Title

Use of Participation to Prevalence Ratio for Evaluating the Representation Status of Women in Oncology Clinical TrialsâReply

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panic populations (overweight rate, 64.1% in Mexico vs 33.8% in China).[6] The influence of BMI on the salutary effects of metformin for patients with NSCLC has been reported.[3] In a study that included 434 patients with stage I NSCLC who were undergoing lobectomy, the authors identified a significant association between use of metformin and better survival outcomes exclusively in patients with a BMI higher than 25.[3] The authors concluded that a high BMI might sensitize patients to the antitumor effects of metformin, and therefore the benefit would be circumscribed to this specific population.[3] Given the considerable differences in overweight and obesity rates between the Mexican and Chinese populations, it is plausible that the differences in both study results were partially caused by a discrepancy in population BMI.

Limitations of this study included its post hoc design and the exclusion of patients owing to incomplete data. Therefore, the results should be prospectively validated.

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Concept and design: Arrieta, Zatarain-Barron, Barrón, Yendamuri, Rosell.
Acquisition, analysis, or interpretation of data: Arrieta, Turcott, Barrón, Cardona.
Drafting of the manuscript: Arrieta, Zatarain-Barron, Turcott, Barrón.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Arrieta, Zatarain-Barron, Turcott, Barrón, Cardona.
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Supervision: Arrieta, Barrón, Rosell.

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COMMENT & RESPONSE

Use of Participation to Prevalence Ratio for Evaluating the Representation Status of Women in Oncology Clinical Trials

To the Editor In their recent Research Letter in *JAMA Oncology*, Jenei et al[1] reported that women with cancer had statistically significant lower enrollment rates than men in global cancer drug trials between 2000 and 2020. The results suggested that women were underrepresented in cancer clinical trials, which may undermine the generalizability of new cancer drugs in women. However, the authors only adopted the Pearson χ^2 test to assess whether there is a significant difference between the enrollment of sexes. Our concern is that such direct comparison does not consider the different disease prevalence between men and women, which can contribute to the disproportionate participation evaluation by sex in clinical trials. Although the authors found that enrollment rates of women were not matched to their incidence (eg, thyroid and colon cancer), it is more appropriate to calculate the participation to prevalence ratio (PPR) by the following formula: percentage of women among trial participants/percentage of women among disease population, for evaluating the representation status of women in clinical trials.[2] A PPR between 0.8 and 1.2 indicates that the proportion of women in clinical trials nearly equals the proportion of women in the disease population, and a PPR less than 0.8 or more than 1.2 indicates that women are either underrepresented or overrepresented, respectively. Notably, in a recent cross-sectional study investigating the representation status, Varma et al[3] observed that women were adequately represented in premarketing (mean PPR, 0.91; 95% CI, 0.90-0.91) and postmarketing (mean PPR, 1.00; 95% CI, 1.00-1.01) studies of novel approved cancer drugs by calculating PPRs. The inconsistent results suggested in the conclusions of Jenei et al[1] may be different after adjusting the participation rate by prevalence.

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In Reply We appreciate the comments from Chen et al on our Research Letter evaluating the inclusion of women in global oncology drug trials over the past 20 years.[1] Our central conclusion was that women were underrepresented in certain tumor types.

Chen et al argue that we ought to have adjusted our analysis[1] for the participation to prevalence ratio. We agree that adjustment is needed for the number of people eligible to participate, but prevalence does not capture that. The incidence of a specific tumor indication (eg, second-line metastatic breast cancer or newly diagnosed multiple myeloma) is a better indicator of individuals eligible for frontline therapy and has been used in similar studies.[2,3]

Accordingly, we reanalyzed our data[1] using a statistical test to evaluate the difference between female incidence and enrollment. We found that the proportion of women enrolled in colon and thyroid cancer trials were significantly underrepresented. These findings support our conclusion that female enrollment is not proportional to expected rates in colon and thyroid cancer.

Finally, Chen et al cite a study that purportedly claimed that women are adequately represented across premarketing and postmarketing studies.[4] However, the study aggregated trials across multiple indications, including female-predominant cancers (breast, cervical, and ovarian). Including multiple trials of female-predominant indications will lead to an overrepresentation of women in the aggregate estimate cited by Chen et al. Looking by disease, the results support those we identified in our study,[1] including the similarity to thyroid cancer, which demonstrated one of the largest disparities in premarketing and postmarketing trials (participation to prevalence ratio, 0.64; 95% CI, 0.60-0.68; and 0.44; 95% CI, 0.72-0.77, respectively).

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Hypofractionated Radiotherapy for Locally Advanced Non–Small Cell Lung Cancer—Does Size Matter?

To the Editor We would like to congratulate Dr Iyengar and colleagues for executing an important randomized clinical trial comparing 2 radiotherapy schedules for patients with stage II/III non–small cell lung cancer who are ineligible for concurrent chemoradiotherapy.[1] While the trial did not meet its primary end point, the study team has demonstrated the feasibility of a clinical trial in this patient population and generated important data to inform future efforts.

We were surprised to see that planning target volume (PTV) and gross tumor volume (GTV), 2 volumetric measures of overall disease burden, were not associated with overall survival in this study (PTV: hazard ratio [HR], 1.00 per mL; 95% CI, 1.00-1.00; $P = .14$; GTV: HR, 1.00; 95% CI, 1.00-1.00; $P = .85$).[1] Previous studies of patients with non–small cell lung cancer treated with definitive radiotherapy indicate that disease volume is a key predictor of disease recurrence and death.[2,3] Distributions of disease volume measures are extremely right-skewed, so the prognostic value of disease burden may only become apparent after data transformation (eg, logarithmic) or if patients are grouped by disease volume. Has the study team tried these analyses?

Interestingly, data in the Supplement[1] display trends, although not significant, suggesting associations between PTV/GTV and overall survival within the hypofractionated radiotherapy study arm (PTV: HR, 1.00; 95% CI, 1.00-1.00; $P = .08$; GTV: HR, 1.00; 95% CI, 1.00-1.01; $P = .13$). Has the study team tested for interactions between disease burden and radiotherapy schedule as predictors of outcomes? Positive findings would support the hypothesis that large-volume disease may need to be treated with relatively conservative radiotherapy schedules