Re: Fruit and Vegetable Intake and Risk of Major Chronic Disease

We read the results on the associations between fruit and vegetable intake and risk of chronic diseases in the Journal (1) with great interest. The results were astonishing: Increased intake had no statistically significant association with cancer risk and had a small, statistically significant association with reduced risk of cardiovascular disease. An editorial in the same issue (2) questioned the accuracy of the intake data as well as the analysis of the multivariate measurement errors and especially the correlations between measurement errors of different variables. Many previous epidemiologic studies on fruit and vegetable intake have reported on their associations with cancer (3) and cardiovascular disease. Many of these studies have shown statistically significant reductions in disease risk, others have shown reductions in disease risk that were not statistically significant, and only a few have shown increased disease risk.

The fact that the effects are not randomly scattered around the no-effect level suggests that fruit and vegetable intake is indeed associated with reduced risk of chronic disease but that its statistical significance cannot be reliably assessed with epidemiologic studies as they are currently undertaken. The reason for this phenomenon may well be that it is not fruits and vegetables themselves that provide protection against chronic diseases but rather certain components within them. One can expect a clear answer from studies that assess associations between food intake and disease only if the levels of these components are relatively constant or if their variability is leveled out by studying a large enough cohort and/or a studying the cohort for a long enough time.

To test whether these conditions are fulfilled in current epidemiological studies, one needs quantitative information on variability in the amounts of active components. Candidate components showing the biggest potential as anticancer compounds are the secondary plant metabolites. The levels of these components in different cultivars show considerable variation. For example, levels of glucosinolates vary by more than 100-fold among different vegetables of the Brassica genus. This variation is even further expanded by taking into account the many ways and conditions of processing, storage, and preparation (4). So by analyzing food intake without any knowledge of the cultivars or the conditions in the food production chain, including the consumer, one introduces enormous uncertainty in the actual intake of protective components from these foods. The consequences of this uncertainty on the outcome of epidemiologic cohort studies have been simulated by Monte Carlo simulations (5). Even if one assumes a strong protective effect of a certain component in fruit and vegetables against cancer, these simulations showed that this effect would not be statistically significantly assessed in an epidemiologic cohort study with food intake as the main input.

We therefore recommend that food intake assessments include, at least, information on the method of preparation and type of (pre)processed products that the consumer is using. Predictive models to correct the level of certain components for the processing or preparation method may help to enhance the sensitivity of future nutritional epidemiologic studies. This additional information may lead to a more consistent outcome of this type of study, ultimately giving better clues to the question of which components in which fruits and vegetables may protect against chronic diseases.

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REFERENCES


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The finding, recently reported in the Journal (1), that total consumption of fruits and vegetables among nurses and other health professionals in the United States is associated with reduced risk of cardiovascular disease but not cancer is very interesting. Many studies have reported that frequent consumption of fruits and vegetables does, indeed, reduce the risk of cancer (2). Compounds found in many fruits and vegetables are well known to have anticancer properties; these include allyl sulfides (in allium-family vegetables), glucosinolates (in cruciferous vegetables), and lycopene (in tomatoes), as well as a large number of antioxidants found in many fruits and vegetables (3). Thus, it is important to seek a reason for the discrepancy in the findings by Hung et al. (1) and those by others.

A likely reason for the discrepancy is that most of the fruits and vegetables consumed by the two cohorts may have been cooked, rather than eaten raw. Green leafy vegetables was the only category for which a statistically significant risk reduction was found for major chronic disease, although a risk reduction was not seen for cancer; it may have represented a very small fraction of total fruits and vegetables consumed by the cohorts. Several researchers have reported that raw vegetables are associated with a statistically significant risk reduction for cancer, whereas cooked vegetables are often not associated with reduced cancer risk and are sometimes associated with increased cancer risk (4–6). Cooking, processing, and storing all generally reduce the amount of vitamins and minerals available from fruits and vegetables, except for tomatoes, for which cooking increases the bioavailability of lycopene, intake of which is associated with reduced risk of prostate cancer (7).

Thus, it would be worthwhile to look further at associations between cancer risk and intake of cooked versus raw fruits and vegetables in this cohort and at which fruits and vegetables were consumed cooked and which were consumed raw. It would also be interesting to know whether eating cooked fruits and vegetables is associated with different dietary patterns than eating raw fruits and vegetables.

The paper by Hung et al. (1) is important because it provides very good data that challenge a common assumption of how dietary factors might affect the risk of cancer. Further investigations should be aimed at identifying the reason for the finding, especially to determine whether intake of cooked fruits and vegetables may actually increase the risk of cancer.

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**REFERENCES**


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**RESPONSE**

Although several writers express surprise that our findings for cancer seem inconsistent with earlier reports, these were mainly case-control studies, which are much more susceptible to bias than prospective studies (1). Our null findings are largely consistent with more recent prospective studies, including the EPIC study of breast cancer (2). We agree that our findings for fruit and vegetable intake do not exclude the possibility that specific compounds in these foods have anticancer properties. In fact, we have provided examples from these same cohorts to support such relationships with specific cancers (3,4). However, if anticancer compounds vary dramatically in foods because of growing and harvesting conditions, degree of maturity, processing, storage, and cooking, then simply eating more fruits and vegetables would not be a reliable way to reduce overall cancer risk. It is this latter issue that our study addressed. Moreover, we have shown that blood levels of even fairly labile nutrients such as folic acid and beta-carotene are predicted by calculated intakes from our questionnaire (5), indicating that variability due to the above factors is not an intractable problem. This is in part because these sources of errors are dampened by the fact that individuals do not always eat exactly the same sample of food; thus, for example, the average nutrient content of carrots consumed by one person is probably not greatly different from the average nutrient content of carrots consumed by another.

Our questionnaire did not have specific questions on how most fruits and vegetables were processed before eating. To examine the issue of raw versus cooked, we assumed that most fruits are...
consumed without processing and cooking, and hence we were unable to distinguish raw fruits from other fruits. We also identified raw vegetables for which we had information on processing or that were likely to be consumed without processing. These vegetables include coleslaw and uncooked cabbage, raw carrot, alfalfa sprouts, celery, raw spinach, iceberg and other head lettuce, and romaine and other leaf lettuce. The results (Table 1) show that intakes of both the raw vegetable group and the remaining vegetables were not associated with risk of cancer. Hence, the reduction of these active vitamins and minerals due to processing is probably unlikely to explain the null association.

**REFERENCES**


**NOTES**

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**Table 1.** Multivariable-adjusted relative risks* (with 95% confidence intervals) for major chronic disease, by intake of raw and other groups of vegetables

<table>
<thead>
<tr>
<th>Food item</th>
<th>Group†</th>
<th>Quintile 1</th>
<th>Quintile 2</th>
<th>Quintile 3</th>
<th>Quintile 4</th>
<th>Quintile 5</th>
<th>Overall</th>
<th>For quintiles 1 and 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw vegetables‡</td>
<td>HPFS</td>
<td>1.06 (0.94 to 1.20)</td>
<td>0.93 (0.81 to 1.05)</td>
<td>0.99 (0.87 to 1.12)</td>
<td>1.04 (0.92 to 1.19)</td>
<td>0.83</td>
<td>0.24, 1.88</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NHS</td>
<td>0.98 (0.91 to 1.06)</td>
<td>1.00 (0.92 to 1.08)</td>
<td>0.95 (0.88 to 1.03)</td>
<td>0.95 (0.88 to 1.03)</td>
<td>1.00</td>
<td>0.3, 2.16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pooled</td>
<td>1.01 (0.93 to 1.08)</td>
<td>0.98 (0.92 to 1.04)</td>
<td>0.96 (0.90 to 1.03)</td>
<td>0.98 (0.90 to 1.06)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other vegetables§</td>
<td>HPFS</td>
<td>0.87 (0.76 to 0.98)</td>
<td>0.86 (0.76 to 0.98)</td>
<td>0.93 (0.82 to 1.05)</td>
<td>0.90 (0.79 to 1.03)</td>
<td>2.05</td>
<td>0.97, 4.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NHS</td>
<td>1.00 (0.93 to 1.08)</td>
<td>1.01 (0.97 to 1.14)</td>
<td>1.05 (0.97 to 1.14)</td>
<td>1.03 (0.95 to 1.12)</td>
<td>1.83</td>
<td>0.94, 3.40</td>
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<tr>
<td></td>
<td>Pooled</td>
<td>0.94 (0.82 to 1.08)</td>
<td>0.94 (0.81 to 1.09)</td>
<td>1.00 (0.88 to 1.13)</td>
<td>0.98 (0.85 to 1.11)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Relative risks were adjusted for total calorie intake, age, smoking status, alcohol use, body mass index, multivitamin and vitamin E supplement use, physical activity, family history of myocardial infarction, family history of colon cancer, personal history of hypertension, personal history of hypercholesterolemia, personal history of diabetes, and, for women only, family history of breast cancer, menopausal status, and use of hormone replacement therapy. Relative risks are given relative to quintile 1, the lowest intake.

†HPFS = Health Professionals Follow-up Study; NHS = Nurses’ Health Study.

‡Raw vegetables include coleslaw and uncooked cabbage, raw carrot, alfalfa sprouts, celery, raw spinach, iceberg and other head lettuce, and romaine and other leaf lettuce.

§Other vegetables include the remaining vegetables that are not included in the list of raw vegetables; these could include vegetables that may be consumed raw or processed.