JNCI Cancer Spectrum (2021) 5(4): pkab052

doi: 10.1093/jncics/pkab052
Response

Reply to Hopper, Nguyen, and Li

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We thank Hopper and colleagues (1) for their interest in our systematic review of clinical trials on chemoprevention agents to reduce mammographic breast density in premenopausal women. We agree with the authors that mammographically dense breasts can mask existing tumors and therefore increase the incidence of interval cancers. Studies have also demonstrated that extensive mammographic density is strongly associated with risk of breast cancer detected by screening and is a strong risk factor for breast cancer (2,3). Notably, data from the Breast Cancer Surveillance Consortium showed that a substantial proportion of breast cancers (39% in premenopausal women and 26% in postmenopausal women) can be attributed to having dense breasts (4).

We acknowledge that there are various breast parenchyma patterns that are not captured within mammographic breast density, which may drive breast cancer development independently. Research in this area has generated novel findings that require confirmation in diverse study populations as a first step toward greater adoption and widespread utility. For instance, a study recently identified radiomic phenotypes that reflect intrinsic properties of mammographic parenchymal complexity beyond mammographic breast density, which was also independently associated with breast cancer risk (5).

In addition to being a strong risk factor, mammographic breast density and breast cancer share similar biological and genetic pathways (6,7) and is thus a surrogate marker of breast cancer development. A recent genome-wide association study meta-analysis of 24 192 women identified 31 mammographic breast density loci, 17 of which were associated with breast cancer risk in an independent meta-analysis (8). Mendelian randomization analyses further demonstrated that genetic estimates of area-based measures of mammographic breast density were associated with breast cancer risk (8).

Finally, we agree that it is ideal that breast cancer chemoprevention trials study breast cancer development as an outcome, not just mammographic breast density. Although this may be an achievable goal in chemoprevention trials among older postmenopausal women, the much lower 10-year probability of developing breast cancer in younger premenopausal women makes mammographic breast density an acceptable and exciting surrogate outcome to use, especially among premenopausal women, and data from the International Breast Cancer Intervention Study I lend credence to this (9).

Funding

This work was supported by the National Cancer Institute at the National Institutes of Health (grants R37CA235602 and R01CA246592 to ATT).

Notes

Role of the funder: The funder had no role in the writing of this response or decision to submit it for publication.

Disclosures: All other authors declare no competing interests.

Author contributions: Writing, original draft—ASS, ATT; writing, editing and revision—ASS, ATT.

Data Availability

Not applicable.

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Received: 10 May 2021; **Accepted:** 13 May 2021

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