
Regarding our article1 on the association of androgen deprivation therapy (ADT) with increased Alzheimer’s disease risk, Bowen et al,2 Froehner and Wirth,3 Leow et al,4 and Brady et al5 highlight a number of significant considerations that will prove important in the design of future studies that investigate the association of ADT and Alzheimer’s disease.

We agree with Bowen et al2 and Leow et al4 that stratification by the form of ADT is a critical future step to understand the association of ADT and Alzheimer’s disease risk. They reasonably point out that our article lacked discussion of a relevant study by D’Amico et al6 that showed an association between gonadotropin-releasing hormone agonists and decreased risk of death from Alzheimer’s disease. As these authors illustrate, there are many distinct categories of ADT, with differing and complex effects on the hypothalamic–pituitary–gonadal axis. In our article, we did not undertake this subgroup analysis secondary to limited power, given 125 new diagnoses of Alzheimer’s disease during the study period. In addition, many individuals were exposed to multiple forms of ADT, which further increased the required sample size to accurately examine the effect of individual forms of ADT. This limitation in power, even in our multi-institutional study with data on > 5 million patients, underscores the need for improved data sharing between medical centers2 to answer critical questions in health care.

A number of authors raised important points regarding the potential mechanisms for bias in our analysis. Froehner and Wirth,3 Leow et al,4 and Brady et al5 point out that patients who receive ADT likely have a greater baseline risk of developing Alzheimer’s disease than ADT is difficult to fully account for in a non-randomized analysis. As we discussed in the limitations section of our article, we agree with this assessment and, it is possible that confounding factors that were both unmeasured and incompletely accounted for could have contributed to our result. In our analysis, we therefore adjusted for a wide range of confounding factors and used both traditional and propensity score matched analyses. Leow et al4 also make the excellent point that patients administered ADT may have more frequent exposures to the health care system and, therefore, be more likely to have an outcome of interest recorded. We accounted for duration of follow-up in addition to conducting falsification analyses to protect against and examine the impact of this source of bias. Although these results were reassuring, we cannot completely exclude this source of bias. Clearly, more work is needed to completely unlock the potential of electronic health record data mining for translation into clinical tools to generate personalized evidence.6,9 In addition, alternative methods, such as Mendelian randomization analyses,10 should be considered to account for confounding in the absence of a randomized trial.

We also agree with Brady et al2 that the age of patients in our study is not only a source of confounding, but also a reminder of the importance of fully considering the implications of cancer therapies on our patients’ long-term health. This applies not only to the geriatric population as Brady et al illustrate, but also to younger oncology patients, given the rapidly growing population of long-term survivors of cancer.11 This is particularly important when considering the impact of medical treatments on cognitive outcomes, given that risk of dementia is a primary health concern among older individuals.12

Finally, we fully agree that the results of this study should be communicated to patients with caution. ADT has been shown in multiple randomized trials to offer a survival benefit in men with prostate cancer,13,14 whereas our study provides data to support further research of the impact of ADT on risk of Alzheimer’s disease.

Kevin T. Nead
Stanford University, Stanford, CA, and University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

Greg Gaskin
Stanford University, Stanford, CA

Cariad Chester
Stanford University School of Medicine, Stanford, CA

Samuel Swisher-McClure
University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

Joel T. Dudley
Icahn School of Medicine at Mount Sinai, New York, NY

Nicholas J. Leeper
Stanford University School of Medicine, Stanford, CA

Nigam H. Shah
Stanford University, Stanford, CA

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
Disclosures provided by the authors are available with this article at www.jco.org.

REFERENCES
2. Bowen RL, Butler T, Atwood CS: Different androgen deprivation therapies operate via different hormonal mechanisms that can increase or decrease the risk of developing Alzheimer’s disease. J Clin Oncol 34:2800, 2016


AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST


The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Kevin T. Nead
No relationship to disclose

Greg Gaskin
No relationship to disclose

Cariad Chester
No relationship to disclose

Samuel Swisher-McClure
No relationship to disclose

Joel T. Dudley
Stock or Other Ownership: LAM Therapeutics, NuMedii
Honoraria: Janssen Pharmaceuticals
Consulting or Advisory Role: LAM Therapeutics, NuMedii
Research Funding: AstraZeneca, GlaxoSmithKline, Janssen Pharmaceuticals, LEO Pharma
Travel, Accommodations, Expenses: LEO Pharma

Nicholas J. Leeper
No relationship to disclose

Nigam H. Shah
Stock or Other Ownership: Kyron
Consulting or Advisory Role: Kyron