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Nutrition and Cancer

ISSN: 0163-5581 (Print) 1532-7914 (Online) Journal homepage: http://www.tandfonline.com/loi/hnuc20

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To cite this article: T. Colin Campbell (2017): Nutrition and Cancer: An Historical Perspective—The Past, Present, and Future of Nutrition and Cancer. Part 2. Misunderstanding and Ignoring Nutrition, Nutrition and Cancer, DOI: 10.1080/01635581.2017.1339094

To link to this article: http://dx.doi.org/10.1080/01635581.2017.1339094

Published online: 25 Jul 2017.

NUTRITION AND CANCER
https://doi.org/10.1080/01635581.2017.1339094

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Nutrition and Cancer: An Historical Perspective—The Past, Present, and Future of Nutrition and Cancer. Part 2. Misunderstanding and Ignoring Nutrition

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ABSTRACT

The role that nutrition plays in cancer development and treatment has received considerable attention in recent decades, but it still engenders considerable controversy. Within the cancer research and especially the clinical community, for example, nutritional factors are considered to play, at best, a secondary role. The role of nutrition in cancer development was noted by authorities as far back as the early 1800s, generally under the theory that cancer is "constitutional" in its origin, implying a complex, multifactorial, multistage etiology. Opponents of this idea insisted, rather vigorously, that cancer is a local unifactorial disease, best treated through surgery, with little attention paid to the etiology and possible prevention of cancer. This "local" theory, developed during the late 1700s and early 1800s, gradually included, in the late 1800s and early 1900s, chemotherapy and radiotherapy as treatment modalities, which now remain, along with surgery, as the basis of present-day cancer treatment. This highly reductionist paradigm left in its wake unfortunate consequences for the present day, which is the subject of this perspective.

ARTICLE HISTORY
Received 20 March 2017
Accepted 6 April 2017

A previous paper explored the pre-1940 history of the science of nutrition and cancer for insight into the origin of this hypothesized association, especially its more contentious aspects (1). The 1940 date represents the earliest research evidence cited in a 1982 landmark report on diet, nutrition, and cancer by the US National Academy of Sciences (NAS) (2). This report is considered "landmark" because it was the first major, institutional, science-based report on this topic. Moreover, it resulted in considerable media attention and subsequently encouraged the development of important policy positions, programs, and newly sponsored research funding at NIH. However, this report also left the false impression that this topic was relatively new as discussed in Part 1 of this Perspective. Although the message of the NAS report was welcome information for many, it also generated intense criticism from others, especially from corporate interests whose products were being questioned for their health value (3). Part 1 of this perspective (1) noted that a connection of food and nutrition with cancer was suggested as early as the mid-1800s. Although notable authorities proposed that nutrition could be a significant cause of cancer, their proposals were vigorously and oftentimes passionately resisted or denied, posing the question, therefore, why this suggestion was not taken more seriously. A major reason stemmed from the hypothesis that cancer was considered a "local disease," initiated by specific causes and treated by specific treatments, such as surgical removal. Nutrition, however, was deemed too complex and unfocused, unless one was to believe in the cancer-modifying effects of specific dietary agents, such as vitamins [Hypotheses on single nutrients effects, for example, β-carotene, have little scientific support (4–6)]. An alternative hypothesis suggested that cancer resulted from the complex interplay between internal and environmental cancer-causing factors, with nutrients being a key environmental factor. But the hypothesis concerning a more comprehensive view of cancer causation and prevention and treatment (7) eventually was discarded—whether purposefully, or not—during the 1800s in favor of the more limited, treatment-centered local theory of disease.

This local theory of disease not only survived but also is deeply embedded in the cancer research community of today. Four major professional societies and institutions in the UK and the USA were founded during the early twentieth century mostly by prominent and influential personalities, many of who were surgeons, thus endowing these societies with programs and practices favoring the local theory hypothesis. Ironically, the founder of the American Cancer Society in 1913, nonsurgeon Frederick Hoffmann, was a staunch advocate for the study of

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nutrition in cancer causation but shortly after the organization's founding, interest in the role of nutrition in cancer dissipated (1).

Here we ask what has been the ramifications of this emphasis on the local theory of disease, which can generally be described as reductionism. I shall start with the 13-member committee report of the NAS (4), which suggested two main goals, based on published evidence from about 1940 to 1980: 1) reduce dietary fat to 30% of total diet calories and 2) consume more vegetables, fruits, and grains (as whole foods, not as nutrient supplements contained therein). The supporting literature for these recommendations included a vast array of epidemiological, experimental animal, and cell culture studies, and the interpretation of this evidence was conservative, being very similar, for example, to recommendations for the prevention of heart disease only 5 yr before (8). Interpretation of this evidence relied, in part, on the nutrient composition of the recommended foods, but the committee did not advocate the consumption of these nutrients in isolation, as in supplements.

From the historical context of the 1800s, recommending increased consumption of plant-based foods, which we now know involves the metabolic interplay of a large number of nutrient components, favored the multifactorial theory of disease. Similarly, the NAS committee's stance against recommending single-nutrient supplements reflected a point of view that no single nutrient could be expected to induce or prevent the conversion of a normal cell to a neoplastic one. I suggest that this tension between the heretofore discarded constitutional theory of disease and the well-entrenched local disease theory of modern times had been resurrected, exposing a fundamental philosophical schism in biomedicine that has long polarized opinions of researchers and others. For some people, it is a polarization that might be described as a struggle between science and antiscience, precision and vagueness, rational logic and irrationality, science and superstition, or certainty and uncertainty. I prefer to call these polarized local versus constitutional views, respectively, as reductionism versus wholism, or the parts versus the whole. Of course, it is improper to fixate on one view or the other because both are essential and complimentary parts of research investigation and problem-solving. They simply represent two perspectives. But if one view dominates while minimizing or ignoring the other, unnecessary and pointless conflict will arise.

Interestingly, two periods of relatively recent nutrition research history have especially relied on reductionist theory. From about 1915 to 1940, several vitamins were discovered as being important in preventing "nutritional deficiency" diseases. Later from about 1985 to 2005, a great number of clinical trials have been conducted on hypotheses that vitamin supplements prevent chronic degenerative diseases, like cancer. These trials have shown little or no evidence that supplements of specific vitamins are able to prevent cancer in human studies despite the fact that they appear to do so in some cell culture and animal experiments. Infrequently, some human trials have shown that vitamin supplements may actually increase cancer incidence.

I suggest that a serious price has been paid during the past century, in lives lost and dollars spent, for relying on various forms of reductionist research in nutrition. Regarding the price paid, I also refer to the diversion of attention away from more productive hypotheses. Here, in no particular order, are several examples that diverted attention away from what nutrition could and should have been.

For more than a half-century, there has been widespread acceptance of the idea that the association of diet with human cancer is largely attributable to the consumption of foods containing chemical carcinogens, mostly meaning those chemicals shown to cause cancer-initiating mutations. This belief mostly arose from observations that (a) chimney soot associated with testicular cancer of young chimney sweep boys (9) and that (b) coal tar dyes, as would be present in chimney soot and applied to the skin of experimental rabbits caused skin cancer (10).

In the US, a 1958 food additives amendment of the US Food, Drug, and Cosmetic Act, known as the Delaney Clause, stipulated that chemicals capable of causing cancer should not be permitted in food. This initial legislation was unusually demanding and narrowly focused, thus ultimately leading to its being seriously questioned (11). Nonetheless, the sentiment that chemical carcinogens are a major cause of human cancer, which is a local theory derivative, has lived on until the present day, whether these chemicals are in food or in occupational and general settings.

The Delaney Clause prompted the need for an experimental animal bioassay program to identify chemicals having this property (12). Indeed, legislation mandated a program to determine and assess chemicals with the potential to cause human cancer (12). Since those earlier days, several government agencies and laboratories have participated in this effort to identify chemical carcinogens, including the FDA, EPA, OSHA, and the Consumer Product Safety Commission (13). The lead organization, however, is the National Toxicology Program (NTP) of the Public Health Service which summarized the evidence in occasional reports on chemical carcinogens. Chemicals are classified into those that are "known to be human carcinogens" and those that are

"reasonably anticipated to be human carcinogens." (12) At the international level, the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) has been conducting since 1971 a relatively sophisticated program of carcinogen evaluation as part of their Monograph Program, gathering information from a variety of sources (11,12).

These research and policy communities acknowledge that conducting experimental research on putative carcinogens and assessing their risk to humans is not a very quantitative science because their activities are affected by a variety of experimental, lifestyle, and environmental factors (13,14). In spite of this precaution, however, media reports and public perceptions of the hazards posed by these carcinogens tend to be more certain—a carcinogen either is or is not capable of causing cancer. This perception has led to unfortunate but a widespread belief that the association of food with cancer is primarily due to the presence of chemical carcinogens in the food we eat.

I have seriously questioned this belief system since 1980 (15), both because of the unacceptable uncertainty of quantitatively estimating carcinogenic risk and, more importantly, because it excluded consideration of nutritional factors that were likely to be more important than chemical carcinogens. I therefore suggested a far less costly and more effective screening program for minimizing and regulating exposure to consumption of chemicals that had the potential to cause cancer (16). That was 35 yr ago and, since then, my concerns have only deepened because nothing much has changed.

The evidence for a clear causal relationship of specific chemical carcinogens with human cancer is very limited (17), possibly including scrotal cancer and polycyclic aromatic hydrocarbons (18), liver angiosarcoma and vinyl chloride monomer, and bladder cancer and benzidine (19,20). During those earlier years, I was invited to give seminar presentations to all three agencies then responsible for this program (Research Triangle Park NC and Jefferson City AR in the USand the IARC in Lyon, France). I did not hear substantive criticisms, except for the comment that this program and its justification were too embedded within the public politic and mindset to be seriously modified.

Regarding chemical carcinogens identified by the rodent bioassay system, there is an embarrassing lack of supporting human epidemiological evidence, especially when compared with the overwhelming evidence on associations of several nutrients (as in food) with various cancers. For example, numerous epidemiological associations of dietary fat with breast and colon cancers have been reported (21–24) and the effect size is very large, although for many of these observational studies that compare countries, this effect is more likely attributable to the consumption of animal protein and nutrients that covary with the consumption of animal-based foods (25).

Aside from this lack of epidemiological evidence, there also is a similar message from laboratory animal research that compares the relative activities of nutrients and carcinogens. The most thoroughly investigated model is that which compares the effect of dietary protein, at modest levels of intake, with the carcinogenicity of aflatoxin (hepatocellular carcinoma), the most potent of all chemical carcinogens (26,27). Carcinogens that initiate cancer—almost all those studied in the bioassay program—require enzymatic activation, usually by the nutrition-modified (28) mixed function oxidase (MFO) enzyme, mostly located in the liver. In this model, aflatoxin is administered at a dose to maximize tumor formation, whereas the level of dietary protein (casein) is provided within a modest and relevant range, 20% of total diet calories versus 5% of diet calories.

Increased dietary protein enhanced tumor development at each mechanistic stage of cancer formation that was tested. Elevated dietary protein increases(a) MFO enzyme activity by three- to fourfold (29–34); (b) MFO-catalyzed activation of aflatoxin (29) to covalently bind to DNA (35) to cause mutations (36,37); (c) the number and/or size of microscopic clusters (foci) of preneoplastic cells in a dose-dependent manner, although this range of dietary protein begins at about 10% of diet calories that exceeds the recommended allowance (38,39) and ultimately; (d) mature tumors that cause premature death (40–42). The protein effect size is substantial at each of these disease mechanism stages, appearing within 8 days but even as early as 24 h after administration (43).

In the laboratory animal (rat) model, the nutritional (protein) effect remarkably and completely controlled the ability of this very powerful chemical carcinogen to produce tumors, both within the various stages of early neoplasia (reviewed above) and among 2-yr lifetime studies (40–42). This observation became even more impressive when the protein-induced increase in tumor development was reversed when the dietary protein was decreased (41,44,45).

The fact that subsequent tumor growth (preneoplastic and neoplastic) could be reversed by nutritional means does not mean reversal of the initiating mutation but reversal that involves subsequent nonmutational mechanisms (the tumor promotion phase). The strength of the protein effect on tumor development is fully consistent with the original observation (46) that led to this series of studies. The results of the 2-yr lifetime study (40,42) were so convincing that it could be said that it was an all-or-nothing response. All animals on the 20% protein diet were dead by 2 yr, with advanced tumor

development. All animals on the 5% protein diet, exposed to the same high dose of carcinogen as animals on the 20% protein diet, were alive and unusually thrifty and energetic.

Still further support for this nutrient–carcinogen comparison was provided by the most comprehensive survey ever conducted on the causes of primary liver cancer (PLC) in humans in rural China (47). This study was unusually comprehensive and expansive for detecting risk factors for PLC mortality. It included a 600-fold range of aflatoxin exposure, a 39-fold range of PLC mortality, and a 28-fold range of hepatitis B virus surface antigen (HBsAg+). PLC mortality was not associated with aflatoxin exposure ($r = -0.17$), but was associated with HBsAg+ prevalence ($P < 0.001$) and plasma cholesterol ($P < 0.01$), which was associated with higher consumption of animal-protein-based foods. This combination of findings from laboratory animal and human studies strongly support the hypothesis that nutrition is far more relevant for human cancer than a powerful initiating, mutagenic carcinogen.

It might be argued that these results do not apply to other carcinogens and/or other nutritional experiences, but this seems highly unlikely. First, epidemiological associations of nutritional experience with cancer are far more convincing than associations of carcinogen exposure with cancer (17) and, second, all initiating carcinogens are dependent on activation by the cytochrome p450 system which itself is profoundly influenced by nutrition (15), especially by dietary-animal-based protein (29–34). These findings have broad implications and seriously question the utility of the chemical carcinogen animal bioassay program. Identifying noxious environmental and workplace chemicals, especially those that are mutagenic, is a reasonable goal, but this can be done much more quickly and easily, perhaps using a more modern version of a short-term bioassay that was earlier suggested (16).

Much of the earlier history of the carcinogen testing program was focused on initiating mutagenic chemicals but with the passing of time, nonmutagenic chemicals that promote cancer were gradually included. But this development still failed to acknowledge the most relevant of all cancer promoters, the nutrients, either affected by their excess or by their absence. A case can be made that, using the rationale for the animal bioassay program, the evidence on tumor promotion by casein, for example, makes this substance the most relevant of all chemical carcinogens ever identified.

It is important to note, however, that the WHO (World Health Organization) agency (IARC) has moved beyond their focus on isolated chemical carcinogens as important causes of human cancer. For more than two decades, the IARC monograph program now assesses, if supporting data are available, "complex mixtures [of chemicals], occupational exposures, physical agents, biological agents, and lifestyle factors" (48). However, this broader scope is still puzzling and quite confusing in its intent. Although this change acknowledges the long-accepted multifactorial etiology of human cancer, it still clings to its original focus on a carcinogen-centered etiology by stating that "national health agencies can use this information as scientific support for their actions to prevent exposure to potential carcinogens" (48). By continuing to defend this program as a search for "carcinogens" means that when these carcinogens are identified, their removal is a primary goal of cancer prevention.

The belief that most human cancer results from exposure to, or consumption of, identifiable chemical carcinogens is extremely misleading. The recent IARC report that processed meats are carcinogenic (49) and other meats (for colorectal cancer) are only "probably carcinogenic," based on a small unimpressive difference (i.e., 12/18 processed meat reports were positive, while 7/14 red meat reports were positive), is an unconvincing distinction, especially when the nutritional contribution to disease is completely ignored. Then, adding even more uncertainty is the speculation that the carcinogenic activity of meat may be due to exogenous mutagens (carcinogens?) like the heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) that are produced in very small amounts in highly heated meat products. There are no human studies that demonstrate these hypothesized cause–effect associations. The highly publicized IARC recommendation on reducing consumption of processed meats was based on a questionable distinction between processed and red meats, and then buttressed with a highly speculative participation of chemical carcinogens for which no supporting human data are available.

Despite 5–6 decades of research, evaluation, policy wrangling, and a crescendo of public comment, only the tiniest of convincing evidence—human and animal—has been produced to show that chemical carcinogens, are significant causes of human cancer. It would appear that our tenacity to hold on to this unsupported hypothesis is testimony to a well-entrenched belief with deep historical roots. A second example of reductionist interpretation gone awry is the intense interest in the hypothesis that micronutrient supplements will prevent, perhaps even reverse cancer, as introduced earlier. This viewpoint became popularized when a relatively small industry became energized in response to the 1982 NAS report on diet, nutrition, and cancer cited at the beginning of this paper (2). That report set goals to consume more vegetables, whole grains, and fruits based, in part, on nutrients

contained therein. Vitamin A (mostly as its precursor, β-carotene), and vitamins C and E were identified as having antioxidant properties that might prevent cancer. No conclusive evidence on cancer-modifying effects of other vitamins or minerals was found by that report, although a few nonnutrient chemicals in plants were identified that might have anticancer properties.

The report explicitly cautioned, however, in its executive summary that its recommendations "apply only to foods as sources of nutrients—not to dietary supplements of individual nutrients." But in spite of this warning, the industry pursued their interest to sell nutrient supplements that has now grown, according to the latest figures, to $27.6 billion annual sales in the USA in 2015, and a projected $31.7 billion for 2021 (50). Current vitamin supplement use in the USA is about 50% for regular users and as high as 69% when counting irregular users (51). During the past 2–3 decades, a very large number of clinical trials have tested for the ability of vitamin supplements to moderate various disease outcomes, including cancer. According to the most recent compilation of the results of several large studies (52), the best that can be said is that there is some evidence that daily use of low-dose multivitamin supplementation (near the RDAs) may decrease cancer incidence. But, it appears that this effect, if validated, depends on the nutritional sufficiency or deficiency of the surveyed individuals, perhaps also on undiagnosed, incipient disease among some users. For healthy, nutritionally sufficient individuals, there is no evidence of benefit and, in some cases, increased disease risk has been observed. Widespread use of these products demonstrates the eternal hope of many people for simple, specific solutions to their health issues, a testament to the survival of the local theory of disease concept begun in the 1800s.

A third reductionist point of view, whose cost is exceptionally far reaching, is the long-held assumption that dietary cholesterol and saturated fat may be the major reasons why high-fat diets associate not only with cardiovascular diseases but also with breast, colon, and other cancers. This story about fat primarily began and has been sustained with regard to heart disease. But from a dietary and nutritional perspective, the story for cancer is approximately the same, as reported in an earlier paper in this journal (27). When these lipids are considered as major cancer causes, a practical solution appears. That is, remove them from offending foods, as has been done in the production of low-fat and skim milk, lean cuts of meat and other manufactured products advertised for their low fat or low cholesterol contents. Both these substances refer to animal-based foods because cholesterol is exclusively found in animal-based foods, while saturated fat, except for a couple plant products, is preponderantly found in animal-based foods. Thus, the removal of these lipids from these foods still leaves animal-based foods rich in protein (27) and devoid of cancer-protective substances. Public discussion of the health value of low-cholesterol and low-saturated fat foods when compared with their normal counterparts has been unusually pervasive and prominent throughout the food industry and the public at large, for many decades. Unfortunately, it is seriously misleading, even though almost everyone considers it well-established, reliable information. Over a century ago, on the basis of the experimental animal findings of several research studies, it was concluded that the most prominent cause of increasing blood cholesterol and its sequel, atherosclerotic pathogenesis, was not dietary cholesterol but excessive consumption of animal-based protein (53,54). Subsequent human studies supported this same conclusion (55,56).

In summary, there are three examples (chemical carcinogens, vitamin supplementation, and dietary cholesterol and saturated fat) of very popular food and health beliefs that became prominent during the twentieth century that stems from the local theory of disease of the nineteenth century. Sadly, these examples focus on the addition or subtraction of parts of whole foods rather than on the benefits of the whole foods, which align with the constitutional theory of disease debated during the nineteenth century. These examples also divert attention away from a more comprehensive nutritional view of health. The cost of this misadventure is incalculable, but it is relatively easy to imagine that it has very likely resulted in too many lives lost and dollars wasted.

Declaration of Interest

The author has no conflicts of interests.

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