Why Do Epidemiologic Studies Find an Inverse Association Between Intraprostatic Inflammation and Prostate Cancer: A Possible Role for Colliding Bias?

Marvin E. Langston[1], Karen S. Sfanos[2,3,4], Saira Khan[5], Trang Q. Nguyen[6], Angelo M. De Marzo[2,3,4], Elizabeth A. Platz[3,4,7], and Siobhan Sutcliffe[8]

ABSTRACT

Inflammation is an emerging risk factor for prostate cancer based largely on evidence from animal models and histopathologic observations. However, findings from patho-epidemiologic studies of intraprostatic inflammation and prostate cancer have been less supportive, with inverse associations observed in many studies of intraprostatic inflammation and prostate cancer diagnosis. Here, we propose collider stratification bias as a potential methodologic explanation for these inverse findings and provide strategies for conducting future etiologic studies of intraprostatic inflammation and prostate cancer.

Inflammation and Prostate Cancer

Inflammation is an emerging risk factor for prostate cancer. This association is supported by several lines of evidence, including the frequent observation of inflammation in prostate tissue (1), particularly in the peripheral zone of the prostate where prostate cancer tends to develop (2, 3), and its frequent proximity to proliferative, atrophic lesions that share genomic similarities to prostate cancer precursor lesions and tumors. A positive association between inflammation and prostate cancer is also supported by findings from rodent models suggesting that inflammation may contribute to prostate epithelial hyperproliferation, atrophy, dysplasia, and precursor lesions (3–9), as well as decreased expression of putative tumor suppressor genes (10) and acceleration of carcinogenesis (11, 12). Finally, findings from patho-epidemiologic studies of intraprostatic inflammation and prostate cancer progression have also tended to be positive (13–16).

In contrast to these largely supportive findings, results from patho-epidemiologic studies of intraprostatic inflammation and prostate cancer prevalence and/or risk have tended to be less supportive, with many observing inverse associations between intraprostatic inflammation and prostate cancer diagnosis [pooled OR = 0.46; 95% confidence interval (CI): 0.34–0.57 based on 22 studies; pooled OR not estimated for aggressive disease; ref. 17]. We discuss in detail one methodologic issue that may have biased findings from many of these previous studies and produced their inverse results. We also provide recommendations for conducting future studies.

Collider Stratification Bias

A likely explanation for previous inverse findings is collider stratification bias (hereafter referred to as colliding bias). This form of selection bias occurs when the study population is stratified or restricted by (i.e., conditioned on) a collider. A collider is a variable, in this case, an elevated PSA concentration or another clinical indication for biopsy, that is a common effect of both the exposure, intraprostatic inflammation (18), and the outcome of interest, prostate cancer (19). Colliding bias has the potential to distort an association in many different ways, including inducing a false association or even reversing an association between the exposure and the outcome, such as from a positive to an inverse association.

An example of colliding bias is demonstrated in **Fig. 1A** and **B**. In this example, we are interested in the potential association between athletic talent and a high grade point average (GPA). In a general population sample (**Fig. 1A**), we have no reason to believe that identifying a student with athletic talent implies anything about his/her GPA (i.e., no association between athletic talent and GPA). However, if we restrict the study population to students who received a college scholarship (i.e., a common effect of both athletic talent and a high GPA; **Fig. 1B**), knowing that a selected student has less athletic talent immediately tells us that he/she likely has a high GPA (assuming, in this simple example, that there are only two reasons to receive a college scholarship). Therefore, by conditioning on receipt of a college scholarship, we have changed the distribution of these two marginally independent traits and induced an inverse association between athleticism and academic performance.

Similar to the example described above, conditioning on a potential collider in the design and eligibility criteria of previous studies of intraprostatic inflammation and prostate cancer may have biased their observed association (in this case, we hypothesize from a positive to an inverse or protective association). In general, prostate tissue is difficult to obtain and typically requires a clinical indication for biopsy, such as an elevated PSA concentration or other findings suspicious for malignancy. However, by examining tissue collected solely for clinical indication—that is, conditioning on clinical indication for prostate biopsy—investigators may have induced a different association

[1]Division of Research, Kaiser Permanente Northern California, Oakland, California. [2]Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland. [3]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland. [4]Department of Urology, James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland. [5]Epidemiology Program, College of Health Sciences, University of Delaware, Newark, Delaware. [6]Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland. [7]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland. [8]Division of Public Health Sciences, Department of Surgery, Alvin J. Siteman Cancer Center, and Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, Missouri.

Corresponding Author: Marvin E. Langston, Kaiser Permanente Northern California, 2000 Broadway, Oakland, CA 94612. Phone: 510-891-3553; E-mail: marvin.e.langston@kp.org

Cancer Epidemiol Biomarkers Prev 2021;30:255–9

doi: 10.1158/1055-9965.EPI-20-1009

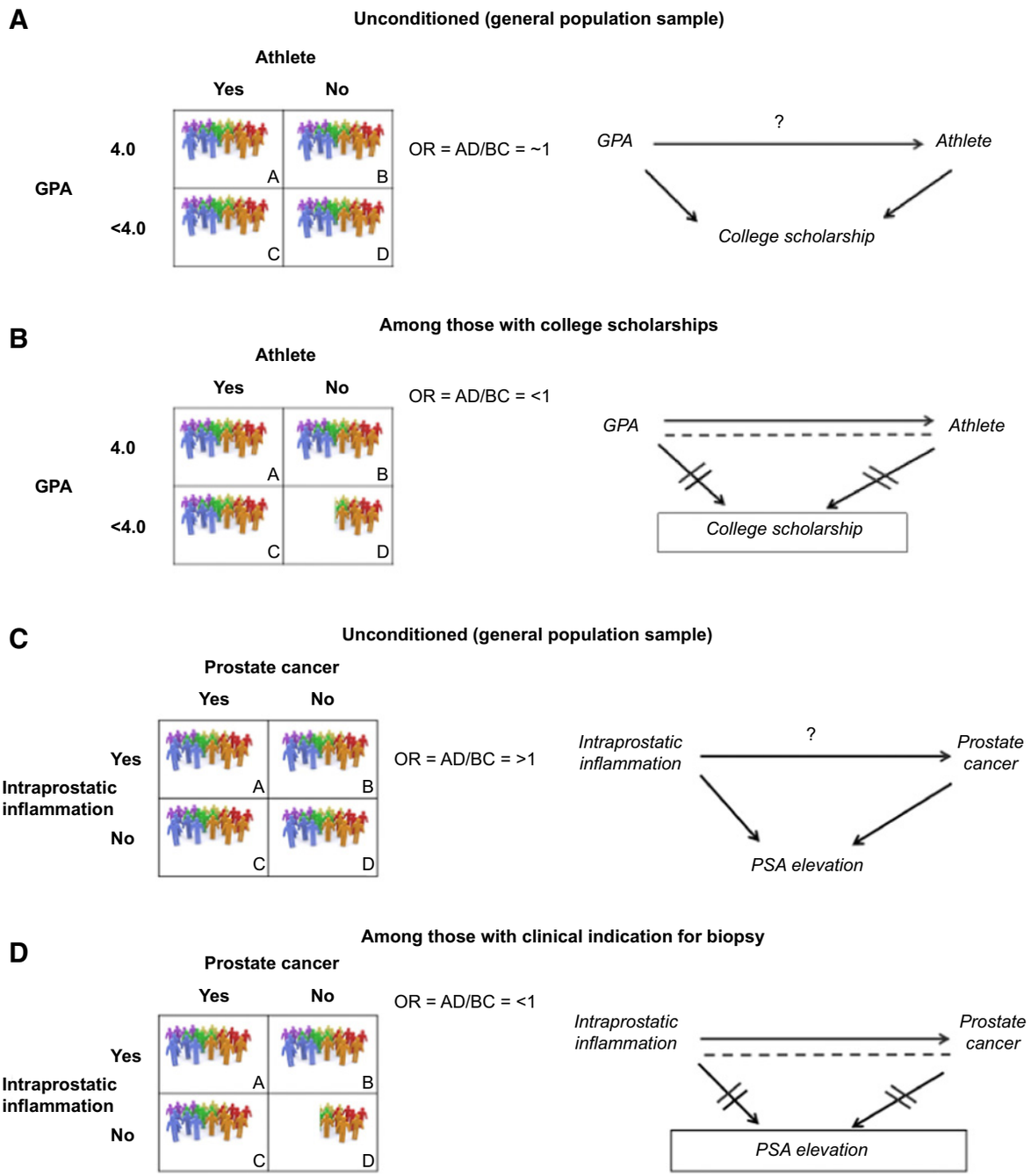

Figure 1.

Illustration of collider stratification bias. The premise of collider stratification bias is shown here using contingency tables and directed acyclic graphs (DAG). In **A,** we are estimating the association between two traits, high GPA, and athletic ability. The two traits are entirely independent of one another as evidenced by an OR = ∼1. However, if we sample participants into this hypothetical study based on receipt of a college scholarship (i.e., we condition on/restrict to a common effect of the two traits), then the number/proportion of those without either trait decreases considerably (**B,** contingency table cell D). Therefore, if we know that a selected person lacks athletic talent, then we immediately know that he/she is likely to have a high GPA. These two traits are no longer independent and a spurious inverse association has been induced (noted by the dashed line in the DAG). The magnitude of our induced inverse association depends on the number of remaining study participants without either trait. **C** and **D,** show this similar concept in studies relying on prostate biopsy samples. Both inflammation and prostate cancer are sources of PSA elevation, a clinical indication for prostate biopsy. In **C**, participants are selected into the study without clinical indication for biopsy. However, if selection into a study is predicated on PSA elevation or another clinical indication for prostate biopsy (i.e., conditioned on/restricted to clinical indication for cancer screening; **D**, then a spurious association will be induced between intraprostatic inflammation and prostate cancer. This induced association is inverse because if participant's PSA elevation was not due to intraprostatic inflammation, then it was more likely elevated because of prostate cancer. The two events, inflammation and prostate cancer, have been forced to be related.

between intraprostatic inflammation and prostate cancer prevalence than they would have observed in a sample unselected for clinical indication. For instance, in a study population of men who underwent biopsy without regard to indication, sampling one individual and finding out that he did not have prostate cancer would not give us any information about his likelihood of having intraprostatic inflammation if there were no association between inflammation and prostate cancer, or would suggest that he was less likely to have inflammation if there were a positive association between inflammation and prostate cancer (**Fig. 1C**). However, in a study population restricted to men who underwent biopsy for indication, the same finding—that is, knowing that a selected individual did not have prostate cancer—would immediately tell us that he likely had another reason for an elevated PSA concentration, such as intraprostatic inflammation (**Fig. 1D**). Therefore, conditioning on clinical indication for biopsy may have introduced a seemingly inverse association between intraprostatic inflammation and prostate cancer diagnosis, the magnitude of which would depend largely on the prevalence of other noninflammatory or nonmalignant causes of elevated PSA such as benign prostatic hyperplasia (BPH) and other prostate conditions (20).

Strategies for Reducing Collider Stratification Bias/Future Studies

Many investigators have attempted to increase the methodologic rigor of their patho-epidemiologic studies of inflammation and prostate cancer by accounting for participants' PSA level, either by adjustment or restriction to men with lower baseline PSA levels and thus lesser indication for biopsy (17). However, as all men still have some indication for biopsy, this approach may not reduce the potential for colliding bias. Even investigating this association in men without indication for biopsy on repeat biopsy, such as in The Reduction by Dutasteride of PCa Events (REDUCE) trial (21), may not effectively remove colliding bias because these men remain a subset of the initial PSA-based sample. However, the fact that the association weakened with each successive repeat biopsy without indication in the REDUCE trial (2-year follow-up biopsy: OR = 0.65; 95% CI: 0.55–0.76; and 4-year follow-up: OR = 0.98; 95% CI: 0.77–1.25; ref. 21) provides some evidence, albeit only intuitive at this time, that the potential for colliding bias reduces with time between the initial selection criteria (i.e., indication for biopsy) and investigation of the association, most likely because the strength of the collider–outcome relationship weakens (22). This type of temporal reduction, including its direction and magnitude, is still an area of active theoretical investigation in the colliding bias field (20, 23–26).

Nearly all patho-epidemiologic studies have investigated the association of intraprostatic inflammation and prostate cancer among men with a clinical indication for biopsy. The Prostate Cancer Prevention Trial (PCPT) and its follow-up study, the PCPT-SELECT (Selenium and Vitamin E Cancer Prevention Trial) are one of the few to assess this association in men without indication for biopsy (PSA concentration <3 ng/mL at baseline and no clinical indication for biopsy)—that is, the opposite stratum of the collider and the one more similar to the general population of U.S. men (27, 28). In the PCPT, Gurel and colleagues observed a positive association between intraprostatic inflammation and the odds of total and high-grade prostate cancer in their end-of-study biopsy [OR = 1.78; 95% CI: 1.04–3.06 and OR = 2.24; 95% CI: 1.06–4.71, respectively (27)] that persisted when restricted to men with low PSA concentration at biopsy (<2 ng/mL) and those without a clinical indication for biopsy over the study course. This finding was corroborated by further prospective investigations of PCPT participants who were followed for prostate cancer in a second trial (the SELECT trial) after the conclusion of the PCPT trial (PCPT-SELECT; OR = 1.66; 95% CI: 0.70–3.96; ref. 28). Although these studies are still susceptible to colliding bias because they include participants sampled based on PSA and/or clinical indication for biopsy, the influence of this bias is not necessarily reciprocal across strata of the collider and its likely effect is still to pull associations in an inverse direction (20). Therefore, the true association between intraprostatic inflammation and prostate cancer in PCPT and PCPT-SELECT may be even more strongly positive than observed. Additional theoretical investigations will be needed to determine the true magnitude of this association and to facilitate future studies in this area (20, 23–26).

Additional opportunities to examine associations between intraprostatic inflammation and prostate cancer without concerns of colliding bias are currently limited, but include cross-sectional autopsy studies (29) and historical cohorts of patients with BPH who underwent transurethral resection of the prostate (TURP) before the PSA era and were subsequently followed for prostate cancer incidence or mortality (15). These studies are less susceptible to colliding bias because neither autopsy nor BPH/TURP are common effects of intraprostatic inflammation or prostate cancer. However, these types of studies are not without limitations of their own, as the first study design (cross-sectional) may be subject to reverse causation (i.e., prostate cancer contributing to local inflammation rather than vice versa) and the second is limited to investigations of inflammation in the transition zone rather than the peripheral zone of the prostate where inflammation and prostate cancer tend to colocalize. Other longitudinal cohorts in the pre-PSA era where prostate biopsy samples might have been taken for other reasons (e.g., bone metastases, acute urinary retention, digital rectal exam abnormalities) may also be effective at investigating this association. Looking further into the future, other more exploratory, but less invasive, approaches may include examining inflammatory cells or markers in banked semen or urine specimens, which may contain prostate secretions, or perhaps with technology development, using prostate imaging to identify intraprostatic inflammation to investigate associations with subsequent development of prostate cancer.

Alternative Explanations for Inverse Associations

Estimating the true association between intraprostatic inflammation and prostate cancer has proven difficult (22). While we suggest that colliding bias is likely a major driver of previous inverse associations, other biological and epidemiologic mechanisms must also be considered. Possible biologic mechanisms include immunosurveillance (i.e., destruction of "foreign" malignant cells by inflammatory cells; ref. 30) and immunoselection for less aggressive or immunogenic tumor-cell variants (31). From an epidemiologic perspective, alternative methodologic explanations include detection bias, reverse causation, and exposure misclassification. However, detection bias is unlikely to explain observed inverse associations because any increase in prostate cancer screening, biopsy, or diagnosis related to prostate inflammation would likely contribute to a positive association, such as seen previously for clinical prostatitis (32), rather than an inverse association. Reverse causation is potentially a major source of bias in these studies; however, an unlikely explanation empirically because much larger differences were observed by clinical indication for initial

biopsy than by cross-sectional versus prospective study design in a meta-analysis of intraprostatic inflammation and prostate cancer studies (17). Also, the PCPT-SELECT study was the sole prospective study to estimate the intraprostatic inflammation and prostate cancer association in men without an indication for biopsy and concluded a positive association (28). Therefore, additional prospective studies with long-term follow-up are needed to confirm this association, which proves challenging due to the complexity of study design in this setting. Finally, exposure misclassification by evaluating all types of inflammation combined is unlikely to explain falsely inverse associations because similar results have been observed for both acute (pooled OR = 0.68, 95% CI: 0.45–0.91) and chronic (pooled OR = 0.50, 95% CI: 0.33–0.67) intraprostatic inflammation (17).

Conclusion

While additional potential explanations for inverse associations between intraprostatic inflammation and prostate cancer in studies of biopsy tissue collected for indication exist, we suggest that colliding bias represents the most important explanation. Additional methodologically rigorous studies are needed to determine the possible etiologic role of inflammation in prostate cancer development without concerns of collider bias. These types of studies will likely require creative new designs and methodologic approaches.

Authors' Disclosures

S. Khan reports grants from Department of Defense during the conduct of the study. E.A. Platz reports personal fees from Kaiser Permanente Northern California, Division of Research outside the submitted work. S. Sutcliffe reports grants from NIH during the conduct of the study. The Editor-in-Chief of Cancer Epidemiology, Biomarkers & Prevention is an author on this article. In keeping with AACR editorial policy, a senior member of the Cancer Epidemiology, Biomarkers & Prevention editorial team managed the consideration process for this submission and independently rendered the final decision concerning acceptability. No disclosures were reported by the other authors.

Acknowledgments

Effort for Langston is supported by the NIDDK grant K12DK111028. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Received July 1, 2020; revised October 6, 2020; accepted December 7, 2020; published first February 5, 2021.

References

1. Nickel JC, Roehrborn CG, O'Leary MP, Bostwick DG, Somerville MC, Rittmaster RS. The relationship between prostate inflammation and lower urinary tract symptoms: examination of baseline data from the REDUCE trial. Eur Urol 2008;54:1379–84.
2. Nickel JC, True LD, Krieger JN, Berger RE, Boag AH, ID Y. Consensus development of a histopathological classification system for chronic prostatic inflammation. BJU Int 2001;87:797–805.
3. De Marzo AM, Platz EA, Sutcliffe S, Xu J, Grönberg H, Drake CG, et al. Inflammation in prostate carcinogenesis. Nat Rev Cancer 2007;7:256–69.
4. Sfanos KS, De Marzo AM. Prostate cancer and inflammation: the evidence. Histopathology 2012;60:199–215.
5. Bernoulli J, Yatkin E, Laakso A, Anttinen M, Bosland M, Vega K, et al. Histopathological evidence for an association of inflammation with ductal pin-like lesions but not with ductal adenocarcinoma in the prostate of the noble rat. Prostate 2008;68:728–39.
6. Elkahwaji JE, Hauke RJ, Brawner CM. Chronic bacterial inflammation induces prostatic intraepithelial neoplasia in mouse prostate. Br J Cancer 2009;101:1740–8.
7. Shinohara DB, Vaghasia AM, Yu S-H, Mak TN, Brüggemann H, Nelson WG, et al. A mouse model of chronic prostatic inflammation using a human prostate cancer-derived isolate of Propionibacterium acnes. Prostate 2013;73:1007–15.
8. Nakayama M, Bennett CJ, Hicks JL, Epstein JI, Platz EA, Nelson WG, et al. Hypermethylation of the human glutathione S-transferase-pi gene (GSTP1) CpG island is present in a subset of proliferative inflammatory atrophy lesions but not in normal or hyperplastic epithelium of the prostate: a detailed study using laser-capture microdissection. Am J Pathol 2003;163:923–33.
9. Sfanos KS, Yegnasubramanian S, Nelson WG, De Marzo AM. The inflammatory microenvironment and microbiome in prostate cancer development. Nat Rev Urol 2018;15:11–24.
10. Khalili M, Mutton LN, Gurel B, Hicks JL, De Marzo AM, Bieberich CJ. Loss of Nkx3.1 expression in bacterial prostatitis: a potential link between inflammation and neoplasia. Am J Pathol 2010;176:2259–68.
11. Simons BW, Durham NM, Bruno TC, Grosso JF, Schaeffer AJ, Ross AE, et al. A human prostatic bacterial isolate alters the prostatic microenvironment and accelerates prostate cancer progression. J Pathol 2015;235:478–89.
12. Sfanos KS, Canene-Adams K, Hempel H, Yu S-H, Simons BW, Schaeffer AJ, et al. Bacterial prostatitis enhances 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)-induced cancer at multiple sites. Cancer Prev Res 2015;8:683–92.
13. Irani J, Goujon J-M, Ragni E, Peyrat L, Hubert J, Saint F, et al. High-grade inflammation in prostate cancer as a prognostic factor for biochemical recurrence after radical prostatectomy. Pathologist Multi Center Study Group. Urology 1999;54:467–72.
14. Klink JC, Bañez LL, Gerber L, Lark A, Vollmer RT, Freedland SJ. Intratumoral inflammation is associated with more aggressive prostate cancer. World J Urol 2013;31:1497–503.
15. Davidsson S, Fiorentino M, Andren O, Fang F, Mucci LA, Varenhorst E, et al. Inflammation, focal atrophic lesions, and prostatic intraepithelial neoplasia with respect to risk of lethal prostate cancer. Cancer Epidemiol Biomarkers Prev 2011;20:2280–7.
16. Zhang Y, Zhou CK, Rencsok EM, Fall K, Lotan TL, Loda M, et al. A prospective study of intraprostatic inflammation, focal atrophy, and progression to lethal prostate cancer. Cancer Epidemiol Biomarkers Prev 2019;28:2047–54.
17. Vasavada SR, Dobbs RW, Kajdacsy-Balla AA, Abern MR, Moreira DM. Inflammation on prostate needle biopsy is associated with lower prostate cancer risk: a meta-analysis. J Urol 2018;199:1174–81.
18. Simardi LH, Tobias-MacHado M, Kappaz GT, Taschner Goldenstein P, Potts JM, Wroclawski ER. Influence of asymptomatic histologic prostatitis on serum prostate-specific antigen: a prospective study. Urology 2004;64:1098–101.
19. Lilja H, Ulmert D, Vickers AJ. Prostate-specific antigen and prostate cancer: prediction, detection and monitoring. Nat Rev Cancer 2008;8:268–78.
20. Nguyen TQ, Dafoe A, Ogburn EL. The magnitude and direction of collider bias for binary variables. Epidemiologic Methods 2019;8:1–29.
21. Moreira DM, Nickel JC, Gerber L, Muller RL, Andriole GL, Castro-Santamaria R, et al. Baseline prostate inflammation is associated with a reduced risk of prostate cancer in men undergoing repeat prostate biopsy: results from the REDUCE study. Cancer 2014;120:190–6.
22. Sperrin M, Candlish J, Badrick E, Renehan A, Buchan I. Collider bias is only a partial explanation for the obesity paradox. Epidemiology 2016;27:525–30.
23. Ding P, Miratrix LW. To adjust or not to adjust? Sensitivity analysis of M-bias and butterfly-bias. J Causal Inference 2015;3:41–57.
24. Elwert F, Winship C. Endogenous selection bias: the problem of conditioning on a collider variable. Annu Rev Sociol 2014;40:31–53.
25. Jiang Z, Ding P. The directions of selection bias. Stat Probab Lett 2017;125:104–9.
26. Porta M, Vineis P, Bolúmar F. The current deconstruction of paradoxes: one sign of the ongoing methodological "revolution". Eur J Epidemiol 2015;30:1079–87.
27. Gurel B, Lucia MS, Thompson IM, Goodman PJ, Tangen CM, Kristal AR, et al. Chronic inflammation in benign prostate tissue is associated with high-grade prostate cancer in the placebo arm of the prostate cancer prevention trial. Cancer Epidemiol Biomarkers Prev 2014;23:847–56.

28. Platz EA, Kulac I, Barber JR, Drake CG, Joshu CE, Nelson WG, et al. A prospective study of chronic inflammation in benign prostate tissue and risk of prostate cancer: linked PCPT and SELECT cohorts. Cancer Epidemiol Biomarkers Prev 2017;26:1549–57.
29. Delongchamps NB, de la Roza G, Chandan V, Jones R, Sunheimer R, Threatte G, et al. Evaluation of prostatitis in autopsied prostates–is chronic inflammation more associated with benign prostatic hyperplasia or cancer? J Urol 2008;179: 1736–40.
30. Finn OJ. Cancer immunology. N Engl J Med 2008;358:2704–15.
31. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. Immunity 2004;21:137–48.
32. Langston ME, Horn M, Khan S, Pakpahan R, Doering M, Dennis LK, et al. A systematic review and meta-analysis of associations between clinical prostatitis and prostate cancer: new estimates accounting for detection bias. Cancer Epidemiol Biomarkers Prev 2019;28:1594–603.