
Note
The authors have no conflicts of interest to disclose.

Affiliations of authors: Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, Rockville, MD (LA-K, JAZ); School of Community Health and Policy, Morgan State University, Baltimore, MD (FK).

DOI:10.1093/jnci/djt239
Advance Access publication September 3, 2013

Hormone Replacement Therapy and Breast Cancer Risk: More Evidence for Risk Stratification?

Mary Beth Terry, Parisa Tehranifar

In this issue of the Journal, Hou and colleagues provide further evidence that the increased breast cancer risk from hormone replacement therapy (HRT) may not be present for all postmenopausal women, and they suggest that risk stratification by body mass index (BMI), race/ethnicity, and breast density could inform the prescription of HRT (1). Although other observational studies have also reported subgroup differences by these factors (eg, references 2–7), this is the largest study to date to investigate all three factors combined. In contrast, the largest randomized clinical trial (RCT) of HRT use and breast cancer, the Women’s Health Initiative (WHI), reported no statistically significant differences in the HRT and breast cancer association by BMI and race when the trial was stopped (8). Inconsistent results between RCTs and observational studies increase complexity for clinical interpretations based on risk stratification.

Discrepant results from RCTs and observational studies are frequently attributed to confounding and other biases. However, subgroup results from RCTs and observational studies may also disagree because RCTs may lack statistical power for specific subgroups. For example, the size of relative risk of breast cancer from HRT use for women with BMI under 25 kg/m² was 1.35 in both the Hou et al. and WHI trial studies, even though the interaction was not statistically significant in the latter (1,8). A lack of association was also observed in both studies in women with a BMI greater than 30 kg/m² (1,8). Unlike the Hou et al. study, the WHI trial did not report any differences by race/ethnicity, but this lack of association may have been because of the smaller numbers of non-white women in the WHI trial (8). Of the two other large observational studies with sufficient numbers of black women, one did not observe an increased risk with current HRT use in postmenopausal women (4), but the other study found an increased risk from HRT when considering the duration of HRT (3). Results from studies such as that by Hou et al. that lack details of HRT use, including type and duration, should be interpreted cautiously before drawing conclusions about risk stratification by race/ethnicity.

Beyond single stratifications by BMI and race, however, the Hou et al. study advances the literature by examining breast density in combination with these factors. Even this large study, though, is underpowered for examining race/ethnicity interactions with both BMI and breast density. Previous observational studies have supported a higher risk from HRT in women with low BMI or women with high breast density (2,3,5–7), but they have not addressed whether these factors operate synergistically. The results from the interaction between BMI and breast density provide added clarity on how to interpret risk for women with a BMI between 25 and 30, a group representing approximately a third of US adult women (9). The overall modest effect of 1.15 seen for women with a BMI of 25 to less than 30 is only elevated in the Hou et al. study.
after adjusting for a large number of confounders. Information on BMI missing on approximately half the sample, and complete case analyses limited to only 12% of the sample. Hou and colleagues perform multiple imputation and sensitivity analyses examining assumptions of nonmissing at random for the BMI data. Results of all three methods—complete case, multiple imputation, and the sensitivity analyses—suggest that women with BMI in the range of 25 to less than 30 kg/m² face an increased risk only if their breasts are heterogeneously or extremely dense. Breast density also provides useful information to refine risk stratification for women with a BMI higher than 30. Indeed, the relative risks for obese women with extremely dense breasts are remarkably similar to those for overweight women with the same breast density: 1.29–1.22. The lack of statistical significance in obese women with heterogeneously or extremely dense breasts may be due to small subgroup sizes, with each subgroup representing less than 4% of the study population. Thus it may not be prudent to advise obese women with dense breasts that they are at low risk.

The Hou et al. study clearly illustrates an increased risk of breast cancer from HRT in women with a BMI under 25. It also reveals that for women with BMI over 25, the most straightforward risk stratification may simply come from knowing their breast density. Both observational and RCTs have supported that HRT use and initiation increase breast density (eg, references 10,11). Further, increases in breast density from HRT did not differ by race/ethnicity in a subcohort of women from the WHI trial (12). Because increases in breast density have been associated with increased breast cancer risk (13), within-individual increases in breast density in all women can inform whether HRT should be discontinued. Regular monitoring of an individual's breast density changes is particularly important because HRT use may not be restricted to the period around menopause, and a nontrivial number of women are likely long-term users of HRT, as evidenced by the fact that more than 40% of HRT users in this study are 60 years or older.

In conclusion, the results of this study serve as a reminder of the importance of reevaluating evidence even after completion of very large and important RCTs. Hou and colleagues challenge us to consider whether HRT use may have minimal to no impact on breast cancer risk in certain subgroups. Properly weighing the risks and benefits of HRT requires an understanding of the absolute differences, in addition to the relative. Although we do not know the adjusted results, data from Table 1 suggest that in only a few subgroups, the rate difference for HRT users versus nonusers (per 1000 mammograms) is greater than 1: women 60–75 years and 80 years or older, Asian women, women with a BMI under 25, and women with extremely dense breasts. Even in these subgroups, the highest absolute rate difference in breast cancer from HRT is no larger than 2.24 per 1000. Ultimately, efforts that improve risk stratification, whether made through improved risk models or through measuring valid intermediate biomarkers such as breast density, will inform appropriate use of not only HRT, but also other medications including chemopreventive drugs.

References

Funding
Dr. Tehranifar is supported by Grant K07 CA151777.

Notes
The authors have no conflicts of interest to disclose. The study sponsor had no role in the writing of the editorial or the decision to submit it for publication. We would like to acknowledge Drs. Jeanine Genkinger and Mary Perrin for their thoughtful comments and review, and Ms. Angelina Protacio for her assistance in the preparation of this editorial.

Affiliations of authors: Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY; and Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY (MBT, PT).