

# Fruit, Vegetables, and the Prevention of Cancer: Research Challenges

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**OBJECTIVE:** A great deal of epidemiologic evidence has indicated that fruits and vegetables are protective against numerous forms of cancer. However, there are many gaps in our knowledge.

**METHODS:** In this pilot study we reviewed more than 200 cohort and case-control studies to determine the shape of the dose–response relationship (i.e., how the risk reduction per extra serving of fruits and vegetables changes with the actual intake of these foods). We found major barriers to investigating this. As part of this pilot study we also investigated whether specific fruits and vegetables are responsible for the anticancer action of these foods or whether a wide variety is required for optimal protection. If the former is correct, then fruits and vegetables may contain one or a small number of “magic bullets”; if the latter is correct, then a “teamwork” concept may be valid.

**RESULTS:** Different findings suggested that the teamwork concept is much more likely. Many studies, especially older ones, have ignored potential confounding variables such as energy intake, alcohol consumption, physical activity, body mass index, smoking, and socioeconomic status (although many recent studies have adjusted for education). Other potential confounders that have generally been ignored are consumption of whole grain cereals and the use of vitamin and mineral supplements.

**CONCLUSIONS:** The inverse association between intake of fruits and vegetables and the risk of cancer of the colon, breast, and stomach has generally been much stronger in case-control than in cohort studies. We have no clear explanation for this. *Nutrition* 2003;19:467–470. ©Elsevier Inc. 2003

**KEY WORDS:** anticarcinogenic agents, case, case-control studies, cohort, cohort studies, epidemiology, confounding factors, fruits, vegetables

## INTRODUCTION

A large body of evidence from case-control and cohort studies has indicated that fruits and vegetables have a strong protective effect against various types of cancer.<sup>1,2</sup> For several common cancers people in the highest quintile, quartile, or tertile of intake have about one-third to one-half less risk than people in the lowest group. Van't Veer et al.<sup>3</sup> estimated the proportion of cancers in the Netherlands that could be prevented if everyone increased their intakes of fruits and vegetables by 100 g/d. Their “best guess” estimate was that incidence would fall by 19%.

There has been much speculation with respect to the substances that might account for this beneficial quality of these foods. For a number of years  $\beta$ -carotene was strongly suspected of being anticarcinogenic.<sup>4</sup> However, results from four randomized controlled trials carried out during the 1990s gave no indication that supplements of  $\beta$ -carotene prevent cancer.<sup>5–10</sup> A considerable research effort is now underway to identify the anticarcinogenic vitamins and phytochemicals responsible for the cancer-preventing action of fruits and vegetables.<sup>5,11</sup>

In this review we discuss three outstanding questions concerning the relation between fruit and vegetables and the prevention of cancer:

1. What is the nature of the “dose–response” relationship?
2. Can the relationship be best explained in terms of “magic bullets” (one or a small number of potent anticarcinogens) or “teamwork” (the concerted action of numerous anticarcinogens)?

3. Why have cohort and case-control studies on colorectal, breast, and stomach cancers produced inconsistent results?

## DOSE–RESPONSE RELATIONSHIP

The relationship between the intake of fruits and vegetables and the risk of cancer is almost invariably reported as relative intake based on quartiles or quintiles of intake. There is a remarkable dearth of information on how risk changes with the absolute intake of fruits and vegetables. Information on this is valuable so as to define the optimal intake of these foods for the prevention of cancer. There are three possible dose–response relationships. An extra serving of fruit and vegetables might achieve:

1. a much greater risk reduction when the total intake is relatively low than when it is high (a vitamin-like minimal requirement)
2. a much greater risk reduction when the total intake is relatively high (a high-threshold effect)
3. the same absolute reduction in cancer risk at all levels of intake

It should be possible to distinguish between these three possibilities by comparing findings from different studies. For instance, if the first possibility is closest to the actual situation, then within cohort studies the risk ratio (RR) per extra serving of fruits and vegetables should be higher at the low end than at the high end of quintiles of intake and the RR per extra serving should be relatively high in populations in which the average intake is low. Of course, the shape of the curve likely will change with factors such as the type of cancer, whether the subjects are smokers, and the main types of fruits and vegetables eaten.

In this pilot study we explored this dose–response relationship. We reviewed more than 200 papers that provided RRs concerning intake of fruits and vegetables and risk of cancer. Our analysis of

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these limited data provided no indication of the shape of the dose-response relationship.

Three cohort studies on colorectal cancer produced conflicting findings. A Swedish study indicated that fruits and vegetables may manifest a protective association only at the low end of the range (i.e., at intakes of approximately two servings a day).<sup>12</sup> In contrast, combined data from the Nurses' Health Study and the Health Professionals' Follow-up Study indicated that very low intakes of fruits and vegetables (fewer than three servings a week) are not associated with an elevated risk of colorectal cancer.<sup>13</sup>

The only obvious conclusions to emerge from this study are the high degree of variability between studies and the difficulty in carrying out this exercise because many studies do not report the absolute intake of fruits and vegetables. Further progress in this regard is likely only when many more studies are published that provide the pertinent information (i.e., the intake of fruits and vegetables as grams per day).

## MAGIC BULLETS VERSUS TEAMWORK

One possible interpretation for the cancer-preventing action of fruits and vegetables is that these foods contain one or a small number of potent anticarcinogens (magic bullets). An alternative view is that fruit and vegetables contain many substances that act in concert to prevent cancer (teamwork).

Definitive answers concerning the anticarcinogenic potential of individual substances will come only from randomized controlled trials. However, these take years to carry out. Moreover, we do not even have the information to permit selection of substances worthy of being tested in trials. Even so, case-control and cohort studies provide clues as to the identity of the anticarcinogenic substances in fruits and vegetables. For instance, if lycopene is an anticarcinogen, as has been suggested,<sup>14</sup> then foods rich in it, such as tomatoes, should consistently manifest a protective association with one or more types of cancer. To investigate this idea, we examined papers that provide RRs concerning intake of fruits and vegetables and risk of cancer. These were the same papers referred to in the previous section. We tabulated the frequency with which different groups of fruits and vegetables were reported as having a protective association with different types of cancer. This was a pilot study rather than a systematic survey.

The picture that emerged is that one group of fruits and vegetables may dominate a particular cancer, and other groups invariably play significant roles. This finding resembles the tables in the paper by Steinmetz and Potter.<sup>2</sup> Quite possibly, the extent to which a single group of fruits and vegetables dominates the picture has been underestimated. This can occur due to measurement error and confounding (i.e., the tendency that people who have a high intake of one particular fruit or vegetable also have a high intake of various others). Nevertheless, when we look at cancer overall, the obvious conclusion is that many types of fruits and vegetables have a significant protective impact. Consistent with this, an Italian case-control study associated intake of diverse fruits and vegetables with protection against gastric cancer.<sup>15</sup> Similarly, other Italian case-control studies associated intake of diverse vegetables with protection against breast cancer<sup>16</sup> and colorectal cancer.<sup>17</sup>

These observations have two major implications. First, the prevention of cancer necessitates a varied intake of fruits and vegetables. Second, inferences can be made as to the substances responsible for the anticarcinogenic action of fruits and vegetables. For individual cancers, one substance may play a major protective role but other substances are also likely to be of importance. For cancer as a whole several substances at a minimum have a major role. In other words, fruits and vegetables prevent cancer by teamwork rather than by providing magic bullets.

We did not consider those studies that reported results in terms of intake of nutrients rather than of foods. However, a detailed

analysis of such studies would likely lead to the same conclusion. For instance, epidemiologic studies have clearly shown that  $\beta$ -carotene<sup>18</sup> and vitamin C<sup>19,20</sup> are negatively associated with several types of cancer.

There is an additional argument in support of the teamwork concept. On the one hand, carcinogenesis is well known to be a complex, multistage process. On the other hand, fruit and vegetables contain many substances believed to influence various aspects of this process.<sup>11</sup> It seems probable therefore that fruits and vegetables prevent cancer by the combined action of many substances acting at different stages of carcinogenesis.

The teamwork concept should be of value in the planning of future intervention trials for the prevention of cancer. The use of supplements containing a small number of vitamins and phytochemicals is unlikely to achieve more than minor success. In contrast, we are far more likely to discover a practical means to prevent much cancer by testing mixtures of several fruits and vegetables.<sup>21</sup>

## PROBLEMS OF CONFOUNDING

Lifestyle variables tend to cluster together. This can lead to confounding errors in epidemiologic investigations if not adjusted for in multivariate analysis.<sup>22,23</sup> This is pertinent to studies of fruits and vegetables: a relatively high intake of these foods is generally associated with a healthy lifestyle. For example, in the Nurses' Health Study a high intake of fruits and vegetables was part of a dietary pattern that included increased consumption of legumes, fish, and whole grains and a lower rate of smoking.<sup>24</sup>

Many studies, cohort and case control, have routinely ignored potentially important confounders such as energy intake, alcohol consumption, physical activity, body mass index, and smoking. In this regard recent studies (i.e., after the mid-1990s) are of generally higher quality than the older ones.

Socioeconomic status (SES) is another possible confounder because a high SES has been inversely associated with risk of cancer.<sup>25</sup> This can be measured in a variety of ways, including education, income, area of residence, and type of employment. Older studies often ignored SES, whereas most recent studies have adjusted for education but not for the other measures of SES.

A possible confounder that is usually ignored is the consumption of whole grain cereals. A generous intake of these foods has been associated with a reduction by one-third in cancer risk.<sup>26,27</sup> A confounder that is rarely considered is the use of vitamin and mineral supplements. Such supplements contain many nutrients that may influence carcinogenesis. In particular, they usually contain folate and this appears to be protective against some types of cancer, especially colorectal and pancreatic.<sup>28,29</sup> It also may be protective against breast cancer, especially in women with a relatively high alcohol intake.<sup>30</sup> Folate may help explain why fruits, vegetables, and whole grain cereals have protective associations with cancer.

Failure to measure these confounders will, in the large majority of cases, tend to overestimate the strength of the inverse association between fruits and vegetables and cancer.

Marshall and Greenland<sup>31</sup> drew attention to the problem of how measurement errors of strong confounders can lead to erroneous conclusions concerning the relationship between a weak risk factor and outcome. As an example of this they discussed the protective association between intake of  $\beta$ -carotene and cancer. Inaccurate estimations of smoking (a strong confounder) may have exaggerated the strength of the negative association between  $\beta$ -carotene and cancer. This also may apply to fruits and vegetables.

Further investigation is required concerning confounding as a source of error in studies of the relationship between intake of fruit and vegetables (and of other dietary and lifestyle factors) and risk of cancer.

## INCONSISTENCIES BETWEEN COHORT AND CASE-CONTROL STUDIES

In recent years it has become increasingly apparent that the protective association between fruits and vegetables and cancer is much weaker in cohort studies than in case-control studies. This has been reported for colorectal cancer,<sup>13</sup> breast cancer,<sup>32</sup> and stomach cancer.<sup>33</sup>

There are several possible explanations for these discrepant findings. The one cited most often is recall bias. If subjects in case-control studies tend to underestimate their past intakes of fruit and vegetables, this will exaggerate the strength of the inverse association with cancer. Cohort studies avoid this problem because diet assessment is made long before diagnosis. Several studies have attempted to investigate this question, but results have been mixed.<sup>34–37</sup>

Another possible explanation is selection bias. If the individuals who volunteer to serve as controls in a case-control study tend to have a history of a relatively healthy diet, including a relatively high intake of fruits and vegetables, then this will have the same effect as recall bias.

A third source of systematic bias is dietary change that results from cancer. This may cause patients to underestimate their pre-cancer diets. Stomach cancer may be especially vulnerable to this problem.

## CONCLUSIONS

We now have a great wealth of data concerning the relationship between fruits and vegetables and cancer. However, simply tabulating and summarizing these data will not tell the whole story. Indeed, that approach may even lead to misleading conclusions, but fully exploiting the available data poses a considerable challenge. It seems reasonable to assume that a systematic analysis of published studies would reveal valuable information. This will require much more than a consideration of the obvious variables: type of cancer, types of fruits and vegetables associated with the cancer, type of study (case-control or cohort), number of subjects, and RRs. It also will require careful attention to more subtle variables: median intake of fruits and vegetables in the study population, RRs at different ends of the intake range, correction for possible confounding variables (including SES, intake of whole grain cereals, and use of vitamin and mineral supplements), quality of diet assessment, and (in the case of case-control studies) the likelihood of recall and selection bias. A systematic analysis along these lines should, we hope, help uncover the true nature of the dose-response relationship and identify which types of fruit and vegetables (or which mixtures of them) have the greatest anticarcinogenic potency.

The same challenges apply to the design of future studies. More attention needs to be given to these variables. In particular, new-generation cohort studies—if the right lessons are learned from the limitations of previous ones—will help answer some of the unresolved questions.<sup>22</sup>

This strategy has great potential public health importance. The findings may permit the formulation of dietary advice that will have the optimum preventive impact on cancer. The findings also will help in the quest for anticancer supplements that are effective yet safe and cheap.

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