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Abstract

Background: The advent of PSA testing in the late 1980s substantially increased prostate cancer incidence rates. Concerns about overscreening and overdiagnosis subsequently led professional guidelines (circa 2000 and later) to recommend against routine PSA testing. We evaluated trends in prostate cancer incidence, including late-stage diagnoses, from 1995 through 2012.

Methods: We used joinpoint regression analyses to evaluate all-, localized/regional-, and distant-stage prostate cancer incidence trends based on Surveillance, Epidemiology, and End Results (SEER) data. We stratified analyses by age (50–69, 70+). We reported incidence trends as annual percent change (APC).

Results: Overall age-adjusted incidence rates for localized/regional stage prostate cancer have been declining since 2001, sharply from 2010 to 2012 [APC, −13.1; 95% confidence interval (CI), −23.5 to −1.3]. Distant-stage incidence rates have declined since 1995, with greater declines from 1995 to 1997 (APC, −8.4; 95% CI, −2.3 to −14.1) than from 2003 to 2012 (APC, −1.0; 95% CI, −1.7 to −0.4). Distant-stage incidence rates declined for men ages 70+ from 1995 to 2012, but increased in men ages 50 to 69 years from 2004 to 2012 (APC, 1.7; 95% CI, 0.2 to 3.2).

Conclusions: Guidelines discouraging routine prostate cancer screening were temporarily associated with declining localized/regional prostate cancer incidence rates; however, incidence rates of distant-stage disease are now increasing in younger men.

Impact: This trend may adversely affect prostate cancer mortality rates. Cancer Epidemiol Biomarkers Prev; 25(2): 259–63. ©2015 AACR.

Introduction

In the early 1990s, the American Urological Association (AUA) and the American Cancer Society (ACS) began recommending routine annual prostate cancer screening with PSA (1, 2). Although these recommendations were not supported by clinical trial evidence, the resultant increase in screening led to a substantial rise in prostate cancer incidence. By 1992, the U.S. age-adjusted prostate cancer incidence rate reached 237.4 per 100,000, nearly double the rate in 1986 when PSA was first approved (3). Incidence rates subsequently dropped, though remaining substantially higher than before the PSA era.

By 2000, given concerns about the potential harms of overdiagnosis and overtreatment, revised ACS (4) and AUA (5) guidelines were recommending against routine screening, advising providers instead to support informed decision making. In 2008, the U.S. Preventive Services Task Force (USPSTF) recommended against screening men older than age 75 years (6). The major screening trials, European Randomized Study of Screening for Prostate Cancer (7) and Prostate, Lung, Colorectal, and Ovarian Cancer Screening trial (8) first published cancer survival data in 2009. The ERSPC reported a modest prostate cancer survival benefit with screening, whereas the PLCO found no benefit. Subsequent guidelines issued by the ACS in 2010 (9) and the AUA in 2013 (10) again affirmed the importance of informed decision making. Meanwhile, in October 2011 the USPSTF issued a draft document recommending against any PSA-based screening for prostate cancer (11), a position endorsed by the final guideline published in July 2012 (12).

Numerous studies have evaluated the temporal associations of publishing screening guidelines and clinical trial results on screening practices and attitudes (13–23). However, most studies focused on the impact of the 2008 USPSTF guidelines. Moreover, we found only one study that comprehensively evaluated stage-specific cancer incidence trends, but data were available only through 2007 (24). Therefore, we used the most recent (April 23, 2015) NCI SEER program data to evaluate age- and stage-specific trends in prostate cancer incidence from 1995 through 2012 (3).

Materials and Methods

Our study was based on incident cases of prostate cancer diagnosed among residents of 13 geographic areas covered by the SEER program. We identified eligible cases by using International Classification of Diseases for Oncology (ICDO-3) topography code C61.9 (prostate) and ICDO-3 behavior code 3 (malignant). We excluded lymphomas (ICDO-3 morphology codes 9590–9989), Kaposi sarcomas (ICDO-3 morphology code 9140), and mesotheliomas (ICDO-3 morphology codes 9050–9055), along with benign and in situ prostate tumors. We
calculated average annual age-adjusted incidence rates by the direct method and standardized them to the age distribution of the projected 2000 United States population. We also calculated average annual age-adjusted incidence rates by stage. The SEER program classifies stage as localized/regional (defined as confined to the prostate/extraprostatic extension into surrounding tissue ± regional lymph node involvement), and distant (defined as invasion to distant organs or distant lymph nodes). We used the SEER Historic A staging to ensure comparability over time. We excluded cancers of unknown stage from trend analyses. We further stratified results by age group (50–69, 70 and older) because screening guidelines now recommend offering screening only to men ages 50 to 69 years (9, 10). We excluded men younger than 50 years because guidelines did not recommend routine screening for this age group and sample sizes were too small to perform longitudinal analyses. We used the NCI’s SEERStat software to calculate incidence rates (25). We analyzed data from 1995 to 2012, the period covered by the SEER Historic A composite stage variable for prostate cancer.

We used joinpoint analyses to assess temporal trends in annual age-adjusted and age-specific incidence rates for all-stage, localized/regional, and distant-stage prostate cancers (26, 27). The joinpoint software fits the simplest model to describe the incidence rate trend data, starting with a straight line (0 joinpoints) and then adding more joinpoints to determine whether multiple connecting lines better describe the data points. The software identifies the year(s) when the annual percent change (APC) trends appear to shift upward or downward and whether these trends are statistically significant. In describing trends, we use the terms increased or decreased only when the slope (APC) was statistically significant (two-sided P value < 0.05). Figure 1 shows joinpoint curves plotted on a logarithmic scale. We used this scale to better display incidence rates for both localized/regional and distant-stage cancer on the same graph because there is a nearly 2 order-of-magnitude difference between the stage-specific rates. The University of New Mexico Human Research Review Committee classified this study as exempt research.

Results

Age-adjusted localized/regional-stage prostate cancer incidence rates increased from 1995 to 2001; rates gradually declined from 2001 to 2010 before sharply declining from 2010 to 2012 (Table 1). The age-adjusted incidence trends for localized/regional cancers closely track with all-stage age-adjusted incidence trends. The incidence rate of distant-stage disease declined sharply from 1995 to 1997, and then declined more gradually from 1997 to 2012.

Among men ages 50 to 69 years, localized/regional stage incidence rates were stable from 1995 to 2010 before sharply declining from 2010 to 2012 (Fig. 1). Localized/regional-stage incidence rates were stable from 1995 to 2000 for men ages 70 years and older; rates declined from 2000 to 2012 with a steeper decline from 2007 to 2012 (Fig. 1). The age-specific incidence trends for localized/regional cancers closely track with all-stage age-specific incidence trends (data not shown).

Among men ages 50 to 69 years, the incidence rate for distant-stage disease declined from 1995 to 2004, but increased from 2004 to 2012. Rates for distant-stage disease among men ages 70 years and older declined from 1995 to 2012, though more gradually from 2001 to 2012.

Discussion

Using SEER population-based cancer data from 1995 through 2012, we found declining all-stage and localized/regional, age-adjusted incidence rates for prostate cancer since 2001 that were temporally associated with ACS and AUA recommendations against routine screening issued around 2000 (4, 5). Age-adjusted incidence rates of distant-stage prostate cancer have also declined since 1995, a time period when prostate cancer mortality rates were significantly declining across all age groups. (3) Age-specific all-stage incidence rates have been steadily decreasing among older men since 2000, a trend consistent with recommendations against screening men with limited life expectancy. Rates have declined only recently among younger men, which could reflect the October 2011 release of the draft USPSTF D rating against screening (28).

Incidence rates of distant-stage prostate cancer were consistently higher for older than younger men. Furthermore, the temporal patterns differed by age. Incidence rates declined throughout the study period for older men, though the rate of decline was less steep after 2001. Among young men, rates declined from 1995 to 2004, but then gradually increased from 2004 to 2012. Several factors could be affecting our observations. Younger men tend to have more aggressive cancers so a decline in screening might more quickly impact them (29). In addition, we may be seeing a lag-time effect where a cancer developing in a man in his late 60s that was not detected by screening could present clinically at a distant stage when the man was 70 years and older. This suggests that the rate of distant-stage disease might not continue to decline in older men.

The initial recommendations for routine prostate cancer screening in the early 1990s by the AUA and ACS clearly influenced clinical practice because they were associated with a dramatic increase in the incidence of prostate cancer, particularly early-stage cancers (1–3). The 2000 National Health Interview Survey (NHIS) found that 57% of men ages 50 years and older reported ever screening, including 34% within the past year (30). The 2001 Behavioral Risk Factor Surveillance System survey found even higher screening percentages; 75% of men ages 50 years and older reported ever PSA testing, including 57% within the past year (31).

However, determining the effects of subsequent recommendations on screening practice is challenging. Most studies have focused on the 2008 USPSTF recommendation against screening men over age 75 years and findings were inconsistent. NHIS data showed no change in screening among older men between the 2005 (43%) and 2010 (44%) surveys (32). Similarly, an analysis of the CDC's Behavioral Risk Factor Surveillance System data showed no changes in PSA testing among older men, with rates of 60% in 2006, 63% in 2008, and 60% in 2010 (20). A limitation of these data is that screening is self-reported by participants. In contrast, screening data captured by the SEER Medicare files did show a significant, though small, decline between Spring 2008 (29.4%) and Fall 2009 (27.8%), with a slight increase in screening among men ages 66 to 74 years (19). Investigators using data from the Medicare Current Beneficiary Survey Access to Care files estimated that the 2008 USPSTF recommendation was associated with a 5.3 percentage point decline in annual PSA testing rate among men ages 75 years and older, from about 47% to 42% (17).

We found only one study that evaluated the national impact of the 2012 USPSTF recommendation on prostate cancer screening...
Between 2010 and 2013, NHIS data showed significant declines in self-reported PSA screening for men ages 50 to 59 years (from 33.2% to 24.8%), men ages 60 to 74 (from 51.2% to 43.6%), and men ages 75 and older (from 43.9% to 37.1%). Several practice-level studies also reported declines in PSA testing by the end of 2012 (13, 14).

The impact of these screening trends on clinical outcomes is uncertain. One early signal that PSA screening might be effective was the decline in the incidence of distant stage cancer by 1995 (34). Therefore, an early indicator that less screening, and resultant decrease in prostate cancer incidence, might be harmful would be an increase in the incidence rate of distant-stage disease. Howard and colleagues, using SEER data, did not observe such an increase immediately following the 2008 USPSTF guidelines; between 2007 to 2009, adjusted overall incidence rate for men 75+ significantly decreased by 25.4%, while the adjusted incidence rate of late stage tumors decreased by 14.3% (16). In extending follow-up through 2012, we found continued declines in the incidence of distant-stage disease among older men, though with a less negative slope. However, we also observed a gradually increasing incidence of distant-stage disease among men 50 to 69 years old from 2004 to 2012.

Other studies have attempted to hone in on the short-term consequences of the USPSTF draft guidelines using more surrogate clinical endpoints. A single-center Canadian study showed a sharp decline in biopsy referrals and the absolute number of cancer diagnoses, including those with high-grade disease, beginning in May 2012 (28). Investigators attributed their findings to decreased screening in response to the USPSTF guideline. Another recent publication looking at incident prostate cancer cases in the National Cancer Data Base diagnosed from January 2010 through December 2012 found a 12.2% percent drop in incident cases in the month following the draft guideline and a 28% decline in the rate of late stage disease.

![Figure 1](image_url)

**Figure 1.** Joinpoint analyses of prostate cancer age-specific incidence rates by stage at diagnosis, 1995–2012, plotted on a logarithmic scale. Localized/regional stage: ■ 50–69 years, ● 70 + years; Distant stage: □ 50–69 years, ○ 70 + years. Trend 1, Trend 2, Trend 3. APC is statistically different from zero at P < 0.05.

### Table 1. Trends in U.S. prostate cancer age-adjusted incidence rates (2000 U.S. standard population) by stage at diagnosis; ages 50 years and older, 1995–2012

<table>
<thead>
<tr>
<th>Stage</th>
<th>Trend 1 Years</th>
<th>APC (95% CI)</th>
<th>Trend 2 Years</th>
<th>APC (95% CI)</th>
<th>Trend 3 Years</th>
<th>APC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1995–2000</td>
<td>1.7 (−0.9 to 4.3)</td>
<td>2000–2007</td>
<td>−2.0 (−3.0 to −1.1)*</td>
<td>2010–2012</td>
<td>−12.5 (−21.9 to −2.1)*</td>
</tr>
<tr>
<td>Localized/regional</td>
<td>1995–2001</td>
<td>2.6 (0.4 to 4.9)*</td>
<td>2000–2010</td>
<td>−2.5 (−3.7 to −1.2)*</td>
<td>2010–2012</td>
<td>−13.1 (−23.5 to −3.3)*</td>
</tr>
<tr>
<td>Distant</td>
<td>1995–1997</td>
<td>−8.4 (−14.1 to −2.3)*</td>
<td>1997–2003</td>
<td>−4.0 (−5.5 to −2.4)*</td>
<td>2003–2012</td>
<td>−1.0 (−1.7 to −0.4)*</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

*The APC is statistically different from zero at P < 0.05.
decline over the following year (35). Significant declines were observed for localized cancer diagnoses, including those with high-risk features, though new diagnoses of nonlocalized cancers did not change.

Our study has some important limitations. More time is needed to tell whether our findings signify a major shift in prostate cancer incidence. Before adding the 2012 data, the estimated increase in APC for distant-stage disease in younger men was not statistically significant. We do not know the screening history of men diagnosed with distant-stage prostate cancer so can note only an association between screening trends and incidence of distant-stage disease. However, with recent ACS and AUA guidelines both taking more cautious approaches to screening and the USPSTF advising against any screening, PSA testing might continue to decrease. Less screening will decrease the overall incidence of prostate cancer and reduce the risk of overdiagnosis. A concomitantly rising rate of distant disease among younger men could potentially increase prostate cancer mortality rates.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References
26. Jointpoint Regression Program. 3.5.2. October 2011; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute.


