EDITORIAL

Breast Cancer, Heart Disease, and Whispering “Fire” in a Public Theater

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In this issue of the Journal, Martin and colleagues describe findings from a prospective analysis of serum lipids and breast cancer risk (1). They observed high-density lipoprotein (HDL) cholesterol to be positively associated and low-density lipoprotein (LDL) cholesterol (non-HDL cholesterol) to be inversely associated with breast cancer risk. They conclude both the discussion and the abstract with a caution that interventions to raise HDL or lower LDL to prevent cardiovascular disease might increase risk for breast cancer.

We believe there is no basis for concern about trade-offs between cardiovascular disease prevention and breast cancer risk and that any such public perceptions could have an adverse impact on public health. In this editorial, we will examine the evidence presented by Martin and colleagues (1) and will argue that because such a trade-off is unlikely to exist, it could be dangerous to whisper such warnings in the theater of public discourse.

The strength of the analysis by Martin and colleagues (1) comes from their multiple measures of serum lipids, which allowed them to both minimize intra-individual variation and also account for confounding effects of time-varying factors related to both endogenous and exogenous female steroid hormones. We think the evidence strongly supports a conclusion that the association between serum lipids and breast cancer risk is because of confounding by circulating steroid hormones or their carrier proteins because of other factors tied to mammographic density variation within this cohort may well be confounding factors in this association with circulating lipids.

Thus, it seems to us quite likely that the inverse association between LDL cholesterol and breast cancer is because of confounding or mediating effects of circulating female steroid hormones. This argues for an important role of female steroid hormones in the relationship between breast cancer risk and circulating lipids.

1. The association between lipids and breast cancer risk was not seen in the overall analysis in which multiple lipid measures were averaged. That association appeared only after creating subaverages for life periods defined by variations in endogenous female steroid hormones (pre- vs postmenopause) and use of hormone replacement therapy (HRT). This argues for an important role of female steroid hormones in the relationship between breast cancer risk and circulating lipids.

2. Both the positive association between breast cancer and HDL cholesterol levels and the inverse association between breast cancer and LDL cholesterol levels were limited to the estrogen receptor (ER)–positive subtype of breast cancer. In many other studies for factors such as HRT and obesity, this same specificity of associations for ER-positive breast cancer has been generally accepted as compelling evidence for mediation of those factors by female steroid hormones.

3. The lipid associations were not seen among women using HRT, which has been shown to raise HDL and lower LDL as well as increase breast cancer risk. This pattern of no effect among HRT users is also seen for postmenopausal obesity and is generally accepted as evidence that elevations in circulating female steroid hormones increase risk regardless of whether they are from endogenous or exogenous sources but without additive effects.

4. Mammographic density is known to be associated with increased breast cancer risk, with female steroid hormones, and also to be positively associated with HDL cholesterol and inversely associated with LDL levels (2,3). The analysis by Martin and colleagues was from a cohort of women selected specifically because of higher than normal mammographic density. Factors associated with mammographic density variation within this cohort may well be confounding factors in this association with circulating lipids.

5. Alcohol is known to be strongly positively associated with both HDL cholesterol levels and breast cancer risk (4,5). Alcohol data were collected during this study, but Martin and colleagues did not account for alcohol in their analysis. Alcohol is a likely confounder of the breast cancer-HDL association they have reported.
hormones, their binding proteins, and/or other factors tied to mammmographic density, and that the positive association between HDL and breast cancer is because of confounding effects from those same factors plus alcohol.

Obesity, physical activity, and HRT are behavioral factors that affect risk for heart disease, breast cancer, and stroke in the same directions (4–7). Obesity increases breast cancer risk via endogenous female steroid hormones and their binding proteins in postmenopausal women, and it increases heart disease and stroke risk via effects on blood pressure, circulating lipids, glucose homeostasis, and chronic inflammation. Mechanisms for the benefits from physical activity are less certain for these diseases but may well include both direct effects on the risk factors listed above as well as indirect effects on long-term weight control and metabolic fitness. Hormone replacement therapy increases risk for breast cancer, heart disease, and stroke: cancer via driving estrogen-mediated cellular growth, and cardiovascular diseases via effects on blood clotting. The only behavioral factor for which the effects on risk for these diseases differ is alcohol, which is positively associated with breast cancer risk and stroke, but inversely associated (only at moderate levels of consumption) with heart disease risk (8).

Randomized controlled trials for heart disease risk reduction using either behavioral modification targeting diet and physical activity or pharmacological interventions targeting circulating lipids have not shown signals of increased risk for breast cancer. In fact, statins may reduce risk of breast cancer recurrence (9). Thus, there is no empirical evidence for any trade-off between cardiovascular disease prevention and breast cancer risk, apart from the theoretical trade-off of increased breast cancer risk with alcohol consumption. However, intervening to increase alcohol use is not a recommended approach for heart disease prevention (4,8). In fact, for most women who consume alcohol, the evidence-based advice to consume no more than one drink a day would result in a reduction in consumption, not an increase, and we are not aware of any cardiovascular disease prevention guidelines recommending initiation of alcohol consumption among nondrinkers. Because of the similarity in risk factors for cancer, heart disease, and diabetes, the American Cancer Society, the American Heart Association, and the American Diabetes Association have joined together in common messaging on disease prevention (10).

We do not disagree with publication of observational association data of this type, but where we do disagree with Martin and colleagues is in their speculation at the close of both the discussion and the abstract about the possibility of a trade-off of causing breast cancer by reducing risk of cardiovascular disease. At the close of the abstract, they state, “The possibility that interventions for heart disease prevention, which aim to reduce non HDL-C and raise HDL-C, may have effects on breast cancer risk merits examination.” Although this type of “more research is needed” statement is far from crying “fire” in a crowded theater, we think it is like whispering “fire” in the crowded theater of public communication. The JNCI is a high-profile journal, and its papers frequently attract national media attention. Any news stories implying this concern about a trade-off of increasing breast cancer risk from following guidelines to reduce risk for cardiovascular disease could cause public health harm. We think speculation about any such trade-off cannot be supported by the evidence.

References