Isolated Tumor Cells in Breast Cancer

TO THE EDITOR: In their article, de Boer et al. (Aug. 13 issue) suggest that adjuvant systemic therapy may improve disease-free survival in breast cancer. However, the apparent treatment effect may also be due to imbalances in prognostic and predictive factors (such as hormone-receptor status) that drive clinical decision making. The failure to distinguish between systemic chemotherapy and hormonal therapy and the use of composite outcomes that are mostly unrelated to nodal involvement further cloud the primary questions. Adjunctive hormonal therapy is currently recommended in most patients with hormone-receptor–positive tumors that are larger than 1 cm in diameter on the basis of the characteristics of the primary tumor alone, leaving the question of any added benefit from chemotherapy unanswered. This study raises important questions, but it should not be interpreted as a practice-changing study.

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TO THE EDITOR: In the absence of standardized therapy for occult nodal disease, de Boer et al. conclude, on the basis of a retrospective analysis involving 2707 patients with early breast cancer, that adjuvant chemotherapy improves disease-free survival in women with micrometastases or isolated tumor cells detected in a sentinel-lymph-node-biopsy specimen.

The lack of randomization and wide heterogeneity limit the power of this study. Among patients with micrometastases at baseline, axillary lymph-node dissection alone and axillary lymph-node dissection, axillary irradiation, or both were more often performed in the adjuvant-therapy group than in the no-adjuvant-therapy group (75.4% vs. 54.6% and 84.6% vs. 61.1%, respectively; P<0.001 for both comparisons). This more aggressive locoregional treatment in the adjuvant-therapy group makes the comparison unreliable. Additional differences in tumor grade and estrogen-receptor status between the previously mentioned groups and the lack of consideration of the
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metastases on disease-free survival, we conclude that small metastases can no longer be ignored.

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Age-Related Memory Decline and the APOE ε4 Effect

**To the Editor:** Cognitive decline is a complex multifactorial process, and so it is important to exclude as many potentially confounding variables as possible when assessing the influence of a single factor. In their longitudinal study, Caselli and colleagues (July 16 issue) apparently did not take into account some such variables, including alcohol consumption, mentally stimulating activities, and smoking. In addition, physical inactivity is reported to be a risk factor for cognitive decline, especially among persons carrying the apolipoprotein E (APOE) ε4 allele.

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**The Authors Reply:** We, too, are concerned about the multiple factors that might influence cognitive trajectories. There is little question regarding the potentially adverse influences of substance abuse and stroke, and so persons who reported a history of substance abuse or stroke were excluded from the study. Furthermore, anyone in whom mild cognitive impairment or dementia developed at any time, for any reason, was excluded.

In our cohort, there was no difference between APOE ε4 carriers and noncarriers with respect to the prevalence of hypertension (24.7% vs. 27.7%,...