Proliferative Breast Disease: Diagnosis and Implications

M. H. Skolnick et al. (1) obtained specimens by multiple fine-needle aspiration from the breasts of women with and without a family history of breast cancer. They assessed the prevalence of certain cytologic changes in these groups of women, which they labeled proliferative breast disease (PBD). Skolnick et al.’s use of this term is unfortunate because PBD is a well-recognized histologic diagnosis (2, 3) of changes that bear only a slight and untested resemblance to the cytologic findings in (1). In order to avoid confusion, we will hereafter use PBD in its conventional sense.

Although PBD is consistently associated with increased breast cancer risk (4), studies have not been performed which show that cytologic abnormalities or similarly defined patterns have such an association. Skolnick et al. cite three papers that discuss fine-needle aspiration criteria for hyperplastic or proliferative lesions of the breast. One of these (5) states, “The limitations of [fine-needle aspiration] for diagnosing mild-to-moderate atypical hyperplasia appear to be greater than those of surgical biopsy since we were not able to define cytologic changes diagnostic for this lesion.” Thus it is not clear why Skolnick et al. conclude that cytologic abnormalities are a significant risk factor for breast cancer. Their use of the term PBD to describe their findings could result in a demand for needle aspirations in asymptomatic women, the clinical value of which is unproved.

It is possible that the cytologic results of Skolnick et al. were affected by nonresponse bias. Case patients had numerous relatives with breast cancer. Controls were women related by marriage to the case subjects. Skolnick et al. do not state how many eligible controls were available, but, because there were 103 case subjects, the number was potentially large. Only 31 women volunteered to serve as control subjects, probably because this meant undergoing eight passes of a needle in each of eight sites within the breasts. It seems likely that participating controls differed from nonparticipants with respect to their concern about breast cancer and other factors associated with breast cancer risk. One of these factors is age; the average age of controls was 6 years greater than that of case subjects (52 versus 46 years). This is important because cytologic changes in the breast epithelium usually become less prominent soon after menopause or in the years immediately preceding it. Thus it is plausible that the different prevalence of cytologic abnormalities among cases and controls was attributable to differences in ages between the groups.

Skolnick et al. found that cytologic abnormalities were only 2.6 times more common in women with family histories of breast cancer than in women without such a history. Using the more conventional and stringent two-sided test, and removing the two women with suspicious mammograms (and, indeed, cancer) from the numerator, we calculate P to be 0.06, rather than the reported 0.02. This weak association links the cancer risk already known to be present because of family history with a cytologic finding of unknown significance. A “lesion” must be shown to be linked to a verifiable clinical outcome, such as cancer development or death from cancer, if it is to be denoted as a valid risk factor.

In our cohort of more than 10,000 women who underwent benign breast biopsy (2) we found no association between PBD without atypia and a first degree family history of breast cancer; the prevalence of these lesions was 27% and 29% in women with and without such a history, respectively. Women with this family history did, however, have a higher prevalence of atypical hyperplasia than did women without this history (4.8% and 3.9%, respectively, P = 0.02, two-tailed). Because family history and atypical hyperplasia have a highly synergistic effect on breast cancer risk (2), it would be appropriate to look for these lesions in women with family members who have developed breast cancer. This, however, cannot be done by fine-needle aspiration.

Response: Page and Dupont suggest that we have misused the term “proliferative breast disease” (PBD), in part because we did not take our samples from histologic sections. Because we preferred to use a less invasive procedure on clinically normal women, we undertook cytomorphicologic examination of specimens obtained by systematic fine-needle aspiration.

The lesions we found appear to represent the same process as those described as PBD on the basis of examinations of histologic sections. Bibbo et al. (1) state that they could not define cytomorphologic criteria that were concordant with mild-to-moderate atypical hyperplasia defined histologically. However, their histologic and cytologic diagnoses were concordant for severe atypical hyperplasia. Their results revealed a continuum of changes between proliferative lesions. There is disagreement among histopathologists about the subclassification of a specific lesion and about the criteria to be used in diagnosis. The consistency of subclassification does not affect our reported findings, as we made no attempt to subclassify atypical hyperplasia. Masood et al. (2) examined the cytologic diagnosis of proliferative and nonproliferative breast disease in mammographically guided fine-needle aspirates and reported that “A high degree of concordance (90% to 99%) was found between the cytologic findings and the histologic diagnosis. This study suggests that it is possible to apply a cytologic grading system to further subclassify benign breast disease and to distinguish these forms from neoplastic lesions.”

Terminology aside, one pathologist performed a blind evaluation of the aspirates in our study using consistent cytomorphic criteria that describe cellular proliferation (3). A parsimonious explanation for our results is that PBD is a phenotypic expression of a susceptibility allele in these kindreds. We therefore chose not to create a new and potentially confusing term. Inherited PBD will eventually be defined genotypically by specific DNA sequences at specific loci, and phenotypically by molecular analysis of expression of specific oncogenes, the inactivation of specific tumor suppressor genes, and quantitative histologic and cytologic analysis.

If there had been nonresponse bias in our

REFERENCES


14 January 1991; accepted 17 June 1991