Re: Biologic Characteristics of Interval and Screen-Detected Breast Cancers

The goal of mammography is to detect breast cancer before it spreads beyond the breast. Two recent studies (1,2) have compared histologic and other prognostic features of mammographically detected breast cancers with cancers that were detected clinically in the interval following a negative screen. These studies find that interval cancers are of higher grade and are more likely to have adverse prognostic features (such as being p53 positive and ER negative) than are mammogram-detected cancers. The tumors that are missed by mammography may, therefore, be more likely to metastasize and to lead to early mortality. Young age and a positive family history of breast cancer have also been associated with screening failure (3). These findings may be relevant for young women from high-risk groups who are enrolled in breast screening programs; for example, the majority of breast cancers associated with BRCA1 mutations appear in young women and are of high grade, are p53 positive and are ER negative (4).

The authors conclude from these comparisons that interval cancers are rapidly growing tumors and that the tumors were likely too small to have been detected on the previous mammogram. Another interpretation is that mammographic detectability per se is associated with favorable clinicopathologic features. To address this question, we reviewed the records of the Ontario Breast Cancer Screening Program for women diagnosed with breast cancer in the province from 1991 through 1998. The women in this program are screened by both clinical breast examination (CBE) and by mammography, usually on the same day. We compared the 84 tumors that were detected by CBE alone with 643 tumors detected by mammography alone. We restricted our study to women whose tumors were at least 1 cm in size.

There was no difference in the mean age of the two groups (62.6 years for CBE-detected tumors versus 63.4 years for mammogram-detected tumors). Tumors detected by CBE alone were, on average, larger than those detected by mammography (2.1 versus 1.6 cm: \( P<.001 \)), were more likely to be of lobular or mixed lobular histology (31% versus 11%; \( P<.001 \)), and were more likely to be lymph-node positive (34% versus 20%; \( P = .01 \)). Lobular histology is also an adverse prognostic feature and has been reported previously to be over-represented in interval-detected tumors (2,5). Our data are consistent with the hypothesis that mammography preferentially identifies cancers with favorable prognostic features. However, our study differs from previous studies in that the CBE-detected cancers were detected on the same day as the negative mammogram; therefore, we cannot claim that the mammography would have performed better if the screening interval were shortened.

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RESPONSES

Recent articles in the Journal by Gilliland et al. (1) and Porter et al. (2) suggest that cancers that are detected in the interval between screening mammograms are more likely than mammographically detected tumors to have features, such as high tumor grade, estrogen receptor negativity, and p53 positivity. One explanation for this is that mammographically occult tumors with such features might proliferate rapidly, growing larger, and becoming palpable in the interval between mammograms. Indeed this argument has been used to suggest there is equipoise for research into the benefits and risks of reducing the time between screening examinations (1). However, an alternate hypothesis is that tumors with these features might be less easily radiographically detectable. Unfortunately, in neither of these articles is there data on whether the interval-detected tumors could be seen on diagnostic mammograms performed at the time of their clinical detection. In an attempt to address this issue, Narod et al. present data from the Ontario Breast Cancer Screening Program showing that palpable tumors not visualized by mammography were more likely to have lobular or mixed lobular histology, to be larger, and to be axillary lymph node positive. However, it is unclear from the data presented whether these features were independently statistically significant on multivariate analysis or whether the features highlighted as important in the previous articles (tumor grade, hormone receptor status, and p53 mutation status) were examined. Indeed, the major finding seems to be that lobular tumors are more likely to be mammographically occult, an observation that has been well documented previously (3,4).

It is suggested that the findings of the studies by Gilliland et al. (1) and Porter et al. (2) may have implications for mammographic screening of BRCA1 mutation carriers. BRCA1-associated breast cancers have a relatively homogeneous phenotype that generally includes high grade, p53 positivity, and estrogen receptor negativity (5). Indeed, one small study of the mammographic appearances of breast tumors from BRCA1 mutation carriers showed that
palpable cancers in BRCA1 carriers are less frequently visualized on mammography than palpable tumors of age-matched control subjects (6).

Screening young BRCA1 carriers with mammography has well recognized problems, including the decreased sensitivity of the test in younger women from increased breast density. The finding that the biologic type of breast cancer usually associated with BRCA1 mutation may be less frequently detected by mammography increases concern that regular mammography may be of less value than hoped in this situation. In addition, some have voiced concern about the possibility of breast cancer induction by mammography in women who are at increased genetic risk (7), an argument that is supported by the proposed DNA repair function of BRCA1, but for which, to date, inadequate clinical data exist to support or refute.

Clearly, further studies are required to elucidate this issue, both in the general population and in women who carry mutations in cancer predisposition genes. In the meantime, some may wish to incorporate these data in the discussion about the pros and cons of various surveillance and prevention options for mutation carriers. Where possible, such women should be offered participation in trials of possible alternate screening methods such as magnetic resonance imaging.

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Drs. Narod and Dube describe a study that compares women with tumors greater than 1 cm detected by clinical breast examination (CBE) mammography. Whereas their control group is composed only of subjects detected by CBE, our control group was composed of all cancers missed by mammography. This is an important distinction because the Narod study only compares a subset of missed cancers to those detected by mammography (only 23% of our mammography-negative [interval/missed] cancers were detected by CBE on the day of the mammogram—the rest were missed by both modalities and detected after developing symptoms). Since the comparison group for our study included women with cancers of any size missed by mammography for any reason, their study and ours resulted in data that are not comparable and the conclusions from each study should be evaluated separately.

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