

and the treatment of postmenopausal women should be deferred until further follow-up data have been obtained.

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To the Editor: The design of the trial of adjuvant chemotherapy for breast cancer conducted by the Cancer and Leukemia Group B¹ unfortunately does not isolate any of the three main chemotherapy variables — dose size, dose intensity, and total dose.² It is notable, however, that despite different dose intensities there is no difference in the outcome of the two groups assigned to receive the same total dose, whereas there is a significantly inferior outcome among the patients randomly assigned to receive the low total dose. One may conclude that the total dose is the underlying basis for the observed differences, whereas the authors prefer to postulate a nonlinear dose–response or intensity–response effect.

If the survival benefit of adjuvant chemotherapy mostly accrues to patients who are incurable³ because of a drug-resistant minority clone, then both theory⁴ and laboratory models⁵ suggest that total dose is indeed the important determinant up to the point at which the sensitive cell population is eliminated in the majority of patients. If so, the conclusion that doses “should not be reduced” is unsound and may lead to inappropriate risk taking in the face of excessive toxicity. Although it is good clinical practice to give the maximal well-tolerated dose, it may be possible to compensate for dose reductions or delays with additional therapy to achieve the target total dose.

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To the Editor: In the study of the dose and dose intensity of adjuvant chemotherapy for breast cancer recently published in the *Journal*, one patient died three years after being treated for cardiomyopathy.¹ Given the well-known toxic effects of doxorubicin on the heart, doxorubicin-free combinations should be carefully evaluated. CMF chemotherapy is equally effective, at least in patients with fewer than four positive axillary lymph nodes.²⁻⁵ It is unfortunate that many clinical trials use doxorubicin as adjuvant chemotherapy for all patients with node-positive disease, regardless of risk factors. In a large proportion of young women with breast cancer, the implications of asymptomatic cardiomyopathy may not be fully realized for many years. I hope that local ethics committees will interfere and that for the time being they

will prevent patients with fewer than four positive axillary lymph nodes from entering trials that offer only adjuvant chemotherapy including doxorubicin.

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To the Editor: The study by Wood et al. evaluating the response of breast cancer in relation to the chemotherapeutic dose and dose intensity used the standard prognostic factors of tumor size and node involvement, along with the estrogen- and progesterone-receptor content of the tumor, to evaluate outcome.¹ We now report that patients with a family history of breast cancer have a shorter time to recurrence than patients with no such history.

We evaluated 137 women receiving radiation therapy for breast cancer between 1984 and 1994. Patients were selected if data were available on their tumor size, nodal involvement, any family history of breast cancer, and survival status. Information on the family history of breast cancer was obtained from the patient's chart or by interview. Tumor size and axillary-node status were determined from the surgical pathology report. The patient was considered to have no axillary-node involvement if histologic examination showed no node involvement after axillary dissection. The axillary nodes were considered to be involved if such involvement was demonstrated by histopathological examination. Only data on patients with

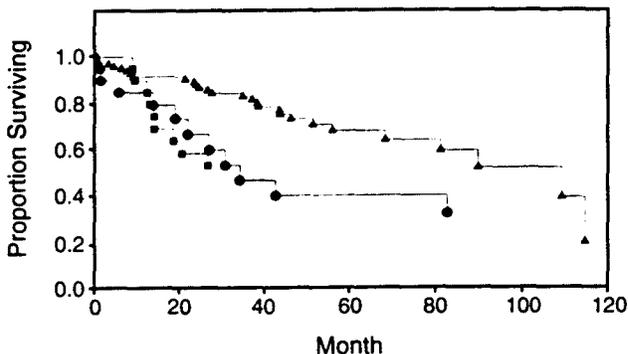


Figure 1. Kaplan-Meier Plot of Cumulative Recurrence-free Survival among 137 Women with Breast Cancer.

Triangles denote women with no family history of breast cancer, circles women with an affected first-degree relative, and squares women with a more distant affected relative.

Table 1. Cox Proportional-Hazards Regression Analysis of Cumulative Recurrence-free Survival among 140 Patients with Breast Cancer, with Control for Family History of Breast Cancer, Tumor Size, and Presence or Absence of Nodal Involvement.

VARIABLE	ODDS RATIO (95% CI)*	P VALUE
Family history	2.7 (1.4-5.0)	<0.003
Tumor size	1.3 (1.2-1.5)	<0.001
Nodal involvement	2.8 (1.6-5.1)	<0.001

*CI denotes confidence interval.

infiltrating tumors were included. Statistical analyses were performed with the SPSS system.²

The 41 women with a family history of breast cancer had a significantly shorter time to recurrence than the 96 women without a family history ($P = 0.02$ by the log-rank test) (Fig. 1). But there was no significant difference in the time to recurrence between 20 women with an affected first-degree relative (a mother or sister) and 21 women with a more distant affected relative (a grandmother, cousin, aunt, or niece) ($P = 0.7$ by the log-rank test) (Fig. 1). Proportional-hazards regression demonstrated that a family history of breast cancer has a significant effect on time to recurrence, independently of tumor size and nodal involvement (Table 1).

Because of the need to identify patients with breast cancer who can benefit from adjuvant therapy and to spare others the side effects, much effort has been spent testing new prognostic indicators.³ Family history of breast cancer, which is an easily obtained prognostic factor, may complement those already in use. Furthermore, it may be the only risk factor that is also a prognostic factor, since there is no association between survival and reproductive or hormonal risk factors, dietary variables, alcohol consumption, or smoking.⁴ Additional studies would be worthwhile in order to determine whether family history is indeed an independent predictor or whether it may be correlated with other predictors already in use.

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To the Editor: Muss et al. (May 5 issue)¹ report that overexpression of *c-erbB-2* (HER-2/*neu*) identifies those patients with node-positive breast cancer who will derive the most benefit from higher doses of cyclophosphamide, doxorubicin, and fluorouracil. They offer the caveat that estimation of the overexpression of this gene may not be ideal for the purposes discussed, since "no standardized assay is available."

We call your attention to our recent article describing a standardized Southern blot-based assay in which DNA derived from human breast-cancer cells and hybridized simultaneously to HER-2/*neu* and to a single-copy, reference-gene

probe accurately measures the gene-copy numbers in tumors.² We have shown that copy numbers of the HER-2/*neu* gene in patients can be readily obtained and compared with standards derived from breast-cancer cell-line DNA with established, amplified copy numbers. As stated by Muss et al.¹ and also shown elsewhere, immunohistochemical analysis of *c-erbB-2* expression correlates closely with HER-2/*neu* gene amplification.³⁻⁵

A large retrospective study using simultaneous hybridization for quantitation may accurately stratify groups of patients according to whether they will respond or will not respond to chemotherapy.¹ The quantitative nature of assays of gene-copy numbers, as compared with qualitative immunohistochemical staining, should delineate even fine differences among groups of patients and thus offer an opportunity for standardization.

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To the Editor: With regard to the article by Muss et al.¹ on the expression of *c-erbB-2* and the response to adjuvant chemotherapy in patients with breast cancer, this report concerns a subgroup of patients from the larger Cancer and Leukemia Group B trial of dose intensity in adjuvant breast cancer. It seems that the subgroup chosen for the investigation of *c-erbB-2* expression is somehow not representative of the total population from which the subgroup was culled, thus calling into question the validity of the results. That is, in the multivariate Cox model discussed on page 1263 and presented in Table 4, the dose of cyclophosphamide, doxorubicin, and fluorouracil (CAF) is not predictive of overall or disease-free survival. The variable prospectively studied and found to be a determinant of survival in the parent study² does not hold up in a Cox regression analysis of the subgroup of patients. I wonder if the authors would comment on this discrepancy.

A potentially more important point relates to the implications of the study by Muss et al. if the results turn out to be reproducible. Although adjuvant chemotherapy for stage II breast cancer is clearly efficacious, one must admit that the benefit is small. This small benefit may indicate either that all women benefited a little bit or that a small subgroup of women benefited a lot. The study of Muss et al. obviously did not include a no-treatment group, but if there is a threshold effect for chemotherapy,² then the low-dose group may be the same as a no-treatment group. One therefore wonders whether, for the 70 percent of patients with low *c-erbB-2* expression, adjuvant chemotherapy is doing nothing, whereas for the patients with *c-erbB-2* overexpression, chemotherapy has a large benefit. Addressing this possibility would be ethically problematic, but it would be impor-