Nutrition and Breast Cancer: Epidemiology and Mechanisms

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Approximately 790,000 women are diagnosed with breast cancer in the world each year [1]. Breast cancer is the third leading cancer worldwide. Rates of breast cancer are generally higher in industrialized countries; these countries account for close to 60% of cases diagnosed each year. However, in spite of lower rates, because of the large number of women living in less developed countries, these countries also account for a sizeable number of cases. Breast cancer incidence rates have increased considerably during this century in industrialized nations. In one study in the US, the incidence rose 45% during the period 1960–1985 [2]. It appears that more recently the incidence in those countries has declined somewhat. Rates have also increased rapidly in some of the countries where incidence rates used to rank low. For example, in Taiwan between 1964 and 1991 the rate of breast cancer increased about 80% [3].

Breast cancer incidence rates differ by more than eightfold when the countries with the highest incidence are compared to those with the lowest incidence. While some of this difference may be the result of genetic differences in the populations, there is considerable evidence indicating that a major portion of the difference is related to environmental factors or to the interaction of genetic and environmental factors. When women move from regions where risk is low to areas where risk is high, there is an increase in the probability of disease. For example, Ziegler et al. [4] examined breast cancer rates among Asian women and women of Asian ancestry living in Southern California in the US. They found that for the group of women born in Asia, the rate of breast cancer depended on the rate of the area
where they were born and the amount of time that they had lived in the West. There was an increase of 80% for those who had lived at least 10 years in the West compared to more recent migrants. Among women who were born in the US, the number of their grandparents born in Asia affected their risk; risk was 50% higher for those women with three or four grandparents born in the West compared to women with four grandparents who were born in Asia.

Further evidence of the environmental component to risk is the change in rates within a population. As noted, the rate in Taiwan has changed 80% in less than three decades. Some of this change may be attributed to changes in screening for breast cancer and increased detection. However, most of the increase is a real change in disease rates and must be attributable to changes in exposures.

There is much that remains unexplained about the epidemiology of breast cancer. Other than age, the most definitively identified risk factors for breast cancer are those related to reproductive events in a woman’s life. Risk is higher for women with early age at menarche, with later age at first birth or who are nulliparous, and those with late age at menopause [5]. Based on this information, it appears that steroid hormones are of considerable importance in breast cancer etiology. Further confirmation of that effect are the prospective data examining blood steroid hormone levels in women who subsequently develop breast cancer compared with those who do not [6], and animal data indicating that steroids have a promotional effect on carcinogenesis in the mammary epithelium [7].

**Diet and Breast Cancer Etiology**

There is still much of a variation in risk that is not explained by the known risk factors [8]. Diet has been examined in some detail as possibly explaining the differences. There are dietary factors that appear to be correlated with breast cancer incidence [9]. While most of the research regarding diet and risk of disease has focused on dietary intake close to the time of diagnosis, there has recently been some speculation that dietary intake earlier in life may also be of significance. Research regarding diet in both time periods is reviewed here.

**Diet in Infancy and Childhood and Risk of Breast Cancer**

Animal models indicate that in the time before a first pregnancy, the breast epithelium is more sensitive to the effects of carcinogenesis [10]. Further, in animal models, there is strong evidence that caloric restriction throughout life, regardless of fat levels, can reduce subsequent risk of mammary carcinogenesis [11]. There is also evidence that fat, particularly polyunsaturated fat intake, will increase risk in virgin animals, although not those who have had a litter [12]. These lines of evidence would indicate that diet in early life is of particular impor-
tance. There has now been increased attention regarding diet in childhood and adolescence. At this time, few papers have been published that examine this association directly. There is some evidence, though not consistent, that having been breast fed as an infant may protect against risk of breast cancer. In a study done among women living in western New York State in the US, we found an about 25% decrease in risk for women who had been breast fed compared to those who had not [13]. One other case-control study had a similar finding of a protective effect [14]. A third study found no association of having been breast fed with risk of this disease [15]. An effect of having been breast fed, if it does exist, may be related to differences in calorie consumption by breast-fed and formula-fed babies. In earlier cohorts, infant feeding practices led to considerable overfeeding and more rapid growth in formula-fed babies. Other possible mechanisms could also include the presence in breast milk of hormones and other biologically active substances that are not present in formula.

With regard to diet in childhood and adolescence, there is some indirect evidence regarding an effect of calorie restriction on risk. A Norwegian study examined risk among women who were in puberty during World War II when food supplies were restricted. In this otherwise well-nourished population, the effect of dietary restriction in just that one time period can be studied. They found diminished risk of breast cancer for women who reached puberty during the war compared to women who reached puberty both before or after that time period [16]. These results need to be confirmed in other European populations experiencing similar conditions during World War II.

There are few studies in which women have been asked about their dietary intake in childhood. From these, there is a weak indication that childhood intake of vegetables may be protective [17, 18], that fat increases risk [18, 19] and that fiber from cereals but not other sources decreases risk [19]. In one of these studies [17], the investigators collected diet from both the women in the study and from their mothers regarding diet during the childhood of the women being studied. In spite of these careful efforts by the investigators to collect reliable data, it may be that an association was obscured because of the difficulty in recall from the distant past. Certainly far more epidemiologic data need to be accumulated before the effect, if any, of diet during childhood and adolescence can be assessed.

There is evidence that diet in early life affects the rate of growth as well as total attained height, within the limits of genetic potential. There is fairly consistent evidence that taller women are at a modestly increased risk of breast cancer, even in countries where presumably food scarcity is rare [20]. Age at menarche is a well-established risk factor for breast cancer. Diet has been shown to affect age at menarche [11], although there is also a strong genetic component to variation in age at menarche. In summary then, it appears that diet may indirectly affect risk via its effects on height and puberty. The evidence for more direct effects of early diet on risk is much less clear and the data far too sparse to make conclusions.
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Adult Diet and Risk of Breast Cancer

Clearly there are important differences in diet between countries with high rates and those with low ones. In particular, it has been noted that incidence rates are very highly correlated with per capita fat consumption [9]. Because of this finding and because of the findings in animals, there has been considerable attention to a possible role of adult fat intake on breast cancer.

Fat Intake and Breast Cancer

The evidence for an epidemiologic association between fat and breast cancer in adults has been reviewed recently [11]. In the 11 prospective studies that have been conducted, there was only one that provided any evidence of a decrease in risk in the lowest category of intake. In the others, there was no significant increase in risk with intake of fat; risk in the highest category of intake ranged from 0.9 to 1.7 [11]. Hunter et al. [21] pooled the data from seven of the same cohorts. In that analysis, there was again no evidence of an increase in risk with increased intake of fat; there was also no indication that intakes as low as <20% of calories from fat were protective. In 23 case-control studies, about half have shown a low or moderate increase in risk; the rest have not shown any increase in risk [11]. In a pooled analysis of 12 case-control studies, Howe et al. [22] observed an increase of 1.35 for a 100-gram increase in intake. As Hunter and Willett [20] point out, the average total intake for women in the US is 70 g; a change in intake of 100 g is a substantial one.

Because the hypothesis relating fat and breast cancer is well known, it is possible that, for the case-control studies, the report of fat intake by women with breast cancer was affected by their disease state, known as recall bias. There have been several studies to determine the extent to which such a bias might affect reports of fat intake by participants in case-controls studies. In two studies of recall bias conducted in Canada [23] and Sweden [24], there was no evidence of important changes in report of fat intake after diagnosis with breast cancer as compared to the report before diagnosis. In one other study, analyses based on retrospective reports of fat intake appeared to indicate that fat was related to risk while analyses of prospective data did not support the hypothesis [25].

It has been suggested that, because all of the cohort data and much of the case-control data come from developed countries where the intake of fat tends to be quite high, most if not all women in these studies may have fat intakes higher than the threshold required for prevention of breast cancer. There are clinical trials now underway that will test whether reductions in fat intake to about 20% of calories will affect breast cancer incidence. While at present the epidemiologic evidence provides little support for an effect of fat intake during adulthood on the risk of breast cancer, these trials will provide important data regarding this question, particularly regarding the effect of recent intake.
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Alcohol Intake

Epidemiologic evidence is fairly consistent that regular intake of alcohol is associated with a moderate increase in risk of breast cancer. This hypothesis has been examined in a large number of epidemiologic studies in different countries with considerable variation in drinking practices. In a recent study that pooled data from six cohorts, the relative risk was 1.09 for each increment of 10 g of alcohol/day, about 1 drink/day [26]. In a meta-analysis of 38 studies, Longnecker [27] calculated that the risk was 1.11 for 1 drink/day. In some studies, it appears that there is a linear increase in risk while in others it would seem that the risk is increased only among those women with the highest intakes. In the study pooling cohort data, while there was a linear increase in risk across intakes, risk was only significantly different from the null in the category of women who drank 30–60 g of alcohol/day [26]. In another study pooling data from six case-control studies, risk was elevated for those who drank more than about three drinks daily but not for those who consumed less [22]. However, in the Longnecker meta-analysis, there was some evidence of a small increase in risk for lower intake amounts [27].

There is some evidence that the age when alcohol consumption begins is of significance and that early consumption confers increased risk. However, these results are not consistent and other studies indicate that more recent consumption is the relevant exposure [11].

Another possibly important modifying factor in terms of risk associated with alcohol consumption are genetic factors influencing alcohol metabolism. In one study, we found genetic variation in alcohol dehydrogenase to be important. Alcohol dehydrogenases are a family of enzymes rate-limiting in the metabolism of alcohol to acetaldehyde. Alcohol dehydrogenase-3 (ADH3) has two genetic variants; there is no clear evidence of the effect of the genotype on in vivo metabolism of alcohol, but ADH31-1 has been found to be associated with increased risk of cirrhosis of the liver and oral and pharyngeal cancers [28]. In Caucasians, about 60% of the population has the ADH31 allele which is the variant coding for the enzyme with apparently greater activity. In our study of women in western New York, we found that for premenopausal women, the risk associated with alcohol consumption was different for those with the ADH31-1 genotype compared to those with either ADH31-2 or ADH32-2. The women whose alcohol consumption was in the top half of the distribution and who had the ADH31-1 genotype had a more than threefold increase in risk compared to women with lower alcohol consumption and either the ADH31-2 or ADH32-2 genotypes. There was no increase in risk associated with either increased alcohol consumption in the group of women with the other two genotypes or for women with the ADH31-1 genotype who were lighter drinkers [28]. As with any single epidemiologic study, it is important that this study be replicated. However, this study is an illustration of the potential importance of genetic variation in terms of risk associated with exogenous exposures. For alcohol and for other dietary factors, it may be that a combination of
genetic factors and environmental factors are significant for breast carcinogenesis.

The mechanism of an alcohol effect on risk is not clear. There is some evidence that there are effects on steroid hormone levels with alcohol consumption [29]. The study of alcohol dehydrogenase described above would indicate that production of acetaldehyde from alcohol may be relevant in terms of carcinogenesis. Acetaldehyde has been designated as a probable carcinogen [30]. Other possible mechanisms are effects on p450 enzymes, cell membrane permeability and inhibition of DNA repair mechanisms [11].

**Intake of Vegetables and Fruits and Related Nutrients**

There has been less attention to other components of diet in relation to risk of this disease. There is, however, mounting evidence that intake of vegetables and fruit may be protective against breast cancer. In a case-control study in western New York, we found a more than 50% decrease in risk for premenopausal women in the highest quartile of intake of vegetables; there was a weaker, nonsignificant association between fruit intake and risk (OR 0.67, 95% CI 0.42–1.09) [31]. Other studies in Europe, North and South America, and Asia have all found some decrease in risk with total vegetable intake or intake of a category of vegetables. While several studies have found no increase in risk, very few have found risk to increase with increased intake [11]. One recent review examined 70 different associations regarding particular fruits and vegetables and groups of fruits and vegetables in 21 epidemiologic studies. Although not all, most of those associations were below the null value [11].

The finding of a protective effect in such widely dispersed populations might argue against the observed effect being the result of uncontrolled confounding. With regard to recall bias as an explanation, in studies conducted in Canada [32] and the US [25], there was no evidence that recall bias would affect estimates of risk associated with most micronutrients (there was some indication in one study of recall bias in the estimate of fiber intake) [25]. Vegetables and fruits would be important sources of those micronutrients. In a study conducted in Sweden of the recall of food groups, there was some evidence of recall bias of vegetable intake [24]; recall may have an impact on some of the reported findings.

In the few cohort studies that have addressed the association of vegetable intake with risk, decreases in risk in the order of 10–25% have been observed. Most of these relative risks were not statistically significant [33–35]. In one of the cohorts, there was a stronger indication of a decrease in risk for premenopausal women with a family history of breast cancer or for those women who also consumed more alcohol [35]. While other sources of bias may explain the findings, again with the consistency of findings across nationalities and study types, this explanation is less likely. Several studies have examined risk related to fruit consumption. These findings are generally weaker and less consistent [11].
Many studies have not examined vegetable consumption but have analyzed risk related to consumption of micronutrients and other food components including vitamins A, C and E, carotenoids, folate, and fiber. For many of these, vegetables and fruits are the major sources of intake. These micronutrients and food components tend to be highly correlated with each other because of patterns of food intake within a population and because the micronutrients and other food components are found in the same foods. Further, there may be other, unmeasured food components that are also correlated with these that are of significance in the prevention of breast cancer. Preventive effects associated with any one of these may also be just a more general indication of a protective association with vegetable and fruit intake. Results of studies examining risk in relation to some of these micronutrients are reviewed below.

**Vitamin A and Carotenoids**

Of the micronutrients, the best studied are vitamin A and carotenoids. Retinol could affect risk via effects on epithelial cell differentiation. Carotenoids are hypothesized to have a protective effect on risk because of their antioxidant and pro-vitamin A properties.

In the studies that have examined retinol separately, results are generally quite inconclusive. In an analysis combining data from 12 case-control studies, retinol intake was not related to risk [22]. Several other case-control studies also reported no association with intake of retinol [36–38]. Cohort studies conducted in the Netherlands and in New York State in the US also did not find evidence for an effect [39, 40]. In the Nurses' Health Study, there was evidence of a weak, protective effect for preformed vitamin A intake of 0.8 (95% CI 0.71–0.98) [41]. Interestingly, among the women with low intakes of vitamin A in this cohort, intake of vitamin A from supplements was also protective. A Canadian cohort found a similar, though not significant decrease and again some protective effect, associated with supplement intake [33]. These findings would indicate that retinol, separate from a carotenoid effect, may be protective. It is not clear, however, why there are so many null findings regarding a role of retinol.

There are more studies that have examined risk associated with β-carotene intake. In the combined analysis by Howe et al. [22], there was some indication of a decrease in risk, particularly among postmenopausal women. Most other case-control studies but not all also found that risk decreased with increasing intakes [11]. Among cohort studies, several have found a weak, often nonsignificant, decrease associated with a reported intake of β-carotene [33–35, 40–43]; there was no association with risk in a Dutch cohort [39]. Other carotenoids have been examined in only a few studies. Both Freudenheim et al. [31] and Zhang et al. [35] reported weak decreases in risk with intakes of α-carotene and lutein/zeaxanthin. A few studies have examined blood carotenoids and risk; blood carotenoids are good indicators of intake. In most of these studies, serum carotenoids were not related to decreased risk [44]. Dorgan et al. [45] examined risk of breast cancer
associated with carotenoid status using prospectively collected blood samples. They found a decrease in risk associated with levels of \( \beta \)-cryptoxanthin, and lycopene and a weak association with lutein/zeaxanthin. \( \alpha \)- and \( \beta \)-carotene were not associated with risk. Among women with breast cancer, there is some evidence that \( \beta \)-carotene intake was more associated with an increased incidence of estrogen receptor-positive tumors [46]. In sum, there is quite consistent evidence of a protective association of carotenoid intake with risk of breast cancer.

**Vitamin C**

Another antioxidant, vitamin C, has also been the object of study in several epidemiologic studies of breast cancer risk. In the combined analysis of Howe et al. [22], vitamin C was the micronutrient most strongly associated with risk, particularly among postmenopausal women. The odds ratio associated with intake of an additional 300 mg/day was 0.63. Results from other case-control studies that have examined vitamin C and risk of breast cancer have generally reported odds ratios of <1.0, that is, some protective effect. In three prospective studies, there was no effect of vitamin C on risk [33, 35, 40]; in one of these, vitamin C was protective for women with a positive family history of breast cancer [35]. In several studies examining supplement use and risk, there was no evidence of a protective effect [31, 33, 35]. The lack of effect of supplements might indicate that another factor or combination of factors in the foods containing vitamin C is the protective agent and that measured vitamin C intake is an indicator for those factors. Alternatively, it may be that a report of vitamin C supplement use indicates only recent exposure and that food intake reports are more indicative of long-term exposures.

**Vitamin E**

Vitamin E is of interest in relation to risk because of its antioxidant properties. The association between vitamin E and risk of breast cancer has been reviewed recently [47]. There have been relatively few studies that have examined risk associated with this nutrient. Results have been somewhat inconsistent with some indication of a protective effect. Vitamin E is relatively difficult to measure accurately by questionnaire. In prospective analyses of blood tocopherols, there has been some indication of a protective effect; most of these studies were quite small [47].

**Folate**

Another nutrient that is found primarily in vegetables and fruits and that may have significance in carcinogenesis is folate. Folate is important in DNA synthesis and methylation and may therefore play a role in gene regulation. Reduced risk associated with increased intake has been reported [31, 37]. A report from the US cohort of nurses observed a protective effect in women reporting higher alcohol intakes [48]; alcohol can increase the requirement for folate.
**Dietary Fiber**

Dietary fiber has been hypothesized to protect against risk of breast cancer; one possible mechanism is that interactions of fiber with enteric reabsorption of steroid hormones affect risk. In one study, there was lower mammographic density for women reporting higher intake of fiber [49]. The results of most case-control studies on fiber and breast cancer risk would indicate some decrease in risk [11]. One cohort study found a decrease in risk with increased fiber intake [33]; two others have not shown any effect of fiber [40, 50]. Most studies do not distinguish between the effects of fiber from fruits and vegetables and that from grains. The effects of these are different and of course the other nutrients correlated with intake of each would be different. In one study that examined these separately, risk was reduced with fiber from vegetables and fruits but not from grains [31].

**Other Modifying Factors**

There appears to be considerable evidence of a protective effect of vegetables and fruit on risk of breast cancer. There is some evidence from the studies that directly examined risk and intake of vegetables and fruits. The evidence from countries with considerable variation in intake of vegetables and fruits, such as Greece, Italy and Japan, is particularly important. Further, the bulk of evidence from nutrients and food components found in vegetables and fruits would indicate that these or other correlated factors from the same foods are protective. The lack of effect for supplements other than vitamin A supplements would imply that perhaps it is the food intake rather than the particular nutrient that is the effective factor.

There may be other factors too that modify the effect, if any, of vegetables and fruits. As noted above, Zhang et al. [48] found that the protective effect associated with folate intake was restricted to women reporting higher alcohol intakes. Obesity is a well-established risk factor for breast cancer in postmenopausal women. Horn-Ross [51] has hypothesized that intake of phytoestrogens from plant sources may be protective against breast cancer particularly in obese postmenopausal women. Further, there are likely genetic factors that modify the effect of diet on risk. Ambrosone et al. [52] reported on a modifying effect of genetic variability in manganese superoxide dismutase, an enzyme important in the modulation of oxidative stress. They found an interaction of risk associated with the genetic variant and intake of vegetables and fruits, carotenoids, vitamin C and E. There may be other genetic factors modifying any effect of vegetables and fruits on breast cancer risk.

**Conclusions**

After several decades of work focused on diet in the epidemiology of breast cancer, several risk factors seem to have emerged as important. There is quite consistent evidence that alcohol increases risk, particularly regular consumption...
of 2–3 drinks/day. The evidence is less conclusive as to whether there is a time period in the life cycle when women are particularly sensitive to alcohol intake; some evidence would indicate that consumption at younger ages is important while the evidence from other studies is that more recent, adult intakes are the relevant exposure.

There is some evidence that dietary exposures in infancy and during the time period up to the first pregnancy may have importance. Research in this area is of considerable interest and much remains to be explored. There are important methodological concerns that need to be addressed in assessing the effect of exposures that are temporally quite separate from disease detection.

The evidence that vegetables and fruits are related to a reduction in risk is also quite consistent. Further, there are also a considerable number of studies that have not examined risk related to intake of vegetables and fruits but have examined associations with nutrients and other food components that are found in those foods and that are highly correlated with total intake of vegetables and fruits. The intercorrelations among these nutrients for intakes by individuals makes it difficult to designate any one of them as the active agent. The possibility cannot be ruled out that these factors are just indicators for other food components with anticarcinogenic effects found in the same foods and it may be that a combination of the nutrients or food components is important. In one study, risk associated with vegetable intake was adjusted for other nutrients. There was a 15–60% decrease in risk associated with vegetables after this adjustment; risk associated with vegetables was weakest after adjusting for some of the carotenoids [31]. The findings from a variety of countries, representing enormous differences in dietary practices, would argue that the observed findings are likely not the result of confounding from nondietary sources. The results from prospective studies would indicate that the effect is likely small. Nonetheless because the exposure is a very common one, it could be of considerable importance in terms of public health. There of course remains much to be determined, however, about this potentially important relationship including the active agents, interactions with genetic factors and the time period in the life cycle when exposure is most important.

References

Discussion

Dr. Haschke: You mentioned the breast feeding issue. Do you have any information from the Scandinavian countries? Scandinavian countries seem to be among those with a high incidence of breast cancer, but on the other hand in Scandinavia there has always been a tradition of breast feeding. Even 40 years ago, 80% of the infants were breast fed.

Dr. Freudenheim: As I mentioned, as far as I am aware there have been just three studies and they were all done in the USA, so I don’t know anything about the Scandinavian countries. The decrease in risk we found isn’t going to explain all the incidence of breast cancer, and as with any of these diseases, many factors are likely to have contributed. The breast feeding finding is interesting in that it suggests the possibility that this is an important time period, and also perhaps that energy restriction or not overfeeding may be important, or that some of the factors in breast milk may be important. But it’s highly speculative at present.

Dr. Haschke: You didn’t focus much on the interaction between whether a woman has breast fed her infant and the risk of developing breast cancer.

Dr. Freudenheim: I didn’t talk about lactation not because I don’t consider that it’s important. It has to do with the diet of that woman’s infant but I don’t consider it to be part of her diet. In fact there is quite consistent evidence that women who breast feed are at lower risk of breast cancer.

Dr. Haschke: Is the number of children important?

Dr. Freudenheim: Yes, there does seem to be some relation with the total duration of breast feeding in the woman’s life. It’s not clear why that is. Breast milk is one of the ways in which things are excreted, for example organochlorines, so maybe it clears the woman’s system of some of those compounds at the infant’s expense. However, it’s not clear at present what the mechanism is.

Dr. Guesry: It is well known that the duration of breast feeding 50 years ago may have been quite short, especially in higher social class groups. How did you obtain information on breast feeding history? If you ask somebody whether they were breast fed 50 years ago, I wonder about the value of the information supplied.

Dr. Freudenheim: I agree that socioeconomic class is a possible confounder and we tried to adjust for that, though the adjustment is rather crude. But in fact we see the same relation in premenopausal women and postmenopausal women, and so the birth dates of these women covered a considerable time period. During that period there was a switch in infant feeding practices in the higher socioeconomic classes from predominantly bottle feeding to predominantly breast feeding. So the pattern was inverted during that time period, yet the same effect was still shown. You’re right, though, that the information we had was very crude. In this study we were not able to ask women how long they were breast fed; we only asked them whether or not they had been breast fed. Obviously there was a lot of variation in terms of duration. In the study that was done at the National Cancer Institute they had a little more information because they interviewed not only the women but also the women’s mothers. Even so, we don’t feel comfortable about the epidemiology and won’t do until we have 15–20 studies.

Dr. Mason: There is some suggestion in colon cancer that if your cancer is driven by genetic predisposition, there’s less opportunity for nutritional modulation of your risk. I wonder whether the same is true for breast cancer. For instance, in your studies with breast feeding or alcohol or vegetables, if you have a BFCA1 mutation, do you then lose the opportunity to modulate your risk with alcohol or with vegetables or with breast feeding?

Dr. Freudenheim: The BFCA1 variants are fairly rare. There are studies being done now looking at whether BFCA1 and BFCA2 are modulated by exogenous factors including diet, but in these population-based studies there are probably very few women with these high-risk genotypes.
Dr. Heimburger: Could you comment on the recent findings from the Nurses’ Health Study that their earlier report from 10 years ago of a strong association of moderate alcohol intake with breast cancer was greatly modified by folate status. They found that the increased risk associated with alcohol in their cohort was only present in women who had a low folate intake.

Dr. Freudenheim: It’s certainly going to be worth looking at folate in greater detail in terms of breast cancer risk. Like colon cancer, it’s another site where you have a fruit and vegetable effect and you have an alcohol effect, which makes you wonder whether folate metabolism is important there. That finding is certainly suggestive that it is.

Dr. Heimburger: Could I just follow up on that? There is a thread of the folate cancer hypothesis suggesting that there may be organ-specific localization of folate deficiency. I don’t know of a mechanism whereby this could occur in the breast, but alcohol intake certainly impairs folate status. This is a situation where two different environmental influences may interact with each other, and possibly with a third factor as well, such as genetic polymorphism and so forth. There appears to be a trend of interactions in these data.

Dr. Freudenheim: Yes. As time goes on we’re going to need bigger and bigger studies, because in order to study these interactions you need very large numbers. But those kinds of interactions might have very important public health implications.

Dr. Argiles: I found your data on alcohol risk and the alcohol dehydrogenase (ADH) enzymes very interesting. However, the levels of acetaldehyde do not only depend on the activity of the ADH enzyme system but they also depend on aldehyde dehydrogenase (ALDH), of which there are two isoenzymes at least. These isoenzymes are extrahepatic, so they could be activated in the mammary gland. Are there any studies associating risk of cancer with ethanol and those isofoms of ALDH?

Dr. Freudenheim: Not that I know of. In our population there isn’t much variation in the ALDH isofom, so that wouldn’t have affected our results, but you’re right, it’s an interesting area to look at further. The problem with ALDH is that it affects metabolism so much that it has an impact on people’s drinking habits. So people with the slow variant have a large accumulation of acetaldehyde which makes them uncomfortable so they’re less likely to drink.

Dr. Hursting: One mechanism that has been suggested for the decrease of breast cancer risk with soy protein is that it can mimic pregnancy and may induce N-terminal differentiation. I’ve not seen any data supporting that. Are you aware of any?

Dr. Freudenheim: No. I’m certainly aware that there has been discussion about soy protein having an estrogenic effect but I never heard of it inducing N-terminal differentiation. But there is some question about whether soy consumption might have differential effects early in life compared with later in life.

Dr. Guesry: I think you could make a very interesting study in the United States because 30% of babies receive soy formula during their first 6 months.

Dr. Freudenheim: We’re very interested in that. We also need to do studies looking at some of the reproductive factors relating to soy formula intake, such as age of menarche for example.