Fruit and Vegetable Intake and Breast Cancer Risk: A Case for Subtype-Specific Risk?

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In this issue of the Journal, Jung et al. (1) report no overall effect of fruit and vegetable consumption on breast cancer risk among women in the large, long-term Pooling Project of Prospective Studies of Diet and Cancer (Pooling Project). When the authors considered hormone-responsive, estrogen receptor (ER)-positive patients separately from the nonhormonal, ER-negative patients under a hypothesis of separate etiologies, a statistically significant protective effect of fruit and vegetable consumption was observed for risk of ER-negative, but not ER-positive breast cancer. Most striking, the authors provide evidence that the protective effect of fruit and vegetable consumption for ER-negative breast cancer, in terms of magnitude and direction, were largely consistent across the 20 pooled studies. With these findings, Jung et al. (1) add to the growing number of studies reporting the differential effect of risk factors, including the classic breast cancer reproductive risk factors such as age of first pregnancy, when breast cancer is considered as separate subgroups such as ER-positive, ER-negative and triple negative breast cancer (2). These studies indicate that considering ER-positive and ER-negative breast cancer as a single disease in diet association studies has likely resulted in an underestimation of risk and a possible failure to detect even modest effects that may modify ER-negative breast cancer risk. These findings support the concept of distinct natural histories of hormone-dependent and hormone-independent tumors, as has been suggested by molecular profiling studies (3) and as heralds back to the findings from the Iowa Women's Study, which described differences in reproductive factors and risk for ER-positive, progesterone receptor-positive, and ER-negative breast cancers (4).

For more than four decades, the role of fruit and vegetable consumption as dietary modifiers of breast cancer risk has been studied (5). Despite several mechanism-based hypotheses favoring a role for a protective effect of higher intake of plant-rich diets (6,7), results from population-based studies of fruit and vegetable intake and breast cancer risk have been inconsistent and suggestive of protection only for hormone-responsive breast cancer (5). Given the evidence for etiologic heterogeneity among breast cancers, questions emerge. Most immediate is whether or not we know enough about the tumor subtypes to begin to separate breast cancer into distinct diseases for testing epidemiological associations. And, importantly, why do so? Support for the separation of breast cancer on ER status as a first approximation of distinct etiological histories exists from hierarchical clustering from gene expression profiling that shows a clear first level split on ER staining positive or negative (8,9). For the question of why, we can look at the present findings. The protective association with the high degree of consistency demonstrated from usual dietary intake of fruits and vegetables for ER-negative breast cancers is evidence of the role of subtypes in segmenting diet–disease risk.

It is critical in this case to consider the biological plausibility of the findings. These findings align well with long hypothesized roles of dietary constituents found in fruits and vegetables (eg, carotenoids, polyphenols, isothiocyanates, folate, etc) as modifiers of protumorigenic oxidative stress, inflammation and related gene expression (10). In fact, the associations of individual fruits and vegetables observed in the study support extensive research on the presence of a number and variety of plant-based bioactives with cancer prevention properties and include those associated previously with lower risk of breast cancer (11). For example, our own research (12), as well as the research of others (13,14), has demonstrated that regular intake of vegetables and fruit may afford protection against oxidative stress in high-risk individuals, including those with poor nutrition and/or with poor health indicators. However, a protective response in short-term feeding studies is not always demonstrated in healthy individuals (15). In the study by Jung et al., a number of individual plant foods were protective against ER-negative disease. These included strawberries rich in ellagic acid, apples rich in quercetin and peaches/nectarines/apricot, carrots and leafy lettuces/greens rich in carotenoids. In fact, total circulating carotenoids were associated with a 19% reduction in breast cancer risk in a recent pooled analysis by Ellisassen, et al (16).

Further, we believe it is important to consider the observation that ER-negative disease, particularly triple-negative disease, is disproportionately higher in younger women and in women of black and Hispanic ethnicity in areas of low socioeconomic status (17,18). The sharing of excess risk in these populations for more aggressive breast cancers has been hypothesized, in part, to reflect different reproductive patterns (eg, higher parity)(19), with others suggesting that the higher prevalence of ER-negative disease is about poverty and not race/ethnicity (20). A study conducted in Scotland found a similar higher frequency of ER-negative breast cancers among women living in poverty (21), an existence associated with high stress, greater exposure to environmental toxicants, higher levels of DNA-damaging reactive oxygen species, and concomitantly poor nutrition (22–24).

So is this a case of yes, fruit and vegetable intake reduces the risk of breast cancers that manifest from oxidative and environmental stressors as opposed to those driven by hormonal factors? Or, conversely, are we still struggling with residual confounding? Although, we would like to think the former because of the opportunity it provides for prevention, we have to consider the latter and approach these findings with some caution. Despite the robust findings of this pooled analysis of a very large set of prospective studies and nearly one million women, limitations in the self-report of dietary measures is a well-recognized source of bias (25). There continues to be a need for greater emphasis on...
validated and more strongly correlated biomarkers of vegetable and fruit exposure in evaluating these associations, especially in relation to variety in intake as well as intake of selective plant-based bioactives with anticancer properties in model systems. Further, interpretation of these findings may also be challenged by the known effects of other potential confounders, including the aggregation of health behaviors (e.g., high vegetable intake, physical activity, nonsmoking, and cancer screening) that make it difficult to separate specific factors that act independently to reduce ER-negative breast cancers.

In the simplest take-home message, the findings of this study support the emphasis of public messages for greater vegetable and selective fruit intake by extending a potential benefit for ER-negative breast cancer. More challenging is the need to confirm the findings across a more diverse population (the Pooling Project includes predominantly non-Hispanic whites) and to consider additional disease heterogeneity, especially given the large percentage of studies with missing information on hormone receptor status. If, in fact, ER-negative, ER-positive, and possibly HER2-positive tumors (26) develop through distinct natural histories, the fields of pathology and epidemiology will be tasked to routinely collect and report information on tumor markers for breast tumors for use in evaluating risk factor associations in a disease-specific manner. Without these data, much of our epidemiological estimates for risk factor associations will be skewed, underestimated, and even missed. Most important, without a reasonable understanding of the extent and discriminators of etiological heterogeneity, we will be unable to identify lead hypotheses from the human population studies to advance efforts in prevention.

References

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