Prostate Cancer Diagnosis and Treatment After the Introduction of Prostate-Specific Antigen Screening: 1986–2005

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Background Although there is uncertainty about the effect of prostate-specific antigen (PSA) screening on the rate of prostate cancer death, there is little uncertainty about its effect on the rate of prostate cancer diagnosis. Systematic estimates of the number of men affected, however, to our knowledge, do not exist.

Methods We obtained data on age-specific incidence and initial course of therapy from the National Cancer Institute's Surveillance, Epidemiology, and End Results program. We then used age-specific male population estimates from the US Census to determine the excess (or deficit) in the number of men diagnosed and treated in each year after 1986—the year before PSA screening was introduced.

Results Overall incidence of prostate cancer rose rapidly after 1986, peaked in 1992, and then declined, albeit to levels considerably higher than those in 1986. Overall incidence, however, obscured distinct age-specific patterns: The relative incidence rate (2005 relative to 1986) was 0.56 in men aged 80 years and older, 1.09 in men aged 70–79 years, 1.91 in men aged 60–69 years, 3.64 in men aged 50–59 years, and 7.23 in men younger than 50 years. Since 1986, an estimated additional 1 305 600 men were diagnosed with prostate cancer, 1 004 800 of whom were definitively treated for the disease. Using the most optimistic assumption about the benefit of screening—that the entire decline in prostate cancer mortality observed during this period is attributable to this additional diagnosis—we estimated that, for each man who experienced the presumed benefit, more than 20 had to be diagnosed with prostate cancer.

Conclusions The introduction of PSA screening has resulted in more than 1 million additional men being diagnosed and treated for prostate cancer in the United States. The growth is particularly dramatic for younger men. Given the considerable time that has passed since PSA screening began, most of this excess incidence must represent overdiagnosis.

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If all cancers detected early were destined to become clinically evident, the number of individuals diagnosed with cancer would be unaffected by screening. Although some cancers would be detected earlier in time, the number of such cancers would be offset by reductions in those detected later (if we assume that the underlying incidence is constant). However, in practice, early detection efforts have been associated with dramatic rises in incidence—raising the specter of overdiagnosis: the detection of cancers that never progress to cause symptoms or death. Overdiagnosis has now been associated with early diagnosis in a variety cancers, including neuroblastoma (1,2); melanoma (3); and thyroid (4), breast (5–8), and lung (9,10) cancers. These data suggest that some degree of overdiagnosis in cancer screening is probably the rule, not the exception.

Nowhere is overdiagnosis more clinically relevant than in the early detection of prostate cancer (11). In fact, it was the recognition of overdiagnosis that led the US Preventive Services Task Force recently to recommend against prostate-specific antigen (PSA) screening in men aged 75 years or older (12). In addition, both of the recently published randomized trials of screening (13,14) observed a dramatic excess incidence in the screened group relative to control subjects—making it clear that a substantial number of men are at risk to be overdiagnosed.

Although many investigators are using advanced statistical techniques to model the population impact of screening (15), we know of no systematic effort to estimate the number of additional men diagnosed and treated for the disease in the United States since the introduction of PSA screening in the late 1980s. Although excess incidence is only a proxy for overdiagnosis—because some of the excess may simply reflect the lead time of diagnosis—the

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CONTEXT AND CAVEATS

Prior knowledge

Prostate cancer screening has led to an increase in diagnosis of the disease.

Study design

Age-specific prostate cancer incidence and treatment data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program and age-specific population estimates from the US Census were used to estimate the excess number of men diagnosed and treated each year after the introduction of prostate-specific antigen screening in 1986 through 2005.

Contributions

Since 1986, an additional estimated 1.3 million men were diagnosed and more than 1 million were treated.

Implications

Prostate cancer incidence has increased since the introduction of prostate-specific antigen screening. Much of the excess incidence may represent overdiagnosis.

Limitations

The effect of transurethral resection of the prostate on prostate cancer incidence, which maximally increased it in 1986, was not adjusted for in the estimates; thus, the estimates of increased incidence with prostate-specific antigen screening are underestimates. Assumptions about effect of prostate cancer screening on mortality may be exaggerated based on data from screening trials.

From the Editors

two measures become increasingly equivalent with the passage of time. In this study, we analyze age-specific incidence trends during the last 20 years to quantify the impact of overdiagnosis.

Patients and Methods

Overview

To calculate the number of additional men who were diagnosed with prostate cancer after the introduction of PSA screening, we used the following steps: 1) select a base year immediately before screening, 2) calculate excess incidence in subsequent years relative to the base year, and 3) transform data on excess incidence to data on nationwide counts. We obtained our data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, which provides more than 30 years of incidence data for the SEER nine areas (based on a population of roughly 30 million in 2000) (16), and the US Census, which provides detailed population estimates for the same years (17).

Choice of Base Year

We chose 1986 as our base year. This was the year immediately before the publication of a seminal article on PSA as a serum marker for adenocarcinoma of the prostate (18)—an article that has been subsequently cited more than a thousand times (19). This was also the year immediately before a more than 10% increase in annual prostate cancer incidence—a magnitude of increase never before observed for prostate cancer in the SEER program and a magnitude that strongly suggests the onset of screening.

Calculation of Excess Incidence

We then calculated the excess (or for elderly men, the deficit) incidence reported to SEER in the ensuing 19 years (1987–2005) relative to the base year of 1986. This calculation involved subtracting the incidence in later years from that reported in 1986 (we also report ratios). To determine whether distinctive age trends existed, we first examined incidence in nine distinct age groups. To simplify our presentation, we then collapsed adjoining age groups with similar incidence patterns to create five age strata: 20–49 years, 50–59 years, 60–69 years, 70–79 years, and 80 years or older. Thus, we calculated 95 year-specific and age-specific excess incidence rates (19 years × 5 age groups).

Transform Excess Incidence to Counts

To calculate the number of additional diagnoses relative to that in 1986, the base year, we needed to determine the size of the male population for each year and within each age group (again, 95 year-specific and age-specific population counts). For this calculation, we obtained year- and age-specific data from the US Census. We then multiplied the year- and age-specific excess (or deficit) incidence to the year- and age-specific population. Finally, we summed these across years and age groups.

Additional Treatment

We also obtained SEER data on the initial course of therapy (reflecting approximately 350 000 prostate cancer patients) for each of the 95 year-specific and age-specific categories. We specifically sought the proportion of patients in each category who received surgery (ie, prostatectomy, excluding transurethral procedures) and radiation (any form). We also determined the proportion who received either surgery or radiation, which is slightly less than the sum of the two proportions because a few patients underwent both. For each category, we multiplied the proportion who received either surgery or radiation by the number of additional diagnoses to calculate the number of additional men treated for prostate cancer.

Extreme Mortality Assumption

Finally, we estimated the potential benefit of this additional diagnosis under the most optimistic assumption possible—namely, that the entire decline in prostate cancer mortality observed during this period is attributable to screening. First, we obtained the observed number of prostate cancer deaths in each year from US Vital Statistics. Second, we calculated the number of deaths expected in each year given the mortality rate observed in 1986. Given our interest in making the assumption as optimistic as possible, we exclude those years in which the expected number of deaths was less than that observed (ie, 1987–1996, when mortality was actually higher than that in 1986). Finally, we subtracted the number of deaths observed from the number of deaths expected to estimate the number of deaths avoided.

Results

Overall prostate cancer incidence rose rapidly after 1986, at about 12% per year, until it peaked in 1992 (at 237.2 per 100 000 men). Incidence then rapidly declined for a 3-year period (at about 10% per year). In subsequent years (1995–2005), incidence has appeared

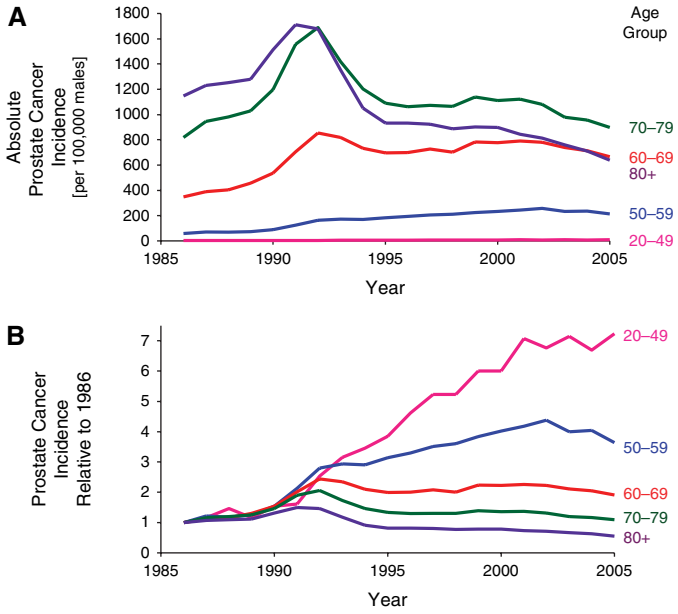

Figure 1. Age-specific trends in prostate cancer incidence in the period 1986–2005. **A**) Absolute incidence rates. **B**) Incidence rates relative to 1986.

to stabilize, albeit at levels considerably higher than those in 1986. During the entire period of 1986–2005, prostate cancer incidence rose 26% (from 119 to 150.5 per 100 000).

This temporal pattern in overall incidence, however, obscured distinct age-specific trends (Figure 1). For men aged 80 years or older, incidence declined dramatically between 1986 and 2005: from 1146.5 to 637.4 per 100 000 (relative rate [RR] 2005 to 1986, RR = 0.56, 95% confidence interval [CI] = 0.53 to 0.60). For men aged 70–79 years, there was little net change: from 819.2 to 896.8 per 100 000 (RR = 1.09, 95% CI = 1.05 to 1.14). For younger men, incidence increased dramatically: almost doubling for those aged 60–69 years, from 349.4 to 666.9 per 100 000 (RR = 1.91, 95% CI = 1.8 to 2.0); more than tripling for those aged 50–59 years, from 58.4 to 212.7 per 100 000 (RR = 3.64, 95% CI = 3.3 to 4.0); and by more than sevenfold for those younger than 50 years, from 1.3 to 9.4 per 100 000 (RR = 7.23, 95% CI = 6.4 to 8.2).

To illustrate the excess (or for men aged 80 years or older, the deficit) in the number of men who were diagnosed with prostate cancer each year from 1987 to 2005 (relative to that expected had nothing changed since 1986), incidence data and data on the size of the relevant population were combined (Figure 2). When these

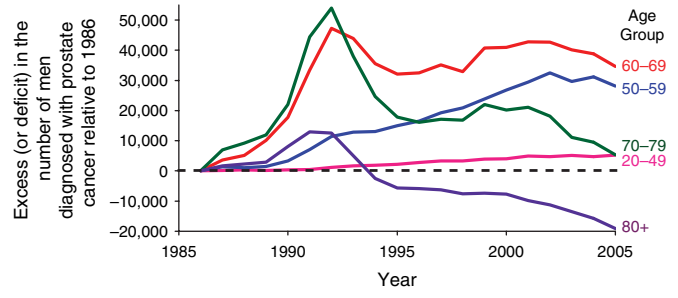

Figure 2. Excess (or deficit) in the number of men diagnosed with prostate cancer relative to 1986.

Table 1. Number of additional men diagnosed and treated for prostate cancer since the start of prostate-specific antigen screening*

Age group, y	No. of additional men diagnosed	No. of additional men treated		
		Surgery	Radiation	Either or both
20–49	50 500	33 800	10 700	42 200
50–59	325 100	194 400	90 800	273 000
60–69	610 100	273 900	221 300	475 200
70–79	386 600	69 700	167 100	227 500
≥80	−66 700	−700	−12 500	−13 200
Total	1 305 600	571 000	477 400	1 004 800

* In the years following 1986 through 2005. Numbers may not add precisely because of rounding.

data were summarized across all years (the area under the curves) (Table 1), we found that, although there was a net deficit in the oldest men (≥80 years; approximately 66 700 men), it was overwhelmed by the excess in other age groups. Combining all age groups, we estimated that an additional 1 305 600 men have been diagnosed with prostate cancer since 1986.

The age-specific treatment patterns over time have changed little (Figure 3)—a little less use of surgery and a little more use of radiation. Combining all age groups, we estimate that an additional 1 004 800 men have been definitively treated for prostate cancer since 1986 (Table 1).

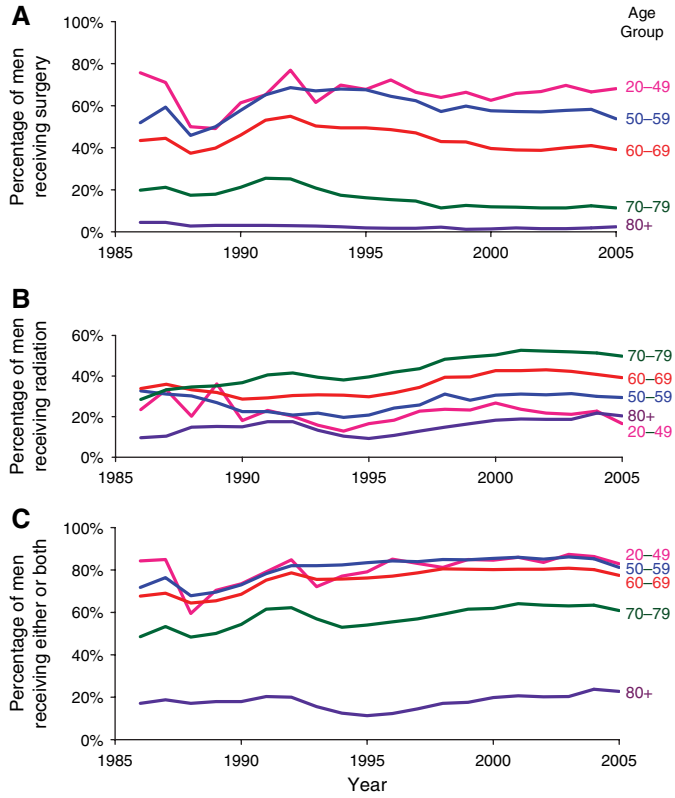

Figure 3. Age-specific trends in the proportion of men receiving definitive treatment for prostate cancer in the period 1986–2005. **A**) Men who received surgery. **B**) Men who received radiation therapy. **C**) Men who received surgery, radiation therapy, or both types of treatment.

Using the most optimistic assumption about the benefit of this additional diagnoses and treatment—namely, that the entire decline in prostate cancer mortality observed during this period is attributable to screening—we estimate that approximately 56 500 prostate cancer deaths have been averted and that approximately 23 men had to be diagnosed and approximately 18 treated for each man experiencing the presumed benefit.

Discussion

In this analysis of US incidence trends during the last 20 years, we estimated that more than a million additional men have been diagnosed and treated for prostate cancer because of introduction of PSA screening. The increase in diagnosis and treatment associated with screening has been most dramatic among men younger than 50 years.

It is important to acknowledge that there can be two sides to screening—it may result in both a cancer-specific mortality reduction and an overdiagnosis. But even using the most optimistic assumption about benefit, the vast majority of these additional 1 million men did not benefit from early detection.

There are a number of methodological concerns that could be raised about our study. First, some might question the choice of 1986 as the base year. It is true that the first "clinical trial" indexed in MEDLINE examining PSA as a screening test did not appear until 1991 (20), but we did not choose 1990 as the base year for several reasons. The report of the 1991 trial is actually cited less often than the 1987 article (21). More importantly, choosing 1990 would miss an 18% incidence increase between 1989 and 1990—an increase undoubtedly related to the initiation of Prostate Cancer Awareness Week, which recruited asymptomatic men to have prostate screening examinations that used PSA testing (22).

Second, others might raise the concern that the underlying (or "true") incidence of prostate cancer is increasing and that it is incorrect to attribute the entire increase since 1986 to PSA screening. In fact, prostate cancer incidence was slowly increasing (approximately 2% per year) during the decade before 1986. Virtually, all of this increase, however, was explained by the growth of incidentally detected prostate cancers associated with the increased use of transurethral resection of the prostate before 1986 (23). Transurethral resection of the prostate-detected cancers actually represented half of all prostate cancers diagnosed in 1986, but then fell off dramatically as the use of the procedure declined (ie, a 50% drop in the rate of transurethral resection of the prostate-detected cancer from 1986 to 1993) (20,24). In other words, in the absence of PSA screening, prostate cancer incidence would have declined after 1986. Because we used 1986 as our base year and because 1986 represents the maximal effect of transurethral resection of the prostate on prostate cancer incidence, our estimates of the effect of PSA screening represent underestimates.

Third, the estimate of the number of additional men treated was based on the assumption that the treatment patterns observed in the general population are the same as for those who were additionally diagnosed. This estimate would be an overestimate if the men who were additionally diagnosed were less likely to receive treatment than those in the general population; it would be an underestimate if they were more likely to receive treatment. The latter seems more probable, given that the additionally diagnosed men must have been screened and that men who are screened are more likely to be healthy and, thus, more likely to undergo surgery or radiation.

Finally, many might point out that our assumptions about the effect of screening on prostate cancer mortality are grossly exaggerated. And they would be correct—it is inappropriate to assume that the entire decline in mortality is the direct result of advancing the time of treatment (early detection) and that none of it is because of advances in treatment itself. Some of the mortality decline is the result of treatment improvements, such as the early initiation of antiandrogen therapies, improved radiation protocols, or chemotherapy. Furthermore, the recent randomized trials of PSA screening have reported mixed effects of screening on mortality—the European finding was favorable (14) and the Prostate, Lung, Colon, Ovary finding was unfavorable (13). These results make it highly unlikely that PSA screening could have the mortality effect that we assumed in this analysis.

Estimating the trade-off between a mortality benefit and an overdiagnosis is problematic when there is uncertainty about whether the benefit exists at all. Our approximation of about one death averted to 20 men overdiagnosed was simply intended to provide an upper-bound estimate. A more plausible estimate would assume the mortality benefit observed in the European trial (14) and its earlier reported estimate that 48% of patients diagnosed in the screened group had been overdiagnosed (25). When we applied this estimate to the overall prostate cancer incidence in the screened group (82 per 1000 men), we obtained an overdiagnosis incidence of 39 per 1000. Given the European trial report that 1410 men need to be screened to avoid one death (25), this translates into a trade-off of approximately one death averted to 50 men overdiagnosed with prostate cancer (=1410 × 39/1000). Because the true mortality benefit approaches zero, the estimate for the trade-off approaches 1 to infinity.

Although no single formula can determine the correct course of action when facing this trade-off, it is important that we begin to explicitly communicate to men who are considering screening the relative magnitude of number of deaths averted to the number overdiagnosed. And regardless of the estimate used—whether it is one death to 20 men being overdiagnosed, one to 50, or one to infinity—it is equally important to make clear the harms of overdiagnosis. The primary harm of overdiagnosis is unneeded treatment. Overdiagnosed patients cannot benefit from treatment because their disease is not destined to progress to cause symptoms or death. Prostate cancer treatment has known risks, including impotence, incontinence, and even death for surgery; and impotence, urgency, painful defecation, and radiation enteritis (26) for radiation. All overdiagnosed patients are needlessly exposed to the hassle factors of obtaining treatment, the financial implications of the diagnosis, and the anxieties associated with becoming a cancer patient—consequences that, by our estimate, have occurred among more than a million American men since the initiation of PSA screening.

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