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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Isolated Tumor Cells in Breast Cancer

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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TO THE EDITOR: Although the study reported on by de Boer et al. accounted for unequal distributions of most established prognostic factors in breast cancer, residual confounding may still have influenced the results. In particular, the lack of regard for molecular subtypes may have played a role. In luminal (i.e., estrogen-receptor–positive, HER2-negative) breast cancer, most events occur after the study end point of 5 years. The basal and HER2-positive subtypes will therefore drive the presented data. Data on HER2 status, however, are not provided. Moreover, trastuzumab was administered within the context of a clinical trial in some, but not all, of the Dutch hospitals during the inclusion period of the study. Small imbalances in the distribution of molecular subtypes and of anti-HER2–targeted therapy may thus have had a large effect on the outcome. The study would benefit from a stratified analysis according to the molecular subtype and with adjustment for the hospital. Also, modern molecular tools such as the 70-gene signature and the 21-gene recurrence score outweigh the impact of traditional prognostic factors. A study that reanalyzed the data from the original article by van ’t Veer et al. showed that a multivariate classification based on tumor grade, tumor size, and lymph-node status had an association with outcome that was as good as the 70-gene signature. Because of the magnitude of the effect of small metastases the influence of systemic therapy would have been even greater.

Sonke and Linn hypothesize that basal and HER2-positive subtypes drive the data, because in luminal breast cancer most events occur more than 5 years after the diagnosis. There is little evidence to support this assumption, since less than 8% of the patients in our study had a grade 3, or hormone-receptor–negative, tumor. Moreover, the decrease in disease-related events due to systemic therapy was largely the result of endocrine therapy. It is not at all clear yet whether gene signatures “outweigh the impact of traditional prognostic factors.” A study that reanalyzed the data from the original article by van ’t Veer et al. showed that a multivariate classification based on tumor grade, tumor size, and lymph-node status had an association with outcome that was as good as the 70-gene signature. Because of the magnitude of the effect of small metastases the influence of systemic therapy would have been even greater.

Roukos questions whether heterogeneity in locoregional treatment or tumor grade explains the results. As reported, after adjustment for tumor grade and axillary treatment, there remained a reduced risk of events among patients who were treated with systemic therapy (hazard ratio, 0.57; 95% CI, 0.45 to 0.73). From 1997 through 2005, neither HER2 testing nor the routine use of adjuvant trastuzumab had been fully implemented (except in some patients in trials). If patients in the adjuvant-therapy cohort had received trastuzumab, the influence of systemic therapy would have been even greater.

Lyman and Peppercorn advise caution because of possible imbalances in factors such as hormone-receptor status. In a Cox proportional-hazards model including hormone-receptor status, we found a hazard ratio for events (including distant metastases) of 1.51 (95% confidence interval [CI], 1.20 to 1.90) if the nodes were abnormal. We found that in patients with small metastases, combined chemotherapy and endocrine treatment was associated with an adjusted hazard ratio for events of 0.34 (95% CI, 0.21 to 0.55), whereas the hazard ratio associated with endocrine therapy alone was 0.60 (95% CI, 0.46 to 0.80). In the treatment-related analyses, we did not consider hormone-receptor status, since it partially determined the treatment allocation. The benefit from combination treatment is consistent with published data.

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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%,...