Mammographic Density, Hormone Therapy, and Risk of Breast Cancer

To the Editors: In their recent article, Boyd et al. (1) sought to examine whether the increased risk of breast cancer associated with postmenopausal hormone therapy was mediated through mammographic density (percentage mammographic density) in three screening programs. They did this by comparing the relative risk of breast cancer associated with hormone therapy with and without adjustment for mammographic density measured at the time of entry to the screening programs when the use of hormones was also recorded. They found that the adjustment for mammographic density made little difference to the relative risk estimates. On this basis, they concluded “that the effects of hormone therapy on mammographic density, and on breast cancer risk, are separate and not related causally”.

In our opinion, this conclusion is not warranted. The question is not whether the increased risk of breast cancer associated with hormone therapy is mediated through mammographic density but whether the increased risk is mediated through a change in mammographic density. To accomplish this, one needs to adjust for mammographic density before hormone therapy and the change in mammographic density after starting hormone therapy.

There is a large variation in mammographic percentage density among postmenopausal women: among the controls in Boyd et al.’s study, the mean density was 24% with a SD of 18%. Much of this variation seems to be genetically determined (2). Although mammographic density can be increased by hormone therapy exposure, particularly combined estrogen and progestin therapy, the effects of hormone therapy exposures are only ~5% on average (3, 4). The contribution of hormonal exposure in determining the variation in the distribution of mammographic density at any point in time is therefore quite small. Consequently, mammographic density is a very poor proxy for mammographic density change, and one can expect it to have little or no effect on the estimates of relative risk (5), precisely what was found.

The question of whether the increased risk is mediated through a change in mammographic density is currently being addressed in a study within the Women’s Health Initiative.

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References
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