Efficacy of Prostate-Specific Antigen Screening: Use of Regression Discontinuity in the PLCO Cancer Screening Trial

The Prostate Lung Colorectal and Ovarian (PLCO) cancer screening trial randomized 76,693 men from 1993 to 2001 to usual care or annual prostate-specific antigen (PSA) screening for 6 years and annual digital rectal examination for 4 years. This study found that PSA screening results in increased detection of prostate cancer but does not reduce prostate cancerspecific or overall mortality. The findings of the PLCO cancer screening trial are controversial largely because of a high rate of PSA screening in the control group, which reached 52% by the sixth year of the trial.1,2 Despite this shortcoming, the PLCO trial is likely to remain the only major trial of PSA screening in the United States.

We used regression discontinuity (RD), a statistical technique used in the social sciences but rarely applied to clinical data, to address the above criticism.3 This technique allows us to examine the effect of PSA screening on outcomes using only the screening arm of the PLCO trial.

Methods | The statistical basis of RD has been described previously.4 Regression discontinuity allows us to leverage that a PSA of 4.0 ng/mL was used as the threshold for further workup in the PLCO trial (to convert PSA to micrograms per liter, multiply by 1). In the absence of a treatment effect, the regression of PSA and a given outcome should be continuous around the PSA cutoff. However, if a biopsy based on PSA screening affects an outcome, we would expect to find a discontinuity in the regression around a PSA of 4.0 ng/mL. Since confounders should be evenly distributed right below and above this cutoff, RD allows us to isolate the effect of screening on outcomes.

We obtained the 13-year screening and outcome data from the PLCO trial. The control arm of the study was dropped from all analyses. We used a first-degree local polynomial approach with the Imbens and Kalyanaraman meansquaredeviation.5 Our results are not sensitive to this bandwidth choice. We used STA/TAC/n (StataCorp) for statistical analysis. An RD analysis code was generated, and we confirmed its accuracy using a Stata module for RD estimation.6 A waiver was obtained from the Office of Research Integrity at Weill Cornell Medical College; institutional review board review was not required as data was deidentified.

Results | The probability of a PLCO trial participant undergoing a biopsy as a function of the maximum PSA value from all tests increased at the 4.0 ng/mL PSA cutoff by 27.3% (95% CI, 23.3%–31.3%; P < 1 × 10−10) (Figure). This translates into a relative 445% increase in the biopsy rate for those with a PSA just above 4.0 ng/mL compared with those just below that cutoff.

At a PSA of 4.0 ng/mL, biopsy based on screening increased the absolute detection rate of low-risk (Gleason score ≤6) at clinical stage T1a or T2a prostate cancer by 7.2% (95% CI, 3.6%–10.8%; P = 8.5 × 10−4) (Figure and Table). There was no effect on the detection of intermediate-risk (Gleason score = 7 or clinical stage T2b) (P = .94) (Table) or high-risk (Gleason score ≥8 or clinical stage T2c–3a) (P = .98) (Figure and Table) prostate cancer.

Examining the pathology from those who underwent prostatectomy yields similar results. There was a discontinuity in the detection of cancers with a Gleason score of 6 or lower (5.6% [95% CI, 2.6%–8.7%]; P = < .001) and no discontinuity in the detection of scores of 7 (P = .52) or 8 to 10 (P = .56) (Table). We found no discontinuity in prostate cancer-specific mortality (P = .27) or overall mortality (P = .62) (Figure and Table).

Discussion | Using RD in the screening arm of the PLCO trial, we were able to effectively instrument for biopsy based on PSA screening. Despite excluding the control arm of the study, we...
Figure. Regression Discontinuity Analyses

Prostate cancer risk categories defined by D’Amico classification without prostate-specific antigen level. Graphs truncated at a maximum prostate-specific antigen of 15 ng/mL for ease of presentation (includes 99% of prostate-specific antigen levels).

Table. Discontinuity in Selected Outcomes at PSA of 4.0 ng/mL

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, No.</th>
<th>Effect Size (95% CI), %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undergo biopsy</td>
<td>4899</td>
<td>27.3 (23.3 to 31.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pretreatment cancer type b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>1891</td>
<td>7.2 (3.6 to 10.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>1239</td>
<td>0.1 (−2.9 to 3.2)</td>
<td>.94</td>
</tr>
<tr>
<td>High risk</td>
<td>544</td>
<td>0.0 (−1.8 to 1.9)</td>
<td>.98</td>
</tr>
<tr>
<td>Postprostatectomy Gleason score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>687</td>
<td>5.6 (2.6 to 8.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>7</td>
<td>671</td>
<td>0.9 (−1.9 to 3.7)</td>
<td>.52</td>
</tr>
<tr>
<td>8-10</td>
<td>157</td>
<td>−0.3 (−1.2 to 0.6)</td>
<td>.51</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate cancer specific</td>
<td>151</td>
<td>0.6 (−0.5 to 1.7)</td>
<td>.27</td>
</tr>
<tr>
<td>Overall</td>
<td>6362</td>
<td>−1.0 (−5.0 to 3.0)</td>
<td>.62</td>
</tr>
</tbody>
</table>

Abbreviation: PSA, prostate-specific antigen.

SI conversion factor: To convert PSA to micrograms per liter, multiply by 1.

a Change in probability at the threshold of 4.0 ng/mL PSA.

b Low pretreatment risk is indicated by Gleason score less than or equal to 6 and clinical stage T1 to T2a; intermediate, Gleason score of 7 or clinical stage T2b; high, Gleason score equal or higher than 8, or clinical stage T2c to T3a.
confirm the study results of the PLCO trial that biopsy at a PSA threshold of 4.0 ng/mL did not decrease prostate cancer–specific or overall mortality. For prostate cancer–specific mortality, the trend was toward increased mortality at the cutoff, which is opposite of what would be expected if there were a benefit to screening.

Interpreting clinical data using RD has many potential applications in medicine since treatment decisions are often based on discrete cutoffs in continuous data.3

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Conflict of Interest Disclosures: Dr Eisner works as a consultant for Percys, Boston Scientific, Olympus, Cook, Radius Pharmaceuticals, Bard. Dr Eisner is also an owner of Ravine Group. No other conflicts are reported.

Additional Information: We thank the National Cancer Institute for access to data collected by the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. The statements contained herein are solely those of the authors and do not represent or imply concurrence or endorsement by the National Cancer Institute.

Correction: This article was corrected on August 27, 2015, to fix a figure error.


COMMENT & RESPONSE

Progesterone and Synthetic Progestin Controversies

To the Editor Scientific veracity is required for translational research. Biological systems of human relevance must model clinical results. The Editorial by Joshi et al1 offered a molecular mechanism, derived from progesterone action in mice, to explain the current update of the Women's Health Initiative (WHI). The role of progesterone and pregnancy to enhance rodent mammary carcinogenesis has been known for half a century but did not translate to postmenopausal women. Specifically, antiprogestin therapies may have merit but were tested unsuccessfully decades ago. Perhaps, a different strategy has merit. For scientific veracity, any mechanism offered must explain the entire results of the WHI. There are 2 trials: estrogen therapy (ET), or ET plus medroxyprogesterone acetate, referred to as hormone therapy (HT). Each trial is against placebo. The offered mechanism2 does not replicate the ET results with the unanticipated decrease in breast cancer. This was a paradox because estrogen mediated the growth of breast cancer.2 Nevertheless, translational research has deciphered the paradox and rules are defined.3 Long-term estrogen deprivation with antihormone therapy creates new cell populations of acquired resistance that are vulnerable to the apoptotic action of estrogen; tumors regress.3

The same rules3 apply to occult disease in estrogen-deprived postmenopausal women in the WHI. The observed decrease in breast cancer incidence would be predicted with ET on the basis of extensive laboratory and clinical data.3 Nevertheless, to conform to scientific veracity there must be a mechanistic rationale for the increase in breast cancer with HT. The solution must incorporate ET killing vulnerable breast cancer cells and the pharmacology of medroxyprogesterone.

The discovery that an inflammatory response precedes estrogen-induced apoptosis4 led to the observation that the antiinflammatory glucocorticoid dexamethasone blocks “estrogen-induced” apoptosis, and the question became “could medroxyprogesterone modulate apoptosis?” Pharmacologically, medroxyprogesterone is not a pure progestin but also has glucocorticoid activity.2 A combination of estrogen plus medroxyprogesterone blunts estrogen-induced apoptosis and cell growth is resurrected over time.5 All scientific requirements for biological veracity are met. We propose that the HT trial causes an increase in breast cancer because medroxyprogesterone aids estrogen-deprived tumor cell survival by blunting estrogen-induced apoptosis.5 This does not exclude any stem cell increase with progesterins to maintain tumor growth but does provide a unifying mechanism for the WHI study.

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