The Protective Role of Fruits and Vegetables against Radiation-Induced Cancer

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The role of fruits and vegetables in protecting against radiation-induced cancer and the positive evidence from epidemiology and ancillary investigations are discussed in this review. The recently reported Hiroshima and Nagasaki atomic bomb survivor studies provide strong evidence for the protective role of fruits and vegetables against radiation-induced cancer. The anticarcinogenic substances contained in, and the anticarcinogenic mechanisms proposed for, fruits and vegetables are reviewed. The anticarcinogenic effectiveness of fruits and vegetables are compared with that of dietary supplements. The reasons for the observed superiority of fruits and vegetables are advanced.

Key words: radiation-induced cancer, radiation-protective agents, epidemiology, fruits and vegetables, anticarcinogenic agents and mechanisms

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INTRODUCTION

While the role of fruits and vegetables is well established and known in protecting against major diseases and disorders of the cardiovascular, digestive, and endocrine systems, their protective role is less known and established with respect to radiation-induced cancer. Their role with respect to radiation appears to be a particular manifestation of their general role in preventing and/or inhibiting cancer. For purposes of this review, radiation encompasses X-rays and gamma-rays, neutrons, alpha and beta particles, high-speed electrons and protons, and other particles capable of producing ions; it does not include non-ionizing radiation such as radio waves or microwaves and visible, infrared, or ultraviolet light.

Since the dawn of the Nuclear Age, there have been concerted efforts to discover and/or develop radioprotectors, agents that inhibit the development of radiation-induced cancer either by blocking the DNA damage that initiates carcinogenesis or by arresting or reversing the progression of premalignant cells in which such damage has already occurred. It is important to make the distinction between natural radioprotectors such as fruits and vegetables and synthetic ones. While there has been a long history of research in synthetic radioprotectors and pharmacological agents, in toto, the results have been at best only equivocal. Much research has been devoted to the sulphhydryl compounds (synthetic sulfur-containing amino acid antioxidants) cysteine and cysteamine, which unfortunately are marked by toxicity and short active periods, and to biological response modifiers such as cytokines, polysaccharides, and prostaglandins.

Although combinations of radioprotective drugs acting via different mechanisms have been found to improve the degree of protection and keep toxicity to acceptable levels in small rodents, attempts to use such treatments in large mammals have been less successful, generally due to poorer protection and higher toxicity. There have also been long-term efforts by radiation oncologists and radiation biologists to develop synthetic chemical radiosensitizers to differentially spare normal tissues (as opposed to tumor cells) from radiation damage, but clinical exploitation has been slow in coming.1 In a review paper summarizing past, present, and future prospects of chemical radioprotection, Maisin2 stated that no radioprotective drug has all of the requisite qualities of an ideal radioprotector, and that it is questionable whether chemical radioprotection in humans has any future prospects. He did, however, hold out some future hope for non-toxic combinations of biological and chemical agents.2 With certain caveats, the prospects for natural radioprotective agents in general, and diets rich in fruits and vegetables in particular, have far greater efficacy. One caveat is that these natural agents would not necessarily be expected to exert a significant influence at
high radiation doses and/or dose rates. However, as will be reviewed here, outside this caveat there appears to be mounting evidence that a diet rich in fruits and vegetables can play a positive and important role in both the prevention and amelioration of radiation-induced cancer.

**BACKGROUND**

The 1981 landmark review by Doll and Peto\(^3\) provided quantitative estimates of the proportion of cancer incidence accounted for by a large range of environmental factors, including diet. Their work established that smoking and dietary behavior each accounted for about one-third of cancer risk, and emphasized that the majority of cancers in those under age 65 are potentially avoidable either by removal of harmful factors or by incorporation of beneficial ones.\(^5\) One harmful factor is ionizing radiation, mostly a result of natural radiation to which everyone is exposed: radon in air, cosmic rays from outer space, external radiation from radionuclides in rocks, soils, and building materials, and internal radiation from naturally occurring radioactive traces of potassium, lead, and polonium in food. Doll has estimated that this ionizing radiation causes approximately 4% of all cancers.\(^5\) A more important harmful factor is improper diet. Harmful dietary factors contributing to enhanced risk include cooked food mutagens, certain preservatives, and fungal toxins including aflatoxins and fumonisins.\(^5\) In contrast, some foods are considered to be beneficial in that they prevent and/or control cancer. These include, most notably, fruits and vegetables.

Evidence for food’s beneficial protective role may be inferred from the fact that numerous epidemiological studies support the likelihood that nutritional preemption is a useful strategy to reduce cancer risk at multiple body sites, with the greatest protection attributable to greater fruit and vegetable consumption. To cite one relatively recent study, Smith-Warner and Giovannucci\(^6\) have presented a comprehensive evaluation of cancer risk in relation to diet using a review of retrospective case control and prospective cohort epidemiological studies conducted in countries with diverse dietary practices using different dietary assessment techniques. Despite limitations in methodologies and variations across studies, they reported convincing evidence that diets high in fruits and vegetables are associated with reduced risk for many different cancer types.

Within the last decade, complementary epidemiological evidence has been reported and discussed. In 1997, an international review panel of the World Cancer Research Fund’s American Institute for Cancer Research (AICR)\(^7\) concluded from an exhaustive collection of worldwide research on this topic that “diets high in vegetables and fruits (more than 400 g/d) could prevent at least 20% of all cancer incidence.” A second extensive review of research on the health benefits of fruit and vegetable consumption and cancer risk was the report of the Chief Medical Officer’s Committee on Medical Aspects of Food and Nutrition Policy (COMA), British Department of Health.\(^8\) The majority of the research reviewed both by COMA and AICR was drawn from epidemiological studies.

Table 1 (adapted from Van Duyn and Pivonka\(^9\)) summarizes the epidemiological evidence related to vegetable and fruit intakes and generically induced cancer as assessed by AICR and COMA. The AICR panel classified the strength of evidence as convincing, probable, or possible. AICR judged that there was convincing evidence that high intake of vegetables: 1) decreases the risk of cancers of the mouth and pharynx, esophagus, lung, stomach, and colon, rectum; 2) probably decreases the risk of cancers of the larynx, pancreas, breast, and bladder; and 3) possibly decreases the risk of cancers of liver, ovary, endometrium, cervix, prostate, thyroid, and kidney. High fruit intake was considered to decrease the risk of most of the cancers previously mentioned, with the exception of cancers of the liver, prostate, kidney, colon, and rectum, for which the data were considered limited or inconsistent. The panel stated that the evidence for a stronger protective effect for vegetables may reflect the fact that they are generally consumed in greater quantities than fruits, and thus in more variable quantities within populations. The AICR study also concluded that there is no cancer site for which the evidence, taken as a whole, supports an overall increase in risk with higher intakes of fruits and vegetables.

The COMA working group used classifications of strongly consistent, moderately consistent, and weakly consistent. In general, COMA tended to be more conservative in its judgment of the evidence than was AICR, and weighed prospective studies more heavily than case control studies. Despite differences in their qualitative assessments, both panels recommended fruit and vegetable consumption to combat cancer. It is a reasonable conjecture that the same protective and ameliorating effects that fruits and vegetables have with respect to cancer in general would also be expected to apply for radiation-induced cancer. As will be developed, this has proved to be the case.

Willett\(^10\) has raised general concerns over the fact that some prospective studies seem to indicate that the efficacious effects of fruit and vegetable consumption on cancer may have been overstated. These concerns presuppose the superiority of prospective over case control studies. In a later paper, Huang et al.\(^11\) reported a large prospective study showing no relationship between fruit and vegetable intake and cancer incidence. However, in an accompanying editorial, Schatzkin and Kipnis\(^12\)
raised concerns about that paper’s methodology; specifically, that errors in assessing diet and other potential confounding may have attenuated (especially in multivariate analyses) a true association between fruit and vegetable intake and cancer risk if such an association exists. While Riboli and Norat’s meta-analysis showed that prospective studies provided weaker evidence than case control studies for an inverse relationship between cancer risk and fruit and vegetable consumption, they too raised some concerns by attributing the discrepancy to recall and selection bias in case control studies coupled with imprecise dietary measurements and limited variability of dietary intakes within prospective cohorts.

It should be noted that the classic sequence of hypothesis testing may not always hold in nutritional epidemiology. Byers has argued that for the testing of many nutritional hypotheses, ecological studies perform better than studies of individuals, retrospective studies perform better than prospective studies, and even that randomized controlled trials, although theoretically supreme and usually regarded as the “gold standard,” often do not offer a practical approach to answering many nutritional questions. Byers has also argued that results from one type of epidemiological study should not be treated as a refutation of evidence from other types of epidemiological studies, especially when such other evidence is backed by data from animal studies and identification of plausible biologic pathways. In his characteristic forthright manner, Shapiro has made some of the same essential points.

In addition to these epidemiological studies, which by their nature could not pinpoint the cause of cancer, over the last 50 years there have been numerous laboratory animal studies of the potential for naturally occurring agents to reduce ionizing radiation-induced cellular damage. Weiss and Landauer have reviewed the radioprotective efficiency of some naturally occurring (i.e., non-synthetic) agents, specifically antioxidant nutrients and phytochemicals/bioactive compounds (i.e., non-nutritive components in the plant-based diet that possess substantial anticarcinogenic and antimutagenic properties), and how they might influence various endpoints of radiation damage. They report that some natural antioxidants (including vitamins E and A, beta-carotene, selenium, and superoxide dismutase) can protect against lethality and other radiation effects even when administered to mice after radiation exposure, albeit to a lesser degree than most synthetic protectors. They also report that some of these antioxidant nutrients and phytochemicals have low toxicity while being generally protective at pharmacological doses, and that they may also provide an extended window of protection against low-dose, low-dose-rate irradiation. In addition, they state that many antioxidant nutrients and phytochemicals have antimutagenic properties.

Weiss and Landauer ended their review of animal studies with the judgment that treatment with some antioxidant nutrients and phytochemicals after radiation exposure is a fruitful area of cancer research.

Table 1. Two Large-Scale Epidemiological Studies (by the American Institute for Cancer Research [AICR] and the Committee on Medical Aspects of Food and Nutrition Policy, British Department of Health [COMA]) of the Protective Role of Vegetable and Fruit Consumption Against Generically Induced Cancer (table adapted from Van Duyn and Pivonka)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Vegetables</th>
<th>AICR</th>
<th>COMA</th>
<th>Fruits</th>
<th>AICR</th>
<th>COMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouth and pharynx</td>
<td>Convincing</td>
<td>Inconsistent</td>
<td>Convincing</td>
<td>Weakly consistent</td>
<td></td>
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<tr>
<td>Larynx</td>
<td>Probable</td>
<td>Moderately consistent</td>
<td>Probable</td>
<td>Moderately consistent</td>
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<tr>
<td>Esophagus</td>
<td>Convincing</td>
<td>Strongly consistent</td>
<td>Convincing</td>
<td>Strongly consistent</td>
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<tr>
<td>Lung</td>
<td>Convincing</td>
<td>Weakly consistent</td>
<td>Convincing</td>
<td>Moderately consistent</td>
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<tr>
<td>Stomach</td>
<td>Convincing</td>
<td>Moderately consistent</td>
<td>Convincing</td>
<td>Moderately consistent</td>
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<td></td>
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<tr>
<td>Pancreas</td>
<td>Probable</td>
<td>Strongly consistent</td>
<td>Probable</td>
<td>Strongly consistent</td>
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<tr>
<td>Liver</td>
<td>Possible</td>
<td></td>
<td>Possible</td>
<td>Weakly consistent</td>
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<tr>
<td>Colon, rectum</td>
<td>Convincing</td>
<td>Moderately consistent</td>
<td>Probable</td>
<td>Insufficient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>Probable</td>
<td>Moderately consistent</td>
<td>Possible</td>
<td>Insufficient</td>
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<tr>
<td>Ovary</td>
<td>Possible</td>
<td>Insufficient</td>
<td>Possible</td>
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<tr>
<td>Endometrium</td>
<td>Possible</td>
<td>Insufficient</td>
<td>Possible</td>
<td>Strongly consistent</td>
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<tr>
<td>Cervix</td>
<td>Possible</td>
<td>Moderately consistent</td>
<td>Possible</td>
<td>Inconsistent</td>
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<td>Prostate</td>
<td>Possible</td>
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<td>Possible</td>
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<td>Thyroid</td>
<td>Possible</td>
<td></td>
<td>Possible</td>
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<tr>
<td>Kidney</td>
<td>Possible</td>
<td></td>
<td>Possible</td>
<td></td>
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<tr>
<td>Bladder</td>
<td>Probable</td>
<td>Moderately consistent</td>
<td>Probable</td>
<td>Moderately consistent</td>
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</tr>
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</table>
of non-synthetic radioprotectors in conferring nutritional amelioration of radiation-induced cellular damage in animals has also been discussed by Fang et al. and Turner et al.

Also germane to this review are the results of animal studies on cancer and the consumption of fruits and vegetables. There have been at least 24 studies in which cancer has been experimentally induced by means of chemical carcinogens in mice, rats, or hamsters fed specified amounts of certain fruits or vegetables (usually cruciferous vegetables, soy products, citrus oils, or oils from allium vegetables). In the majority of these studies, it was unequivocally found that the animals fed fruits or vegetables experienced fewer tumors, smaller tumors, fewer metastases, less DNA damage, higher levels of enzymes involved in the detoxification of carcinogens, or other outcomes indicative of lower cancer risks. Fewer animal experiments with non-chemical carcinogens have been carried out. Troll et al. reported that a raw soybean diet significantly lowered breast cancer tumor incidence in 250 kilovolt (peak) X-ray-irradiated rats, while Robinson et al. reported that raw fruits and vegetables markedly reduced squamous cell carcinoma in ultraviolet-irradiated hairless mice. Although Steinmetz and Potter have cautioned that extrapolation of animal studies to human beings is difficult given species differences, the use of administered carcinogens and genetically susceptible animals, and the relative doses of fruits and vegetables being well above those typically consumed by human beings, Maltoni et al. have advanced strong arguments regarding the general utility of animal studies.

IMPORTANT AND CONFIRMATORY RECENT HUMAN EVIDENCE FOR NUTRITIONAL RADIATION PROTECTION

Up to this point in this review, the evidence for protective and ameliorating effects of dietary factors on radiation-induced cancer in humans has been indirect; for example, the epidemiology of generically induced cancer and animal laboratory studies suggesting human applicability. This section will present recent important and confirmatory evidence for nutritional protection, particularly by fruits and vegetables, against radiation-induced cancer in humans.

Until fairly recently, there have been only limited studies of the effect of diet on radiation-exposed populations. Some of the initial work involved people exposed from the Chernobyl nuclear reactor accident. One approach involved measurement of clastogenic factors that result in chromosomal breakage and are considered biomarkers of oxidative stress. These chromosome-damaging substances have appeared in the blood of emergency workers (liquidators) and exposed children even many years after the accident. Kordysh et al. reported that fresh fruits and vegetables suppress these long-persisting factors in children exposed to radiation from the incident. Emerit et al. reported suppression of these long-persisting factors in exposed children by intervention treatments with Gingko biloba extract and another plant extract containing various flavonoids, oligo-elements, vitamins, and minerals. Another approach involves measurement of long-persisting lipid peroxidation products in exposed children. Ben-Amotz et al. report that a “natural” isomer mixture of beta-carotene-containing multiple constituents common to green plants served as a radioprotector by decreasing these products. It is important to note that each of these studies monitored multiple nutritional constituents, each of which may synergistically contribute to the observed beneficial effects.

Prospective epidemiological studies of Hiroshima and Nagasaki atomic bomb survivors and non-exposed controls have proved to be invaluable. Nagano et al. reported that frequent consumption of green-yellow vegetables and fruit were associated with a decreased risk of bladder cancer, with no association with radiation exposure. Two other atomic bomb survivor studies provide strong evidence for the protection provided by fruits and vegetables against radiation-induced cancer, with fruit intake referring to total fruit consumption and green-yellow vegetables defined as vegetables containing more than 1000 IU of carotene per 100 g (carrots, spinach, pumpkin, lettuce, asparagus, parsley, etc.). Sauvaget et al. have investigated cohorts of some 38,000 atomic bomb survivors with radiation dose estimates who had their diets assessed in 1980–1981. These cohorts were monitored over the following 20-plus years, some 55 years after exposure. Sauvaget et al. reported that daily or almost daily fruit consumption was associated with a significant (12%) reduction in total cancer mortality, while daily or almost daily green-yellow vegetable consumption was associated with a marginally significant (8%) reduction in total cancer mortality. Green-yellow vegetable consumption was associated with a significant reduction in liver cancer mortality, while fruit consumption was associated with a significantly reduced risk of stomach cancer and lung cancer mortality. Other appreciable cancer reductions that escaped statistical significance were also noted. Sauvaget et al. concluded that fruit and vegetable intake reduced significantly the risk of death from digestive and respiratory cancers. Later, more quantitative epidemiological analyses by Sauvaget et al. of all solid cancers, stomach cancers, lung cancers, and liver cancers likewise concluded that a daily intake of green-yellow vegetables and fruit benefited those exposed to radiation.
in reducing cancer risk. These two complementary studies provide the most critical and convincing evidence yet for the positive role that fruit and vegetable consumption plays in protecting against and ameliorating the effects of radiation-induced cancer.

While these atomic bomb survivor studies suffer from some of the inadequacies that are almost of necessity the hallmark of epidemiological analyses, they have the important attribute of comparing observational cancer risk with quantitative radiation dose estimates. Radiation dose is the amount of ionization energy absorbed in matter and herein expressed in Sievert (Sv) units.

Members of the general public receive a non-occupational average annual radiation dose of about 0.0036 Sv (with both natural and man-made contributions, including medical usage ionizing radiation). Atomic bomb survivors received an essentially instantaneous dose (i.e., high dose rate), although not what would be considered a “high” dose in the parlance of radiation incidents. Preston et al. reported that for a cohort of atomic bomb survivors who received a broad range of doses with a mean of 0.1 Sv, radiation accounted for 5% of cancer deaths. Sauvaget et al. reported mean radiation doses tightly centered around 0.11 Sv, while Sauvaget et al. reported a mean dose of 0.2 Sv for those exposed above an adopted background threshold dose of 0.005 Sv.

Sauvaget et al. have analyzed solid cancer data for those exposed at 1 Sv using two different interaction models. They reported that 1 Sv radiation exposure coupled with low fruit and vegetable intake (once or less per week) caused about a 50% increase in solid cancer death. Solid cancer death was reduced to about a 37% increase with daily fruit and green-yellow vegetable intake. At 1 Sv radiation exposure, daily intake of fruit and green-yellow vegetables also caused large quantitative reductions at specific cancer sites (stomach, lung, liver). It is to be expected that the salutary effects of fruit and vegetable consumption manifested in these atomic bomb survivors would of necessity also apply for the lesser radiation doses and dose rates of non-emergency situations, i.e., the norm.

As noted above, some have expressed concerns that the protective actions of fruits and vegetables may have been overstated. An additional benefit of the atomic bomb survivor studies is that they lend additional credence to previous epidemiological reports of the general efficacy of fruits and vegetables as anticarcinogenic agents. The evidence for nutritional radioprotection of humans is summarized in Table 2. The atomic bomb survivor studies are by far the most complete. They provide convincing evidence that the consumption of fruits and vegetables protects against radiation-induced cancer.
FRUITS AND VEGETABLES: ANTICARCINOGENIC SUBSTANCES

Compared with other food groups, fruits and vegetables are rich in vitamins and minerals. Although different types have different nutrient profiles, they are generally good sources of fiber, carotenoids, folate, potassium, and bioactive compounds. Some specific vegetables are good sources of B vitamins, calcium, and iron. Dried fruits are concentrated sources of energy, sugar, dietary fiber, and iron.7

Fruits and vegetables are complex foods. It has been estimated that about 25,000 different chemical compounds occur in fruits, vegetables, and other plants eaten by man. As of 2002, more than 500 of these compounds have been identified as potential modifiers of the cancer process.35 Some of the potentially anticarcinogenic substances in fruits and vegetables include the following: allium compounds, carotenoids, coumarins, dietary fiber, dithiolthiones, flavonoids, folate, glucosinolates, indoles, inositol hexaphosphate, isoflavones, isothiocyanates, limonene, plant sterols, phytosteroids, protease inhibitors, saponins, selenium, and vitamins C (ascorbate) and E (tocopherols). Cruciferous vegetables such as broccoli, cauliflower, cabbage, and Brussels sprouts contain dithiolthiones and indole-3-carbinol. Allium vegetables such as onions, garlic, scallions, leeks, and chives contain allium compounds. Citrus fruits contain coumarins (also found in some vegetables) and D-limonene (specifically found in oil from the skin of fruit). Many fruits and vegetables contain the potentially anticarcinogenic flavonoids quercetin and kaempferol (which are also found in tea and wine).7,22,36,37

There is recent evidence for the role of nutrient deficiencies in radiation damage. Ames38 has reported that laboratory evidence ranging from likely to compelling indicates that deficiency in folic acid (folate) and vitamin C, as well as niacin, iron, zinc, vitamin B12 (not derived primarily from fruits and vegetables), mimosine, and indole-3-carbinol, mimicks radiation in damaging DNA by causing single- and double-strand breaks and/or oxidative lesions. Double-strand breaks are considered the most serious DNA lesion caused by radiation, while oxidant-by-products of normal energy metabolism (superoxide, hydrogen peroxide, and hydroxyl radicals) are the same mutagens produced by radiation and appear to play a major role in cancer induction. Dietary insufficiencies in these dietary components may confound radiation effects by synergistically adversely affecting DNA synthesis and repair. If so, preventing deficiencies in these components would be expected to be protective against oxidative damage and promote repair of radiation-induced strand damage. Some laboratory studies have shown this to be the case. For example, folic acid deficiency alone causes strand breaks in Chinese hamster ovary cells.39 When these cells are exposed to gamma-irradiation, the incidence of DNA strand breaks increases. Adding folate has been found to decrease the initial strand break incidence and increase the rate of repair after irradiation exposure.

FRUITS AND VEGETABLES: ANTICARCINOGENIC MECHANISMS

What are the anticarcinogenic mechanisms of fruits and vegetables? Some that have been advanced include: 1) inhibiting genetic damage caused by exogenous agents through antioxidant scavenging of oxygen radicals and preventing DNA binding; 2) influencing the repair of structural/functional genetic defects by enhancing endogenous repair and restoring proper methylation; 3) eliminating damaged cells or clones by inducing apoptosis (programmed cell death), promoting differentiation, and enhancing immunosurveillance; and 4) suppressing growth and clonal evolution by slowing or stopping proliferation, retarding angiogenesis, and inhibiting invasion.22,40,41 It is noteworthy that many of these mechanisms, especially antioxidant scavenging, repair, and apoptosis, are currently in the forefront of likely candidates for inhibiting and controlling radiation-induced cancer.

An obvious recommendation to reduce the oxidative damage that occurs from radiation exposure is the consumption of additional amounts of antioxidants. As already noted, Weiss and Landauer17,18 have reported on laboratory studies showing that many natural antioxidants, whether consumed before or after radiation exposure, are able to confer some level of radioprotection. A general review of antioxidants and their effect on specific reactive oxygen compounds has been provided by Fang et al.19 Machlin and Bendich42 concluded that because many dietary antioxidants (e.g., tocopherol and ascorbic acid) have the capacity to protect against the reactive molecules formed during radiation exposure, the benefit of using safe levels of such nutrients should be evaluated as a mechanism against radiation damage.

Carcinogenesis and tumor progression are controlled by the cancer-related cell signaling transduction pathways. Included among these pathways are p53, NF-κB, Akt, MAPK, AR, and ER. By modulating cell signaling pathways, various nutrients (among other mechanisms) activate cell death signals and induce apoptosis in pre-cancerous or cancer cells, resulting in the inhibition of cancer development and/or progression. Some of these nutrients and their means of controlling the cancer-related cell signaling pathways have been cited and referenced by Kong.43 The apoptosis process is a very efficient mechanism for inhibiting cancer development and/or progression, whereas the endogenous DNA repair...
process is somewhat error-prone. Recent laboratory studies have indicated that apoptosis and endogenous repair are intimately juxtaposed in inhibiting and controlling cancer induced at the relatively low levels of background radiation prevalent in non-emergency situations. Rothkamm and Lobrich\textsuperscript{44} and Collis et al.\textsuperscript{45} have separately shown that repair only occurs above a DNA damage threshold, below which apoptosis reigns.

**FRUITS AND VEGETABLES COMPARED WITH INDIVIDUAL ANTICARCINOGENIC DIETARY SUPPLEMENTS**

Can specific nutrients taken as synthesized and concentrated individual dietary supplements have the anticarcinogenic efficacy of multinutrient fruits and vegetables? There appears to be a weaker relationship between cancer prevention and amelioration by supplement usage than for nutrients absorbed from eating fruits and vegetables, indicating that nutrients taken in the broad combinations found in whole food are more effective against cancer than nutrients taken as individual supplements. Ames and Gold\textsuperscript{46} have declared that epidemiological studies of supplement use (vitamin and mineral intake by pill) have shown at most only modest support between intake of these substances and lower cancer rates. They have also noted that many problems complicate those studies, including the difficulty in measuring supplement use over long time intervals and the potential confounding of supplement usage with many aspects of a healthy lifestyle that are related to it (e.g., exercise, better diet, and not smoking). Clinical trials of supplements are generally too short to measure cancer risk, since cancers usually develop slowly and the risk increases with age; moreover, such trials cannot measure the potential reduction in risk if supplements are taken throughout a lifetime. Additionally, the cancer risk of supplement users may be overestimated because they are more likely to undergo early screening such as mammograms or tests for prostate cancer, which are associated with increased diagnosis rates and can artificially increase the apparent incidence rate. Such confounding factors have not usually been taken into account.

Some clinical intervention trials of high-dose beta-carotene supplementation have not proven to be effective against cancer, and in some instances even increase lung cancer risk (e.g., the ATBC Study and the CARET Trial of persons at high risk of lung cancer because of either smoking or asbestos exposure). These deleterious results have had the effect of placing a pall over all supplementation usage. But these particular intervention studies have been criticized both on general grounds and on grounds particular to the intervention.\textsuperscript{7,29,47} For example, Wang and Russell\textsuperscript{48} have suggested that carcinogenesis could be promoted in the lungs of cigarette smokers by several possible mechanisms if high-dose beta-carotene supplementation results in the formation of large quantities of undesirable beta-carotene oxidative metabolites. In addition, Greenwald\textsuperscript{49} has noted that the synthetic beta-carotene used in the ATBC Study was composed almost entirely of trans-isomeric beta-carotene, which is thought to represent the most common isomer found in the body after metabolism. The fact that this is just one of the more than 272 commercially synthesized isomers of beta-carotene that have been commercially synthesized introduces serious testing uncertainties and concerns. The large number of epidemiological studies showing that dietary sources and amounts of beta-carotene from carotenoid-rich fruits and vegetables are beneficial and antiproliferative might also indicate that beta-carotene acts synergistically in concert with other dietary compounds or serves as a marker for other correlated constituents of fruits and vegetables.

Fruits and vegetables contain myriad phytochemicals that may act as cancer-protective agents. The combined exposure to the multitude of compounds present together in fruits and vegetables may be critical for cancer protection.\textsuperscript{6} Lamprecht and Lipkin\textsuperscript{50} have observed that single compounds are invariably only partially effective as anticarcinogens, and that in the field of medical chemotherapy, combinations of agents are frequently more effective than any one drug in isolation. This is just as likely to be true of the anticarcinogenic effects of food components acting through the medium of self-selected human diets, where weak and/or small amounts of anticarcinogenic agents would be expected to act synergistically in combination and in concert with other compounds and with concomitant minimum toxicity. Since the overall goal should be the prevention and/or amelioration of all cancer types, the message is that the myriad phytochemicals contained in a wide variety of fruits and vegetables is important in achieving maximum anticarcinogenic benefit.

**CONCLUSIONS**

This review has discussed evidence for the protective role of nutritional agents against radiation-induced cancer, and in particular the protective effects of fruits and vegetables. The convincing epidemiological evidence for the positive effects of fruit and vegetable consumption in the Hiroshima and Nagasaki atomic bomb survivors are important in at least three respects. First, these results offer very important evidence for the protection afforded by fruits and vegetables against radiation-induced cancer. Second, these results lend additional credence to previous epidemiological reports of the general efficacy of fruits and vegetables as anticarcinogenic agents. Third, the positive radioprotective effects of fruits and
vegetables in the atomic bomb emergency situation would be expected to also apply for the lesser radiation doses and dose rates of non-emergency situations, i.e., the norm.

The anticarcinogenic substances contained in, and the anticarcinogenic mechanisms proposed for, fruits and vegetables have been reviewed here. The proposed anticarcinogenic mechanisms are important since they are also some of the same mechanisms that have been proposed for preventing, inhibiting, and controlling radiation-induced cancer. In addition, reasons have been advanced to explain the observed superiority of the multiple (albeit most likely weak) anticarcinogenic compounds found in fruits and vegetables compared with synthesized and concentrated individual dietary supplements. These multiple weak anticarcinogenic agents would be expected to act synergistically in combination and in concert and with concomitant minimum toxicity. Maximal protective benefit would therefore be expected to be obtained from a wide variety of fruits and vegetables.

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