Response

Zuchetto and colleagues (1) have presented results of a study of high- and low-fat dairy and breast cancer survival based on dairy consumption in Italy. The investigators' results differ from the results we presented from the Life After Cancer Epidemiology (LACE) study in which higher consumption of high-fat dairy was associated with an increased risk of breast cancer mortality in long-term breast cancer survivors. There is a considerable amount of research to be done in this area, and we are pleased that our work has stimulated others to examine this question.

There are study design differences that could produce differences in findings. Our study examined postdiagnosis diet in a population of early-stage, primarily postmenopausal, primarily hormone receptor–positive breast cancer survivors diagnosed from 1997 to 2000, whereas the Italian study used prediagnosis diet and included women with any stage breast cancer diagnosed from 1991 to 1994. Zuchetto et al. (1) indicated finding similar associations for those with early-stage cancer and postmenopausal women, although the proportions of those women who were pre- vs postmenopausal or who had hormone receptor–positive vs hormone receptor–negative breast cancers in Zuchetto et al.'s study are unclear. However, postdiagnosis diet may provide a more valid measure of the influence of diet on breast cancer outcomes. In previous work, we found that associations of diet and breast cancer mortality differed depending on whether diet was measured pre- or postdiagnosis (2). For example, a greater intake of a prudent diet measured prediagnosis was unrelated to postdiagnosis mortality, although prudent diet measured postdiagnosis was related to a lower risk of mortality from causes other than breast cancer. This might help to explain the stronger findings in our study; diet measured after diagnosis may be the more relevant point in time with regard to mortality outcomes after breast cancer diagnosis (3). However, this does not help to explain the discrepant findings within the Zuchetto et al. (1) study because, although high-fat cheese was related to a lower mortality risk, high-fat milk intake appeared to be positively related to breast cancer mortality.

One concern indicated by Zucchetto et al. (1) was that the only component of high-fat dairy with sufficient intake in LACE was butter. We indicated we had limited power to look at individual dairy items, although associations for high-fat dairy products, not just butter, appeared generally positive with breast cancer mortality. High-fat milk and yogurt intakes were acknowledgedly small. However, women in the LACE study consumed more high-fat dairy desserts and cheese than low-fat versions. We found evidence for graded, increasing associations for those dairy products with sufficiently varied intake. Compared with women in the lowest tertiles of butter, high-fat cheese, and high-fat dairy dessert consumption, those in tertile 2 (hazard ratio [HR] = 1.03; 95% confidence interval [CI] = 0.73 to 1.46) and tertile 3 (HR = 1.58; 95% CI = 1.04 to 2.41) of butter, tertile 2 (HR = 1.26; 95% CI = 0.89 to 1.78) and tertile 3 (HR = 1.40; 95% CI = 0.82 to 2.39) of high-fat cheese, and tertile 2 (HR = 1.18; 95% CI = 0.79 to 1.77) and tertile 3 (HR = 1.33; 95% CI = 0.83 to 2.15) of high-fat dairy dessert had apparently higher risks of breast cancer–specific mortality for these individual items, leading to the statistically significant, positive overall association of high-fat dairy and breast cancer mortality. Zucchetto et al. (1) also report an apparently positive although non-statistically significant association of high-fat milk intake and breast cancer survival. The reason for the apparently conflicting findings in their own study regarding associations of high-fat milk and cheese with breast cancer–specific mortality is unclear, although some findings in epidemiologic studies may be due to chance.

A related concern presented by Zucchetto et al. (1) was that high-fat dairy intake in our study was merely a proxy for unhealthy diet. However, in a previous study of dietary patterns and breast cancer survival in LACE (4), prudent dietary pattern, generated by factor analysis and including high intakes of fruits, vegetables, whole grains, and poultry was not related to breast cancer–specific survival. This was also true in a Nurses' Health Study of intake of prudent diet and breast cancer–specific survival (2). Moreover, we adjusted for several dietary factors indicative of healthy diet, including fiber, fruit, and red meat intake, and adjustment for these factors had little effect on associations. Although we cannot rule out residual confounding, which is true in all observational studies, previous findings for prudent diet and breast cancer–specific survival (2,4) and attention to adjustment for numerous potential confounding associations cause us to rule out this explanation.

It is ultimately difficult to comment on the reasons for the discrepant findings without knowing more about common farming practices in Italy. We do not presume to know the nature of farming practices all around the world. The basis for our argument, that high-fat dairy contains more estrogen, is not about the inherent properties of high-fat dairy but that changes in farming practices toward industrial farming have led to the common practice of pregnant cows being bred and fed to be able to be milked and be pregnant at the same time. It is these changes in farming methods that have presumably led to higher levels of estrogens in high-fat dairy, which was hypothesized by Ganmaa and Sato (5). They demonstrated that estrogen levels differ when comparing high-fat dairy in Mongolia vs high-fat dairy in the United States, but that (skim) milk in the United States, in which the fat has been removed, is also low in estrogens. Thus, we would expect that associations between high-fat or low-fat dairy and breast cancer survival might differ depending on a country's predominant farming practices. Zuchetto et al. do not comment on this, although this information would be useful to enable comparison.

There are exceedingly little data which address associations between dairy and breast cancer survival, including related issues as to whether estrogens are lower in organic or raw milks. Considerable work remains to be done. For this research to be maximally useful, it will be necessary to understand the context of farming in populations under study and ideally evaluate levels of estrogens in dairy products consumed by those populations.

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Re: Height as an Explanatory Factor for Sex Differences in Human Cancer

In a thoughtful mediation analysis, Walter and colleagues (1) have concluded that "[h]eight is an important explanatory factor for the excess risk for men [compared with women] for many shared-site cancers." In an early paper of ours (2), we had argued that because "several cancers, including those of the breast … as well as all cancers as a group, have been associated with height … the difference between men and women in the incidence of cancer of non-sexual organs could be accounted for by their relative mass or number of cells." An example at the extreme is breast cancer, which is much more frequent among women than men, as would be expected by the difference in mammary gland mass size between the two sexes (3). Walter and colleagues (1) also argue that "it is early exposure that influences both height and risk of cancers in adulthood" and that childhood insulin-like growth factor 1 (IGF-1) levels may be implicated. We had reached a similar conclusion, but we have also pointed to the intrauterine life as a critical period (2,3). Indeed, cord blood IGF-1 has been correlated with stem cell potential, much more so than steroid hormones (4), and both cord blood IGF-1 and stem cell potential are correlated with birth weight (5). Birth weight, in turn, is higher among boys than among girls and predicts both adult height (6) and overall (7) cancer risk.

It appears that what we have postulated (2) and what Walter and colleagues have elegantly documented (1) point to early life as a relevant period for carcinogenesis and represent a step toward our understanding of an important aspect of cancer etiology. Plausible mechanistic aspects of this web of causation have already been reported (4,5). However, as far as primary prevention is concerned, this particular aspect of cancer etiology remains, at present, all but intractable.

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Erratum: "Effects of vascular-endothelial protein tyrosine phosphatase inhibition on breast cancer vasculature and metastatic progression," by Shom Goel, et al. [J Natl Cancer Inst 2013; 105(16)]. Shom Goel, MD, is also affiliated with the Centenary Institute of Cancer Medicine and Cell Biology at the University of Sydney, Camperdown, Australia. The authors regret the error.

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