EDITORIALS

Micronutrients and Cancer: Time for Action?

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The National Academy of Sciences' report *Diet, Nutrition, and Cancer* was published in 1982. Since that year, over 175 case–control or cohort studies have been published on the relationship between fruits and vegetables or their antioxidant nutrients and cancers of various sites. The epidemiologic data are extraordinarily consistent in finding an inverse relationship between those factors and risk of at least 15 different cancer sites, as noted in a recent review of all published studies on that relationship (*1*). Not only were most results in the inverse direction, but over 80% of the studies showed statistical significance. For no other risk factor besides smoking are the data as consistent and abundant.

A number of hypotheses have been advanced regarding the factor or factors responsible for this inverse association—all of them supported by a body of epidemiologic data and also by biological and biochemical rationale and data. The potentially responsible agents include antioxidants, fiber, folic acid, and other nutritive and nonnutritive factors.

There is substantial epidemiologic support for an inverse relationship between antioxidant micronutrients (vitamins C and E and carotenoids) and cancer (*2-4*). This relationship is reinforced by biochemical data on the role of oxidation in cancer etiology and on the ability of antioxidants to prevent or reduce oxidation and inhibit carcinogenesis in animal and in vitro studies (*5-8*).

Dietary fiber has been suggested as another of the important factors in cancer prevention, and biologic rationales for its role in prevention of colorectal cancer have been proposed. These rationales include effects on stool transit time and on bile acids (*9*). It is important to note, however, that most epidemiologic studies of the role of fiber have asked respondents about their consumption of many different foods, which typically included numerous fruits and vegetables but usually only a few grain sources. In the United States, fruits and vegetables are major sources of dietary fiber, contributing approximately 50% of the total fiber intake, compared with only approximately 31% from grains (*10*). Thus, while fiber may have a role in colorectal cancer, a role for other components of fruits and vegetables remains a major possibility as well.

Fruits and vegetables are the major dietary sources not only of the antioxidants and fiber, but also of folic acid. Indeed, orange juice, the top source of vitamin C in the U.S. diet, is also the top source of folic acid (*11*). Folic acid, required for DNA synthesis and cell replication, has also been hypothesized to play an important role in cancer prevention (*12*).

Two articles in this issue of the Journal contribute to the body of literature on micronutrients and cancer risk and enrich the etiologic hypotheses associated with it. Giovannucci et al. (*13*) have found dietary intake of folic acid to be significantly associated with reduced risk of colon adenomas. They hypothesize that hypomethylation of DNA may be one mechanism of cancer initiation or progression and cite data on the relationship of DNA hypomethylation to expression of the c-myc oncogene and to cancer progression. The authors suggest that this process is reduced by adequate intakes of folic acid (a cofactor in the synthesis of *S*-adenosylmethionine, the principal methyl donor) and is exacerbated by alcohol (a folate antagonist).

Sandler et al. (*14*) also examined dietary factors in risk of colorectal adenomas. They found dietary fat to be significantly associated with increased risk and, in women, dietary fiber from fruit to be significantly associated with reduced risk. Fiber from grains or legumes showed no association.

These studies (*13,14*) illustrate some of the interpretive and analytic issues in this body of data. The first question that is raised is what component of the foods is in fact the effective agent? As noted above, strong data and biologic rationales exist for vitamin C, carotenoids, vitamin E, fiber, and folic acid as preventive agents. Can we sort out these nutrients? Need we sort them out? Perhaps the argument over which is the "right" nutrient reflects a medical model, a search for the magic bullet, rather than a public health model. Is it likely that one mechanism *instead* of another is responsible for an inverse effect? Is it not more likely, given the persuasive biochemical and animal data for all of these nutrients, that *all* of them have a role? One mechanism may be more important in one cancer site, while another is more important at other sites. Some of these nutrients appear to have different roles in the face of different carcinogenic insults and vary in their concentration, solubility, and action in different tissues. That is, they have different roles, and are all needed. At the same time, total antioxidant capacity of the tissues is likely to be important, and thus, to some extent, the different antioxidants can substitute for or reinforce one another.

Another issue raised but not resolved by these studies (*13,14*) is the role of interaction—the possibility of different effects of one nutrient within strata of other nutrients or factors. For example, in the study by Sandler et al. (*14*), one wonders what the association between fruit fiber and adenomas would be within strata of dietary fat intake or within strata of vitamin supplement use. Could different effects in different strata partially explain why an effect of

*See "Notes" section following "References."

fruit is seen in women but not in men? Since both fruit intake and vitamin supplement use vary considerably by gender (*15-17*), one wonders whether interactions such as this (as well as, for example, interactions with smoking) may explain some of the varying effects by gender that have been seen in a number of studies (*18,19*). Very few epidemiologic studies have examined whether one dietary factor, like fruit, might have different effects at different levels of another factor, such as fat, smoking, or vitamin supplement use. One that did address that question (*20*) found important differences in the effect of high meat intake on development of cancer, depending on the level of fruit intake and of vitamin supplement intake. The risk associated with a high-meat diet was substantially greater among persons with low intakes of fruit, vitamin C, or vitamin supplements than among persons with high intake of those substances. Similarly, Butterworth et al. (*12*) found the cervical dysplasia risk from human papillomavirus to be limited to those with low folic acid status. It is likely that such analyses by strata will refine our understanding.

Another issue raised by these articles and others is that the increased risk is not limited to what has previously been defined as actual deficiency of these nutrients. Giovannucci et al. (*13*) note that in a large sample of persons selected from their study cohorts, there were no cases of folate deficiency. It is also notable that Giovannucci et al. found that folate intake from diet alone had a weak and non-significant inverse effect on cancer. The effect was achieved only when intake from vitamin supplements was included.

The conjunction of epidemiologic and biochemical data provides strong evidence of an important role of fruits and vegetables—as well as the antioxidants, folate, fiber, and other nutrients they contain—in reducing the risk of cancer at a host of sites. What is the appropriate response to this body of data? Surely, one unarguable response should be to promote consumption of these foods, not only through educational efforts (as in the National Cancer Institute's "5 a Day" program), but through fiscal policies that make them more affordable. And surely, inquiry about our patients' consumption of these foods and counseling about their benefits should be an integral part of primary care prevention activities.

In addition to such educational activities, I suggest that it is appropriate to consider such additional steps as food fortification and vitamin supplementation with antioxidants and folate. There can be no disagreement that people *should* eat a balanced diet rich in fruits, vegetables, and whole grains. Only then will they obtain all of the beneficial components of those foods, including the hundreds of different carotenoids, to mention but one example. But people *are not* eating enough of these foods and are unlikely to do so in the foreseeable future. Results from a national survey (*15*) suggest that on any given day, only 60% of Americans had even one serving of a fruit or juice. In another national survey (*21*), only about half of the participants had even one serving of a citrus fruit or juice in 4 days, and only one third had a dark green or yellow vegetable once in 4 days. Only 9% of Americans consumed the recommended five or more servings of fruits and vegetables per day (*15*). If we were to achieve a health education triumph and double that number, there would be only 18% who consumed the recommended servings.

Moreover, the cancer burden and the dietary inadequacies fall disproportionately on the poor and the poorly educated. This is the group least likely to be reached by our education messages. To the extent that we are seeing desirable changes in dietary patterns—increased consumption of salads, for example—it is primarily among the affluent, well-educated, and White.

It may be time to consider that major public health effects of the sort obtained when we eliminated rickets, pellagra, beriberi, and goiter may be obtained less through education and exhortation and more through fortification and supplementation. Do we know *all* of the effects of *all* of the components of fruits and vegetables? Obviously not. Research has already shown effects of isothiocyanates, phenolic compounds, bioflavonoids, and numerous other components. Clearly, research to identify more potent or site-specific compounds present in foods is warranted. But the possibility of other effective agents should not justify a failure to take action on what now appears quite clear based on laboratory data supported by epidemiologic data: that antioxidants and folic acid do indeed have a role in reducing the risk of some cancers. It is time for serious debate and consideration of public health measures, including fortification and supplementation, to increase intake of these nutrients.

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Breast Cancer Risk Estimation: A Translational Statistic for Communication to the Public

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During the 1990s, the attention of the public and the media has been repeatedly focused on the threat of breast cancer. In addition, to educate the public about breast cancer and to increase access to prevention and early detection techniques and state-of-the-art treatment, breast cancer activists' groups are functioning in communities in nearly every state in the United States. Statistics describing an "epidemic" of breast cancer are quoted and misquoted in the press nearly every day. Clearly, breast cancer has shifted from a topic never discussed in public just a few years ago to a topic of extensive popular deliberation today (*1*).

Fear is a common reaction to reports of increasing incidence of breast cancer: Women at increasingly younger ages are frightened that they will develop breast cancer. In the March 15, 1993, issue of *U.S. News and World Report*, an article entitled "The Breast Cancer Scare" refers to breast cancer statistics, describing increasing numbers of cases as having created "math anxiety" (*2*). This article states: "To many younger women, it means that breast cancer has become real and frightening, an epidemic in their ranks." Some of the fear arises from the presentation of statistics that suggest an overwhelming epidemic and that are not accompanied by clear discussions or explanations. Eloquent women are at the forefront of educating women about breast cancer, and they need simple, easily understood statistics with which to communicate concepts of risk (*3*).

In this issue of the Journal, Feuer et al. (*4*) present a modified methodology for calculating women's risks of breast cancer at different ages, by race, and in keeping with patterns of breast cancer that are changing dramatically over short periods of time. The authors propose not just a single lifetime risk estimate, but rather, a method to evaluate risks at different periods of a woman's life. The estimate that Feuer et al. (*4*) have developed is a "translational" statistic, i.e., a statistic that can move from the esoteric deliberations of biostatisticians and epidemiologists to daily communication with the general public. Indeed, over the past 2 years, the National Cancer Institute has given priority to translational cancer research, which includes investigations that take either laboratory results into the clinic or clinical results into the community.

How can this method of calculating the risk of developing breast cancer improve our ability to accurately communicate both the changing patterns of breast cancer incidence and mortality and the risks in groups of women of specific age and race? After all, we now have *the* lifetime risk that we see and hear in the media constantly—the risk of breast cancer is one in eight. That estimate is compared with a risk of one in 10 just a few years ago or one in 20 in the 1960s, with the end result often being a discussion of today's breast cancer "epidemic." As Feuer and colleagues (*4*) point out, the public often interprets this *lifetime* risk to mean that this estimate is a woman's risk *next year*. Developing modifications of previous methodology, Feuer et al. (*4*) reduce the potential for misinterpretation by explaining women's risk of breast cancer in three ways: 1) lifetime risk by 5-year age groups, 2) risk of developing breast cancer at age Z if one has reached age *Y* without developing breast cancer, and 3) risk of dying from breast cancer.

Before discussing the value of this estimation technique for communicating lifetime breast cancer risk, it is important to highlight the improvements in this methodology that enable us to develop more accurate and more relevant estimates of risk. Methods used in the past have been criticized primarily because they do not consider either prevalent (previously diagnosed) cancers or the presence of multiple cancers in the same individual (*5*). As Feuer et al. (*4*) describe in detail, their method has four specific advantages:

1) It uses age-specific incidence rates for the first primary breast cancer.

2) It allows risk estimates to be adjusted for prevalent cases.

3) It assumes that deaths from causes other than breast cancer occur according to a standard mortality distribution.

4) It enables researchers to calculate and modify lifetime

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