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Reconsidering Prostate Cancer Mortality — The Future of PSA Screening

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From its peak in the early 1990s, U.S. mortality due to prostate cancer has decreased from 39 per 100,000 men to 19 per 100,000 men — essentially by half. Although everyone agrees that this reduction is good news, there is considerable disagreement about why it happened. The controversy has profound implications for the future of prostate-specific antigen (PSA) screening.

A long-term perspective on trends in cancer-specific mortality among patients with three common causes of cancer-related deaths since 1950 is provided in Figure 1A. The substantial rise and fall in the largest component of cancer-related mortality, lung cancer mortality, reflects the rise and fall in rates of cigarette smoking decades earlier. In contrast, breast cancer mortality was remarkably stable until 1990 and then began to fall. Prostate cancer mortality was similarly stable until 1970 and also began to decrease in the early 1990s. During the intervening years, however, prostate cancer mortality rose.

A likely cause of this rise is illustrated in Figure 1B. During the 1970s and early 1980s, urologists performed increasing numbers of transurethral resections of the prostate (TURP) to treat benign prostate enlargement in older men. As more resected prostate specimens were sent for pathological examination, more prostate cancer was incidentally detected — and the incidence of (recognized) prostate cancer gradually rose. By 1986, half of all prostate cancers were TURP-detected.[1] The increased prevalence of prostate cancer diagnoses in an age cohort in which death is a relatively common event caused more deaths to be attributed to prostate cancer — a phenomenon called sticky diagnosis bias.[2]

PSA SCREENING AND DETECTION

The advent of widespread PSA screening in the United States during the late 1980s and early 1990s exacerbated this bias.[3] Screening was rapidly embraced and often offered for free at health fairs and to men with limited life expectancy. Despite a 50% drop in TURP-detected cancer incidence (coinciding with the declining use of TURP in favor of medical therapy),[1] overall prostate cancer incidence doubled in a 6-year period (1986–1992), as shown in Figure 2. This spike in cancer incidence is unprecedented in the United States — and makes the influence of diagnostic practice on reported cancer incidence starkly apparent.[4] Many older men received a diagnosis of prostate cancer, and for a fraction of them, the diagnosis "stuck" at the time of death.[5]

The increase in prostate cancer mortality thus most likely reflected increased labeling rather than a true increase in deaths from this disease (a tiny portion may also reflect an increase in treatment-related mortality). If the increase was largely spurious, some of the subsequent decrease must have been as well — instead reflecting the decline of TURP in general and less aggressive PSA screening in men with limited life expectancy. To mitigate these influences, we believe that the drop in prostate cancer mortality is best measured from its 1950–1970 baseline: a decrease of 37%. Nevertheless, a 37% decrease in cancer-specific mortality is substantial and warrants an explanation — the simplest of which would be PSA screening.

The past three decades have provided important insights into the natural history of prostate cancers detectable by PSA screening. Autopsy

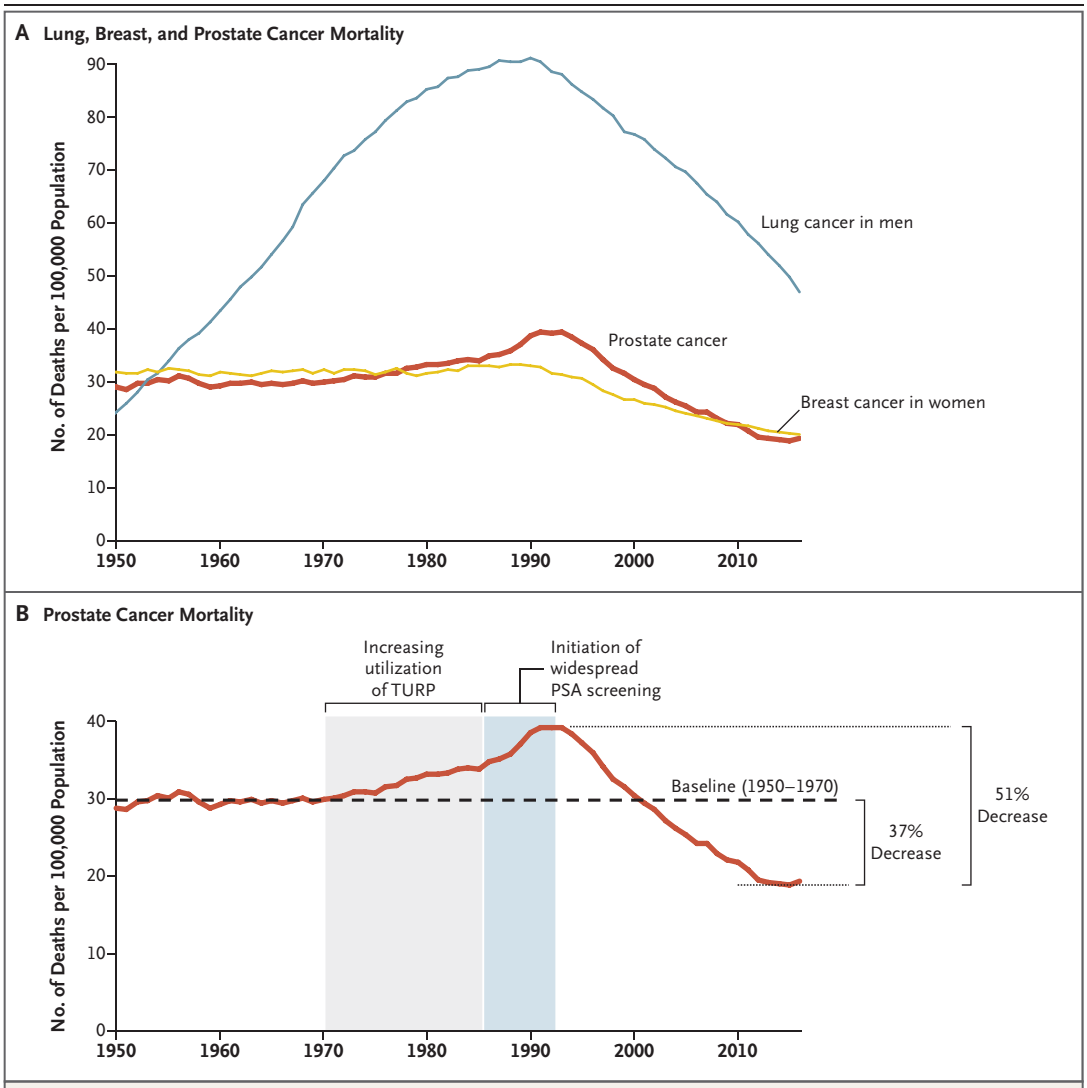

Figure 1. Prostate Cancer Mortality in the United States, 1950–2016.

Panel A includes mortality from lung cancer (in males) and breast cancer (in females) to provide context. Panel B illustrates the stable baseline prostate cancer mortality from 1950 through 1970 and the subsequent system exposures that most likely influenced reported mortality. All rates are age-adjusted to the standard 2000 U.S. population. PSA denotes prostate-specific antigen, and TURP transurethral resection of the prostate.

studies documented the substantial reservoir of potentially detectable disease: more than half of men who have died after 60 years of age from some other cause have pathological evidence of prostate cancer.[6] The advent of ultrasound-guided transrectal needle biopsy combined with the practice of taking multiple samples allowed this reservoir to be tapped. In a chemoprevention trial in which all participants underwent biopsy, one quarter of men in the control group were found to have prostate cancer.[7] Many men with PSA-detected prostate cancer were subsequently observed to survive for 15 to 20 years, often with minimal treatment, and many ultimately died from something else.

Most PSA-detected prostate cancers thus act more like a chronic disease than an aggressive malignancy. Most are well-differentiated cancers — that is, in a low Gleason score group. A few are at the other end of the spectrum — poorly

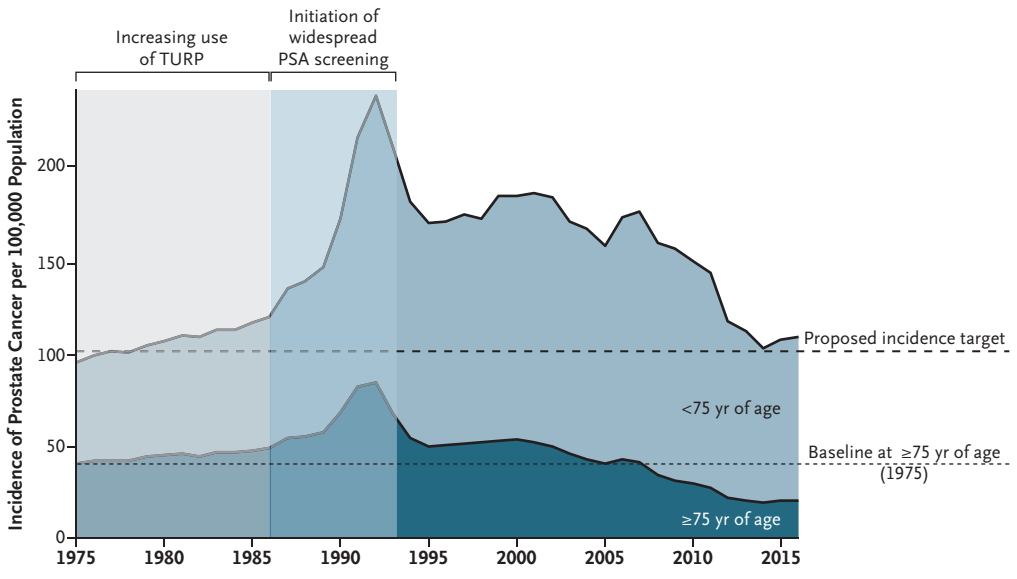

Figure 2. U.S. Prostate Cancer Incidence Including Age-Specific Components, 1975–2016.

The age-specific component is the product of overall incidence and the proportion of cancers in the age group. The proposed incidence target reflects a "not to exceed" incidence benchmark intended to minimize overdiagnosis. Data are from the Surveillance Epidemiology and End Results (SEER 9) Program; all rates are age-adjusted to the standard 2000 U.S. population.

differentiated cancers in a high Gleason score group. Men with poorly differentiated disease often die within 10 years after diagnosis, often despite undergoing radiation, surgery, or both. PSA screening primarily finds well-differentiated prostate cancers; poorly differentiated cancers, the ones that usually kill men, are found much less frequently. In fact, some men with the most poorly differentiated and deadly prostate cancers have a normal PSA level.[8]

TRIALS AND OBSERVED SCREENING EFFECTS

The 37% decrease in mortality observed in the United States is larger than the decrease observed in the most favorable of the three major randomized trials of PSA screening, the European Randomized Study of Screening for Prostate Cancer (ERSPC) (Fig. 3).[9-11] Clinicians would generally expect the reverse: that the effect observed in a trial would be degraded when put into practice — reflecting the distinction between efficacy and effectiveness. Furthermore, two other randomized trials have shown that for most men with prostate cancer detected on PSA screening, the reduced risk of death associated with prostatectomy or radiation is, at best, minimal (not statistically significant), and it requires more than a decade to appear.[12,13] But prostate cancer mortality began to fall soon after the initiation of PSA screening. What could explain these findings?

Some other element of prostate cancer treatment must have improved. We believe that just as in breast cancer, adjuvant hormonal therapy is a central part of the story. The introduction of luteinizing hormone–releasing hormone (LHRH) agonists in the 1990s resulted in urologists routinely treating men with locally advanced, clinically significant prostate cancer (undoubtedly aided by generous reimbursement for LHRH injections[14]). A recent meta-analysis of randomized trials concluded that adjuvant hormonal therapy is associated with a 30% reduction in prostate cancer mortality.[15]

Figure 3 includes another metric of cancer burden, the incidence of metastatic disease, which has also decreased more in practice than in the ERSPC. Patients counted as having inci-

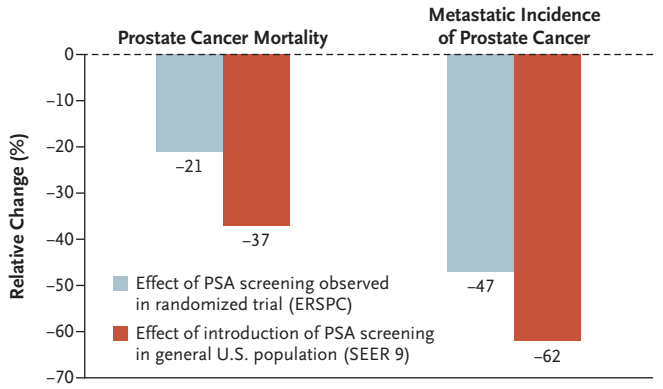

Figure 3. Relative Change in Two Metrics of Disease Burden in a Trial as Compared with Practice.

Observations are from two settings: the European Randomized Study of Screening for Prostate Cancer (ERSPC; intervention vs. control), and the general population in the United States after the introduction of PSA screening. The change in mortality in the U.S. population was measured from the 1950–1970 baseline (30 per 100,000 men), and the change in metastatic incidence was measured from the late-1980s baseline (28 per 100,000 men).

dent metastatic prostate cancer include only those who are found to have metastases (generally bone lesions on plain-film or bone scans, or lymph nodes on computed tomography) when they are first diagnosed with prostate cancer. Thus, this metric is not affected by treatment but instead reflects changes in the diagnostic process. Decreasing incidence of metastases (or late-stage cancer in general) is evidence that cancers destined to cause death are being diagnosed earlier. A decrease in cases presenting at a late stage is one prerequisite for screening to reduce cancer mortality. The other is that earlier treatment must confer an advantage over treatment initiated later in the course of the disease.

The introduction of PSA screening was associated with a remarkable decline in the incidence of metastatic prostate cancer — from about 28 per 100,000 men to 11 per 100,000 men. In contrast, the introduction of screening mammography produced no decline in the incidence of metastatic breast cancer.[16] But why has the decline been greater in practice than it was in the trial? A likely explanation is the frequency of PSA screening. In the European trial, screening was conducted every 2 to 4 years; in the United States, screening is typically conducted annually.

Another metric in Figure 2 also illustrates the effect of changes in the diagnostic process: a declining incidence of prostate cancer among the oldest men. Among men 75 years of age or older, prostate cancer incidence is now half that observed in 1975. This finding suggests that some of the additional cancer detection in younger men translated into fewer cancers appearing in older men — providing evidence that some cancers destined to appear later in life were, in fact, found earlier. This compensatory decline is not seen in breast cancer.[17]

PSA screening caused an absolute decrease in metastatic incidence of 17 per 100,000 men — a reduction that exceeds the absolute decrease in mortality from the 1950–1970 baseline (11 per 100,000 men). During the same period, published studies demonstrated the value of adjuvant hormonal therapy. Given these facts, we believe that prostate cancer mortality has decreased largely because PSA screening has identified men who were otherwise destined to present with metastatic prostate cancer who instead benefited from the early introduction of adjuvant hormonal therapy. In other words, the observed effectiveness of screening derives less from the provision of curative therapy to the many men found to have localized disease and more from medical management in the few discovered to have more aggressive disease.

WHY NOT TO SCREEN

So why not advocate for PSA screening? Unfortunately, the decrease in prostate cancer mortality has been achieved at enormous human cost: incidence soared to over 200 per 100,000, and more than a million men were diagnosed with a clinically insignificant "cancer" and received treatment for pathologic findings not destined to cause symptoms or death.[18] PSA screening represents a textbook case of overdiagnosis and overtreatment in medical care. On that basis alone, we believe that the U.S. Preventive Services Task Force was right not to recommend it.

Furthermore, decreasing prostate cancer mortality may be a misleading metric in evaluating PSA screening. A reduction in cancer-specific mortality does not reliably translate into increased longevity, which requires a reduction in all-cause mortality. This problem was highlighted in the 30-year follow-up of arguably the

most influential randomized trial of colorectal cancer screening: the Minnesota Colon Cancer Control Study.[19] The curves illustrating cumulative colorectal cancer mortality showed a clear advantage for annual fecal occult blood screening, which resulted in a 33% relative reduction (or a 1% absolute reduction) in cancer-specific mortality. Nevertheless, there was no change in all-cause mortality — the curves illustrating cumulative all-cause mortality were perfectly superimposed over the entire 30-year period (see figure at NEJM.org).

In other words, screening may more easily change the distribution of causes of death (trading off one cause for another) than extend life (as implied by promises to "save lives"). This issue is particularly relevant to PSA screening, since the median age at death due to prostate cancer is so high — 80 years (as compared with 72 for lung cancer and 68 for breast cancer).[20] For the elderly, the combination of a high burden of competing risks for death and high rates of intervention-related complications conspires to limit any reduction in all-cause mortality offered by screening.[21]

Of course, length of life is not the only relevant outcome; quality of life is equally important. If screening helped avert the pain that can be associated with metastatic disease, that would change the calculus, but it is not clear that it often does. Furthermore, the quality-of-life question has two sides. Prostate cancer treatment itself results in substantial morbidity: surgery and radiation can produce impotence and bowel and bladder problems; antiandrogen therapy leads to hot flashes, decreased stamina, and metabolic syndrome. Which group of men — the treated or the untreated — feels a bigger effect on quality of life can be debated.

There are also important externalities germane to screening. Screening programs necessarily recruit many people to potentially help a few. Screening efforts may distract primary care providers from more important issues: patients' current problems, as well as health promotion efforts affecting broader determinants of health. Another externality raises medicolegal concerns: efforts to promote screening typically feature blanket statements about the value of early detection — ironically opening the door to litigation over "missing" early prostate cancer.

On balance, we would continue to argue against contemporary PSA screening, particularly in light of our volume-driven health care system. But we acknowledge that our position reflects a value judgment. A few people receive a substantial benefit (avoiding death from prostate cancer), while many more are exposed to needless biopsies, operations, and another source of financial stress. We have no common metric for comparing these benefits and harms — they are like apples and oranges. Thus, there is no calculus or decision model that can produce a single "right" answer.

IF YOU'RE GOING TO SCREEN ANYWAY

We believe that providers who arrive at the opposite value judgment and support PSA screening must offer patients a better deal by protecting them from overdiagnosis and overtreatment. Doing so requires an incidence target — a "not to exceed" incidence benchmark. Currently, prostate cancer incidence is about where it was in 1975: roughly 100 per 100,000. That should be the incidence target.

Meeting this target while screening will require a higher test threshold for biopsy.[22] The conventional PSA threshold of 4 ng per milliliter was chosen to maximize cancer detection. We believe that this threshold is too low, identifying far too many men with low-grade, clinically insignificant disease. A higher biopsy threshold would not only reduce overdiagnosis, it would also reduce the number of biopsies and their associated harms.

For generalists, this approach simply requires a higher PSA threshold for referral to urology (and thus biopsy): say, 10 ng per milliliter. Of course, it's not perfect — it will undoubtedly miss some men with clinically significant disease. But it is simple and easy to remember. Furthermore, the PSA-value distributions from the National Health and Nutrition Examination Survey indicate that this threshold produces a group requiring biopsy that is approximately the same size as the group of men expected to die from prostate cancer in the next 10 years.[23]

Specialists would have to use a more precise — and more complex — approach. Rather than reacting to an isolated PSA value, urologists would make use of the diagnostic value of time.

PSA values rise with age; the key question is how much and whether the increase is linear or exponential. Thresholds for biopsy would be both time-dependent and age-specific — resulting in a complex algorithm that should be hard-wired into the test (e.g., the physician orders a PSA test, the lab determines whether there's been enough of a rise to warrant biopsy, given the patient's prior PSA values and age). Further refinements are possible, such as performing more complex PSA testing (e.g., free PSA), adjusting for prostate volume, and restricting biopsies to lesions visible on magnetic resonance imaging.

The goal would be a screening strategy that minimally affects current prostate cancer incidence while still identifying clinically significant disease at an earlier stage. Both the generalist and the specialist approaches would probably need to be fine-tuned to meet the incidence target. Such adjustment would require an organized screening program that could systematically implement the strategy, gather contemporaneous data on the number of people affected (screen positives and diagnoses), and react accordingly.

Ideally, the effectiveness of any screening strategy would be informed by randomized trials. But screening trials require heroic effort: tens of thousands of men need to be followed for a decade or more, since the primary outcome, death from prostate cancer, is so rare and the effect being sought is so small. Furthermore, the potential number of options to test is limitless — even a generalist's approach could test myriad PSA thresholds.

From our mistakes with PSA screening, clinicians have learned about issues that are relevant to all cancer-screening efforts. We have learned that the conventional goal of screening — to maximize cancer detection — is wrong. The appropriate goal is more complex: identify the few cancers that matter, while not disturbing the rest of the population. Fortunately, the population signals are now positive: prostate cancer mortality has declined substantially, as has the number of men diagnosed with the disease. We will never have perfect data on the effectiveness of various screening approaches in reducing cancer-specific mortality — the trials required are too big and take too long. What we can have, however, is feedback on how many people are adversely affected by our actions.

Disclosure forms provided by the authors are available at NEJM.org.

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