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Response

Response to Pederson et al. and Chlebowski et al.

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We thank Pederson and colleagues (1) and Chlebowski and colleagues (2) for their thoughtful correspondence related to our study. As previously reported, our study did not suggest that vaginal estrogen therapy (VET) or menopausal hormone therapy (MHT) were associated with increased risk of recurrence or mortality. The concern expressed by Pederson and colleagues (1) is not linked to the overall conclusion but to a subgroup analysis that suggested an increased risk of recurrence, but not mortality, in patients receiving VET with adjuvant aromatase inhibitors (AI). Risk stratification is addressed with emphasis on HER2 expression and molecular signatures, which were not available for this cohort covering 1997-2004. The study included patients with low-, intermediate-, and high-risk tumors with 67% of the patients with a tumor size no larger than 2 cm, 57% of the patients with node-negative disease, and an anticipated relatively low number of HER2-positive and/or HER2-enriched patients (all having 10%-100% estrogen receptor expression) (3). Further, VET users more often had better prognostic characteristics, and multivariable analysis was applied to adjust for these differences. Pederson et al. (1) seem to infer that evidence obtained before introduction of HER2-targeted therapy and multigene profiles should be disregarded, which is a topic that extends far beyond our study. However, the individual randomized trials included in the Early Breast Cancer Trialists' Collaborative Group meta-analysis demonstrating a benefit from tamoxifen and AI were performed before HER2-targeted therapy was introduced, and the results appeared to apply to a small subset with known HER2-positive breast cancer (4).

The strengths of our study include the treatment of breast cancer patients according to national guidelines (5). As such, we expect that the risk of treatment allocation bias is small. Furthermore, the inclusion of periods where patients were untreated or received tamoxifen as the only endocrine treatment allowed comparisons with AI. Our ability to quantify endocrine therapy adherence, because of prospective therapy registration in the database of the Danish Breast Cancer Group, is another major strength that has been previously described (6). Our major concern regarding adherence to adjuvant endocrine therapy is unopposed genitourinary syndrome of the menopause, rather than when these symptoms are treated with VET. We considered VET use as the redemption of at least 2 prescriptions registered in the Danish National Prescription Registry. Yet, we cannot be certain that patients used their medication. Increasing our definition of VET use to more prescriptions may have increased the likelihood of prescription compliance. Still, in Denmark, patients pay a proportion of the cost of redeemed prescriptions, so prescription redemption is likely to reflect actual use (7).

We strongly agree with Chlebowski and colleagues (2) that randomized trial evidence should guide clinical decisions whenever available. Consequently, we referred to the available randomized evidence on MHT in breast cancer patients in our manuscript. We also explicitly stated that firm conclusions should not be drawn from our study regarding the use of MHT following breast cancer because of the small number and the nonrandomized design of our study. For the same reasons, we have restrained from presenting MHT therapy in categories.

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Data availability

No new data were generated or analyzed for the response.

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