizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a bi-annual basis, and the NCI makes the data available to the public for scientific research.

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