Protective Effect of Cigarette Smoking on Breast Cancer Risk in Women With BRCA1 or BRCA2 Mutations??

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By reporting, in this issue of the Journal, a protective association of cigarette smoking and breast cancer risk among women with germline BRCA1 or BRCA2 mutations, Brunet et al. (1) have placed themselves at the intersection of several controversial currents in contemporary cancer research. Cancer genetics and genetic epidemiology are progressing at an exciting pace. However, understanding of how genetic and environmental factors act independently and together to define breast cancer risk remains fragmentary. Similarly, although there is active research into how genetic factors might modify the cancer risks associated with cigarette smoking, few clear patterns have emerged (2). Lack of understanding of the hormonal effects of smoking and of the hormonal basis of breast cancer adds to the difficulty of clarifying how smoking might affect breast cancer risk (3).

In its general design, the investigation by Brunet et al. (1) is simply a case–control study. However, details of the investigation are complex, and several aspects of the research affect interpretation of the findings. Most of these are discussed by the authors, i.e., the use of prevalent cases, convenience samples of case and control subjects, and the possibility of selection bias through differential recruitment. The last issue bears further consideration. Most case subjects in the study were presumably the affected women whose diagnosis led to genetic testing and the identification of the high-risk families. In contrast, the control subjects were unaffected and probably had different reasons to receive genetic testing. While smoking is likely to have been irrelevant to the decision of case subjects to be tested, control subjects who smoke might have been particularly motivated to attend the genetic counseling center. If this were the case, it would have led to a higher prevalence of smoking among study control subjects, and so might account for some or all of the observed protective association. Such a pattern of differential recruitment seems to have occurred in a mammography screening study conducted in the U.K. (4).

Two other considerations are also relevant. The case and control subjects were drawn from groups of families, but this clustering (in effect, a “matching”)) was not taken into account in the analysis—a feature that would tend to bias the findings conservatively (5). Family history of breast and ovarian cancers was also not taken into account, but it could conceivably have acted as a confounding factor if cancer occurrence in a family alters smoking patterns in unaffected relatives.

Cigarette smoking is a well-known cause of cancer in the aerodigestive tract, at sites having direct contact with the cigarette smoke. Smoking has also been causally associated with cancer at anatomic sites that lack direct smoke contact, such as the urinary tract and pancreas (6). As a result, cigarettes almost certainly represent the most prevalent potent carcinogenic exposure in the industrialized world. In this context, the temptation might be to dismiss the findings of Brunet et al. as simply implausible. However, breast cancer is usually considered to be an estrogen-dependent cancer and women who smoke cigarettes do appear to be relatively estrogen deficient, having an early menopause, an increased risk of hip fracture, and decreased risks of endometrial cancer, uterine fibroids, and endometriosis (3). Indeed, some studies of sporadic breast cancer have also found an inverse association of breast cancer risk with smoking (3,7).

It is plausible that cigarette smoking might interact with genetic factors in its actions on breast cancer risk. An interaction of smoking with another genetic trait, N-acetyltransferase-2 (NAT2) genotype, has also been proposed (8), although conflicting data have been presented (9). More generally, it is possible that in the breast, the carcinogenic effects of smoking are counterbalanced by antiestrogenic effects. This could create an unstable balance of factors, leaving no net effect on risk, or a net effect that varies according to the genetic makeup of the individual woman and her environmental exposures. However, for several reasons, the estrogen dependence of breast cancer and an antiestrogenic effect of smoking are not completely satisfying explanations for the findings of Brunet et al. As discussed above, this study cannot be considered conclusive; rather, it raises the possibility of a protective effect. Also, the relationship between cigarette smoking and breast cancer risk has been extensively investigated and, overall, smokers do not have a materially increased or decreased risk (3,7). Suggestions that smoking may increase risk in certain subgroups, e.g., women who begin smoking at an early age (7), have not generally been reproduced (10). It has been hypothesized that passive smoking may increase breast cancer risk (11), but this suggestion needs to be clarified in the context of the null findings overall regarding active smoking versus nonsmoking, and the fact that active smokers are the most heavily exposed passive smokers. Moreover, the estrogen dependence of breast cancer is not well characterized and, in any case, is less marked than that for endometrial cancer. While the risk of breast cancer is plainly related to ovarian hormones, it is less clear that estrogens alone explain this dependence or that the estrogen association is a direct,

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simple one (3). Finally, the basis of the antiestrogenic effect of smoking is not understood. Among women who take oral estrogens, smokers have lower circulating estrogen levels than non-smokers, but endogenous estradiol and estrone levels are not lower in smokers (3,12,13).

The study by Brunet et al. raises other important questions. For example, do estrogen-related exposures other than cigarette smoking modify the risks conferred by BRCA1 or BRCA2 mutations? The authors mention hormone replacement therapy, and we would add the question of oral contraceptives, since BRCA1 or BRCA2-related breast cancer tends to occur in women at the premenopausal ages when these drugs are used. In this regard, there has already been one published study suggesting a possible interaction between oral contraceptives and BRCA1 or BRCA2 (14). These findings also raise the question of whether genes involved in estrogen metabolism may modify risk in BRCA1 or BRCA2 carriers.

This study certainly should not be taken as encouragement for women with BRCA1 or BRCA2 mutations to smoke. However, the study findings, if confirmed, raise the possibility that smoking—or a constituent of cigarette smoke—could benefit these women. In order for the net harm or benefit of smoking to be estimated, the findings of Brunet et al. need to be confirmed and put into the context of accurate estimates of BRCA1 and BRCA2 penetrance. The possibly decreased breast cancer risk associated with smoking could then be quantified and weighed against its abundant and well-known detrimental effects. If smoking is truly protective among women carrying BRCA1 or BRCA2 mutations, and if the underlying mechanisms are understood, a more appropriate pharmacologic intervention may be possible. On all of these accounts, further research with well-designed, population-based investigations and appropriate chemoprevention studies is needed.

References