Acquisition, analysis, or interpretation of data: Yu, Tian, Drilon, Borsu, Arcila, Ladanyi.
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1. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res*. 2013;19(8):2240-2247.

2. Zhou W, Ercan D, Chen L, et al. Novel mutant-selective EGFR kinase inhibitors against EGFR T790M. *Nature*. 2009;462(7276):1070-1074.

3. Janne PA, Ramalingam SS, Yang JC-H, et al. Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients (pts) with EGFR inhibitor–resistant non-small cell lung cancer (NSCLC) [suppl; abstr 8009]. *J Clin Oncol*. 2014;32:5s.

4. Yu Z, Boggon TJ, Kobayashi S, et al. Resistance to an irreversible epidermal growth factor receptor (EGFR) inhibitor in EGFR-mutant lung cancer reveals novel treatment strategies. *Cancer Res*. 2007;67(21):10417-10427.

5. Schwartz PA, Kuzmic P, Solowiej J, et al. Covalent EGFR inhibitor analysis reveals importance of reversible interactions to potency and mechanisms of drug resistance. *Proc Natl Acad Sci U S A*. 2014;111(1):173-178.

6. Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med*. 2014;370(24):2286-2294.

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 cancer-specific 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 mean squared error minimizing bandwidth.[5] Our results are not sensitive to this bandwidth choice. We used STATA/ICv13.1 (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.

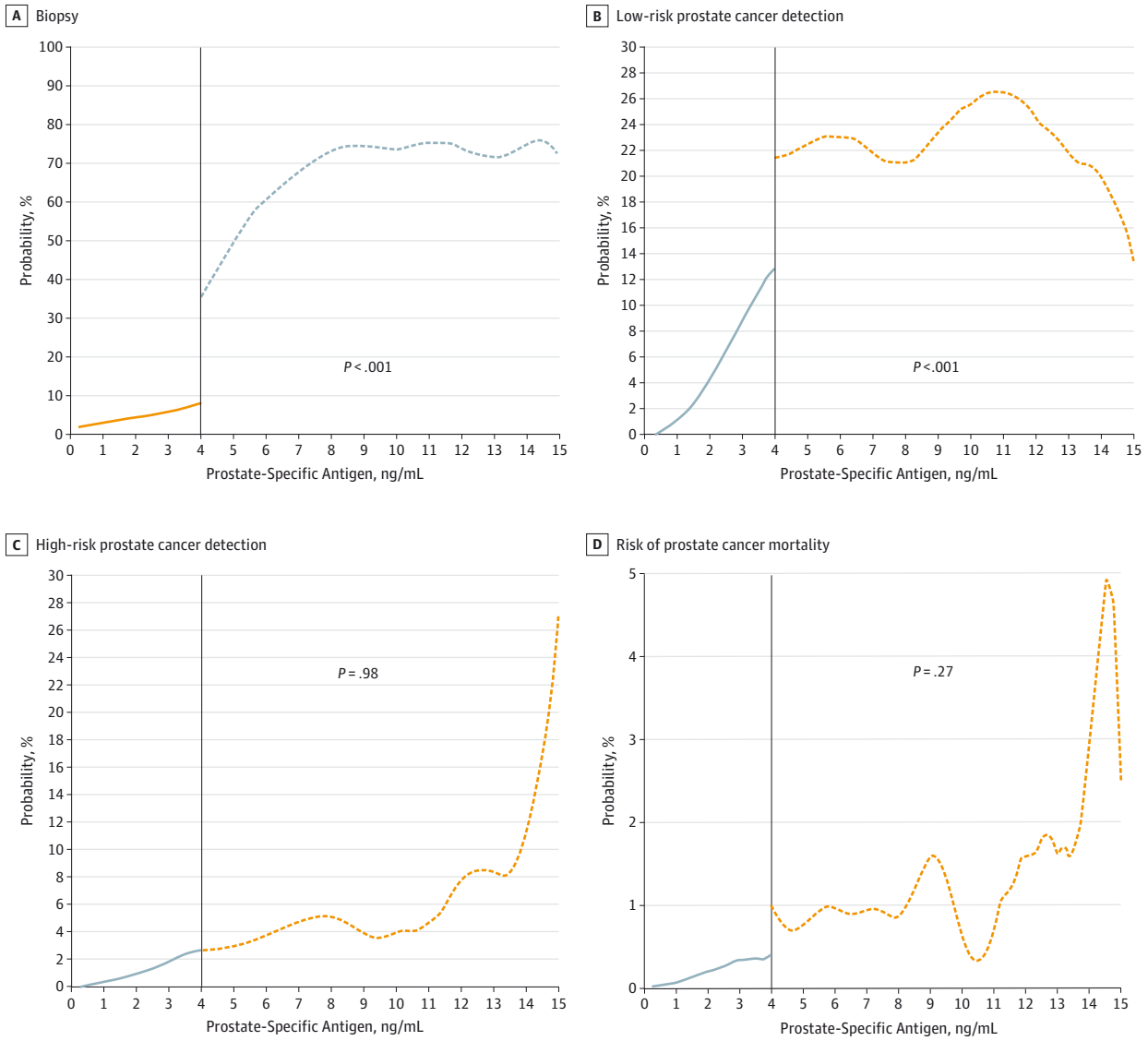
Results | The probability of a PLCO trial participant undergoing a biopsy as a function of the maximum PSA value from all tests increased at the 4.0 ng/mL PSA cutoff by 27.3% (95% CI, 23.3%-31.3%; $P < 1 \times 10^{-10}$) (**Figure**). This translates into a relative 445% increase in the biopsy rate 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 T1-2a) prostate cancer by 7.2% (95% CI, 3.6%-10.8%; $P = 8.5 \times 10^{-5}$) (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

Characteristic	Patients, No.	Effect Size (95% CI), %[a]	*P* Value
Undergo biopsy	4899	27.3 (23.3 to 31.3)	<.001
Pretreatment cancer type[b]			
Low risk	1891	7.2 (3.6 to 10.8)	<.001
Intermediate risk	1239	0.1 (−2.9 to 3.2)	.94
High risk	544	0.0 (−1.8 to 1.9)	.98
Postprostatectomy Gleason score			
6	687	5.6 (2.6 to 8.7)	<.001
7	671	0.9 (−1.9 to 3.7)	.52
8-10	157	−0.3 (−1.2 to 0.6)	.51
Mortality			
Prostate cancer specific	151	0.6 (−0.5 to 1.7)	.27
Overall	6962	−1.0 (−5.0 to 3.0)	.62

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]

Jonathan Shoag, MD
Joshua Halpern, MD
Brian Eisner, MD
Richard Lee, MD
Sameer Mittal, MD
Christopher E. Barbieri, MD, PhD
Daniel Shoag, PhD

Author Affiliations: Department of Urology, New York Presbyterian Hospital, Weill Cornell Medical College, New York (J. Shoag, Halpern, Lee, Mittal, Barbieri); Department of Urology, Massachusetts General Hospital, Boston (Eisner); Department of Public Policy, Harvard Kennedy School, Cambridge, Massachusetts (D. Shoag).

Corresponding Author: Jonathan Shoag, MD, Department of Urology, New York Presbyterian Hospital Weill Cornell Medical College, 525 E 68th St, Starr 900, New York, NY 10021 (Jes9171@nyp.org).

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Study concept and design: J. Shoag, Eisner, Lee, Mittal, D. Shoag.
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Drafting of the manuscript: J. Shoag, Halpern, Barbieri.
Critical revision of the manuscript for important intellectual content: J. Shoag, Halpern, Eisner, Lee, Mittal, Barbieri, D. Shoag.
Statistical analysis: J. Shoag, Halpern, Lee, D. Shoag.
Administrative, technical, or material support: Lee.
Study supervision: J. Shoag, Eisner, Lee, Barbieri.

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1. Andriole GL, Crawford ED, Grubb RL III, et al; PLCO Project Team. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med*. 2009; 360(13):1310-1319.

2. Andriole GL, Crawford ED, Grubb RL III, et al; PLCO Project Team. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. *J Natl Cancer Inst*. 2012;104(2):125-132.

3. Moscoe E, Bor J, Bärnighausen T. Regression discontinuity designs are underutilized in medicine, epidemiology, and public health: a review of current and best practice. *J Clin Epidemiol*. 2015;68(2):122-133.

4. Imbens GW, Lemieux T. Regression discontinuity designs: a guide to practice. *J Econom*. 2008;142(2):615-635.

5. Imbens K, Kalyanaraman K. Optimal Bandwidth Choice for the Regression Discontinuity Estimator. http://www.nber.org/papers/w14726. 2009. Accessed July 14, 2015.

6. Nichols A. RD: Stata module for regression discontinuity estimation. http://ideas.repec.org/c/boc/bocode/s456888.html. 2011. Accessed July 7, 2015.

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 al[1] 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 mechanism[1] 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 rules[3] 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 apoptosis[4] led to the observation that the anti-inflammatory 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.[5] 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 progestins to maintain tumor growth but does provide a unifying mechanism for the WHI study.

V. Craig Jordan, OBE, PhD, DSc, FMedSci
Philipp Y. Maximov, MD, PhD
Ping Fan, MD, PhD

Author Affiliations: Department of Breast Medical Oncology, University of Texas, MD Anderson Cancer Center, Houston, Texas.