Your mother was right: Eat your vegetables

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A lower risk of cancer at many different sites is seen in association with higher intakes of vegetables and fruit. There are many biologically plausible reasons for this potentially protective association. It is argued that increasing intake of plant foods to 400–800 g/day is a public health strategy of considerable importance for individuals and communities worldwide.

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Introduction

Consumption of particular vegetables and fruits has long been believed to be useful in the prevention and cure of disease. Until recently, the practice of Western medicine largely involved the prescription of specific plants and foods, a practice that has its origins in ancient Egypt, Greece and Rome. The modern medical practices of China and India remain closer to their roots.

In 1981, Doll and Peto produced a wide estimate of 10–70% of all cancer as being attributable to diet.[1] Much of this interpretation was based on studies showing increased risk in association with particular foods — particularly foods of animal origin. Particularly over the past decade, however, a substantial number of studies have examined the effect of plant food consumption on health and disease. That high consumption of vegetables and fruit is protective against cancers at many sites is now better supported by the scientific literature than most of the other dietary hypotheses.

As early as 1933, a case-control study by Stocks and Karn in Britain suggested such an association between the intake of certain vegetables against cancer at all sites.[2] These researchers acquired data on 462 cancer patients and 435 patients without cancer, each of whom provided a diet history. The most common cancers in the case group were cancers of the breast, colon and rectum, uterus and tongue. These cases reported lower consumption of carrots, turnips, cauliflower, cabbage, onions, watercress and beetroot than the control group. The combined intake of these vegetables was significantly lower in the cancer patients than the control group. Although the methods employed in this study were crude by modern standards, it is striking that this apparently protective effect of vegetable consumption, along with the risk-enhancing effects of pipe smoking, beer drinking, and an inverse association with unboiled milk were the major findings of their study.

The epidemiologic data

Since then, over 200 epidemiologic studies have been conducted in many different parts of the world to investigate the role of vegetables and fruit in altering the risk of cancer in different organs of the body.[3–6] Statistically significant inverse associations have been reported for one or more vegetable and/or fruit categories in a high proportion of these studies and in more than half of the studies of every cancer site, except prostate. The evidence strongly suggests that it is not consumption of one or two varieties of vegetables and fruit that confer benefit but rather that the intake of a wide variety of plant foods is a common factor in those who have a lower risk of cancer. Indeed, of all the vegetables studied, perhaps only legumes and potatoes appear to show no evidence of direct benefit. The fact that individuals who consume higher intakes of plant foods also have other healthy habits, such as a lower likelihood of smoking, does not account for all — or probably even most — of the differences seen.

More than 20 cohort studies have examined the relationship between vegetable and fruit consumption and different types of cancer.[5,6] Of these, almost all found an inverse association for at least one category of vegetables and/or fruit and, in 12 studies, statistically significant associations were shown. Of these studies, four reported on all cancer sites; four on lung cancer; three each on colorectal and stomach cancers; two each on pancreas, bladder and breast cancers; and one on prostate cancer. It is lung cancer for which the cohort study evidence is the most consistent; inverse associations for vegetable and/or fruit consumption have been shown in populations of Norwegian men, postmenopausal women in the United States, Seventh-Day Adventists and members of a retirement community.

The majority of the human evidence for an inverse association with vegetable and fruit consumption comes from case-control studies.[5,6] Stomach cancer has been the most studied, followed by cancers of the colon, oesophagus, lung, oral cavity and pharynx, rectum and breast; more than 10 studies have focused on each of these sites. Statistically significant inverse associations have been reported for one or more vegetable and/or fruit categories in more than 70% of the studies for cancers of the following sites: stomach,

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oesophagus, lung, oral cavity and pharynx, endometrium, pancreas, colon and skin. Prostate cancer is the only cancer for which the majority of studies have not reported at least one statistically significant inverse association and, indeed, for prostate cancer, no study shows an inverse association.

Animal experimental and *in vitro* studies show that a multiplicity of agents present in vegetables, fruit and other plant foods are capable of preventing cancer either directly or via complex interactions with the body's metabolic and molecular processes.

Mechanisms

There are many biologically plausible reasons why the consumption of vegetables and fruit might reduce the likelihood of cancer. These include the presence of potentially anticarcinogenic substances such as carotenoids, ascorbate, tocopherols, selenium, dietary fibre, dithiolthiones, isothiocyanates, indoles, phenols, protease inhibitors, allium compounds, plant sterols, limonene and others. These are increasingly being called, collectively, phytochemicals or bioactive compounds; that is, chemicals of plant origin that play a crucial role on mammalian metabolism. Some of these are discussed in more detail in other publications.[6,7]

When the body is first exposed to specific carcinogens, many are not in their active form. Simplistically, the steps between exposure to the pro-carcinogen and the conversion of a normal cell into a cancer-prone cell (transformation) can be considered as follows: (i) the pro-carcinogen is activated to the ultimate carcinogen form by P450 enzymes (it is worth keeping in mind that the body is not trying to make carcinogens — it is trying to solubilize insoluble foreign compounds and therefore enable excretion in the urine; this is complicated by the fact that the same enzyme reaction can often make one compound less carcinogenic and another more carcinogenic); (ii) either of the forms of the carcinogen (pro-carcinogen or ultimate carcinogen) may be converted by Phase II enzymes into a form that is relatively inert and even more easily excreted; these are typified by glutathione S-transferase; (iii) if not excreted, the carcinogen can pass through the cell membrane and the nuclear membrane; (iv) the carcinogen can then interact with the DNA forming adducts and/or producing mutations; (v) DNA synthesis and replication (or DNA repair) subsequently occur; (vi) repair has varying degrees of fidelity; that is, if the DNA is not repaired accurately, cell replication, which produces daughter cells with copies of the mutated DNA, occurs. These cells then synthesize an abnormal protein or fail, altogether, to synthesize a protein crucial to the normal function of the cell or even crucial to controlling cell replication itself (this is almost certainly what happens when a tumor suppressor gene (e.g. p53) mutates or is deleted).

This sequence of stages brings a cell a step closer to becoming a cancer cell (alternatively, even with abnormal DNA, the cell may cease to replicate and then undergo differentiation or apoptosis). DNA damage probably has to occur several times before a cell becomes completely free of growth restraint and a fully cancerous cell. Finally, the abnormal cells obtain a growth advantage over the normal cells and steadily increase in numbers (promotion), often becoming more malignant and able to spread (progression). These are steps that themselves involve further changes in the cellular DNA.

At almost every one of these stages, known phytochemicals/bioactive compounds can alter the likelihood of carcinogenesis, occasionally in a way that enhances risk but usually in a favorable direction. For examples, such substances as glucosinolates and indoles, isothiocyanates and thiocyanates, phenols and coumarins can induce a multiplicity of solubilizing and (usually) inactivating enzymes; ascorbate and phenols block the formation of carcinogens such as nitrosamines; flavonoids and carotenoids can act as antioxidants, essentially disabling carcinogenic potential; lipid-soluble compounds such as carotenoids and sterols may alter membrane structure or integrity; some sulfur-containing compounds can suppress DNA and protein synthesis; and carotenoids suppress DNA synthesis and enhance differentiation. For more detail on this process as well as a discussion of the role of other dietary and lifestyle-related exposures in the aetiology of cancer, the reader is referred to chapter 2 of *Food, Nutrition and the Prevention of Cancer: A Global Perspective*.[6]

Public health implications

As the constituents of tobacco smoke were enumerated, it became increasingly clear that making a non-carcinogenic cigarette was not an achievable goal and that behavioural, economic and legislative programmes to eliminate smoking were more appropriate. At present, the dominant approach to the harnessing of plant foods to prevent cancer is focused on finding *the* anti-carcinogenic constituent and packaging it as a pill. The initial human trials — experiments — have proved to be a serious disappointment with evidence that not only are some specific agents such as β-carotene not able to reduce cancer rates in high-risk populations but they actually increase risk. It may suggest that behavioural approaches (paralleling the successful smoking cessation programmes) to increasing plant food intake may be more fruitful. Economic incentives to increase human plant food production are also worthy of consideration.

There are other arguments, based on the biology of cancer, to support an increased intake of plant foods as a primary strategy.[8] The use of single agents has proved to be ineffectual and, ultimately, counter-productive in the treatment of many cancers. This is largely because resistant clones arise readily in the presence of potent cytotoxic/chemotherapeutic agents. In rapidly proliferating tissues with elevated levels of cell death, selection for survival in the presence of the agent will occur rapidly. In tissues where there are large numbers of initiated cells, it is plausible that similar selection will happen in the presence of a single *chemopreventive* agent. If the action of the agent is to induce differentiation, those cells that are incapable of differentiation may gain a proliferative advantage. Similar arguments apply to a single agent that increases the rate of apoptotic cell death. Again, those cells that are resistant to apoptosis may continue to proliferate.[6]

It follows that, while we should continue experimental studies to understand the role of specific agents in cancer prevention, we should not be surprised if the effect of the agent differs at different stages of carcinogenesis or if it differs when used alone rather than in combination with other compounds.

The safest public health strategy seems to be to advocate increased intake of intact plant foods with the multiplicity of agents that they contain. It is less likely that any clone of malignant cells can survive the polypharmacy of plant food. At present, it is not exactly clear what quantity we should eat each day; however, it *is* clear that many people do not eat enough. The recent report of the World Cancer Research Fund presented a variety of recommendations that could, collectively, reduce the world's cancer burden by 30–40%.[6] Included in those recommendations was the following: 'Eat 400–800 g or five or more portions (servings) a day of a variety of vegetables and fruits, all year round'. The panel preparing the report estimated that perhaps 20% of the cancer burden could be reduced by this step alone. At this level of consumption, there are likely to be few dangers for any part of the population. Supplements and pills, on the other hand, will not provide the diversity of compounds available in food and certainly do not provide the taste and enjoyment. For any community or even nation, some specific incentives for the production of more vegetables and fruit would allow the changes at the individual level to be made more easily and, ultimately, may prove to be a useful investment in lowering the burden of chronic disease.

Plant foods appear to exert both a general risk-lowering effect and the possibility of site-specific effectiveness; the patterns of exposure to cancer initiators and promoters and of genetic susceptibility may determine the variations in the site-specific risks of cancer seen across populations. Increasing vegetable and fruit intake to 400–800 g per day is a good start. However, appropriate public health action involves changing many other aspects of human societies, including agriculture, trade, transport, land use, water use, etc. Specific multiple-agent chemoprevention may need to be devised for those at very high risk. However, until we understand better the protective mechanisms for specific compounds and the possible reasons why single agents, even with protective potential, can increase risk, your mother's advice may be preferable — eat your vegetables!

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