**Editorial**

Smoking and Breast Cancer: Is There Really a Link?

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Epidemiology suggests that environmental factors are important in the etiology of the vast majority of cases of breast cancer, the leading cause of cancer death in women worldwide, but thus far has given only limited indication of what they are (1, 2).

Are genotoxic agents involved? Indirect evidence suggests that, for at least a proportion of cases, they might be (3, 4). Could tobacco smoking be a cause of breast cancer? Most epidemiology says no (5). Yet the hypothesis is at least plausible (6); some of the genotoxic carcinogens in tobacco smoke are mammary carcinogens in rodents (7), the enzymatic machinery required for their metabolic activation is present in human mammary epithelial cells (8), and there is evidence for the presence in human mammary tissue of carcinogen-DNA adducts (9, 10), some of which may be smoking related.

Why then do most epidemiology studies conclude no effect of smoking on breast cancer? Perhaps because (a) there really isn’t one; (b) there is, but the association/risk is too small to detect; (c) for some women there is a risk, whereas for others there is some protection (e.g., smoking is known to lower the age of menopause, thereby reducing a woman’s lifetime exposure to estrogen). Thus, it is conceivable that epidemiologic studies that stratify the population in the right way might reveal a hitherto undetected association.

In 1996 Ambrosone et al. (11) reported that NAT2 slow acetylators who smoked had a significantly elevated risk of breast cancer. Fast acetylators had a statistically nonsignificantly decreased risk. If the population was unstratified, no effect was observed. Eleven years on, these researchers have conducted pooled and meta-analyses using the 13 studies that have addressed the same issue (12). Both analytic approaches lead to the same conclusion: NAT2 slow acetylators have increased risk of breast cancer from smoking. Unlike many initial epidemiologic observations, the association has not gone away in repeat studies.

Genotoxic agents that are detoxified by NAT2 might linger longer in the breast tissue of an NAT2 slow acetylator than of a fast acetylator. Tobacco smoke is a source of such agents. One study showed higher DNA-adduct levels in mammary tissue of NAT2 slow acetylators compared with fast acetylators (13). The gene-environment interaction between cigarette smoking and NAT2 slow acetylator polymorphisms has also been observed for bladder cancer (14).

It has been known for some time that the different phenotypes for NAT2 are associated with different outcomes for risk of cancer at specific sites. Although the slow acetylator alleles are associated with increased risk for bladder and lung cancer, the rapid acetylator alleles have been associated with higher risk of colon cancer (15). To add to this complexity, it also seems that, across certain cancer sites, the specificity of the carcinogen might also determine which NAT2 phenotype is the riskier one. In contrast to the interaction between smoking and slow acetylation, Hein et al. (16) reported that NAT2 rapid acetylation is associated with breast cancer for people consuming well-done meat, a result similar to that seen for meat consumption and bladder cancer.3

It seems that, for breast cancer, the relative risk due to NAT2 slow acetylator status is rather modest, ~1.5. There can still be considerable uncertainties about whether such small values define real associations; indeed, in one analytic approach (the pooled analysis), the lower 95% confidence interval is perilously close to unity (1.08). For the individual woman smoker who is an NAT2 slow acetylator, the risk of breast cancer would perhaps not be the primary health concern, given the larger risk of many other adverse health outcomes from tobacco smoking. However, from a public health perspective, the high prevalence of breast cancer means that the relative risk of ~1.5 for the 50% or so of the population who are NAT2 slow acetylators equates to a heavy burden of extra and avoidable cases of the disease.

Other studies have focused on the age when smoking begins, and suggest that there is a susceptible period early in adult life (17), akin to the risk of breast cancer from ionizing radiation observed among atomic bomb survivors (18). For the majority of smokers, the first exposure to tobacco smoking is in adolescence and smoking remains popular among the young. Thus, smoking may well be a contributing factor to the etiology of breast cancer in western societies, at least for a sizeable subpopulation.

Whether it is legitimate to carry out subgroup analysis when a main effect of the exposure is not seen has been debated by epidemiologists. It has been maintained (19) that such subgroup analysis, with respect to genetic

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polymorphisms, is not only legitimate but is required to truly understand the biology of environmental carcinogen risk. The beginning of an understanding of the genetic differences across populations and individuals that confer differences in susceptibility to the effects of environmental carcinogens (a reality that has been recognized for decades) represents a strong advance. A recent study suggests that BRCA1 and BRCA2 mutation carriers who smoke have 2.3-fold (95% confidence interval, 1.6-3.5) and 2.6-fold (95% confidence interval, 1.8-3.9), respectively, higher risk of breast cancers than carriers who do not (20). The Ambrosone paper on breast cancer, smoking, and NAT2 genotype is another important step (12).

References
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