ADVANCES IN CANCER RESEARCH

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ADVANCES IN CANCER RESEARCH

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THE EPIDEMIOLOGY OF DIET AND CANCER

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I. Introduction

There is growing interest, both within the scientific community and the general public, in the relationship between diet and cancer etiology. Attesting to this interest is a rapidly expanding scientific literature as well as many articles in commonly read lay periodicals and newspapers. This literature, considered in sum, is complex and frequently contradictory and is thus confusing for the critical reader.

Much of the complexity in nutrition–cancer literature results from the multidisciplinary nature of the field. Nutritionists, clinical physicians, epidemiologists, biochemists, pathophysiologists, and a variety of other professionals, each sharing a common conviction that nutritional factors are of some consequence in cancer risk, must glean from the language and logic of each other's discipline those findings which integrate with their own. The complexity of the literature, however, is also reflective of the underlying

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complexity and uncertainty of the nutrition–cancer connection itself. At the present stage of incomplete understanding, we often must take large inferential leaps as we travel the road from incomplete biological understanding to personal dietary choices to public dietary policy.

Awareness of the possible relationship between diet and health is not new. Over 400 years before the birth of Christ, Hippocrates wrote (Adams, ed., 1939):

> this I know, moreover, that to the human body it makes a great difference whether the bread be fine or coarse; with or without the hull, whether mixed with much or little water, strongly wrought or scarcely at all, baked or raw. . . Whoever pays no attention to these things, or, paying attention, does not comprehend them, how can he understand the diseases which befall man? For, by everyone of these things, man is affected and changed this way or that, and the whole of his life is subjected to them, whether in health, convalescence, or disease. Nothing else, then, can be more important or more necessary to know than these things.

Despite Hippocrates' early interest in diet and health, research in the area of the nutritional factors in cancer etiology is still in its early stages of development, particularly investigations involving humans. Because of the advantages of experimental study designs, we know much more about the nutritional requirements and the implications of nutritional excesses and deficiencies in most experimental animals than we do about the human species. Understanding the relationship between nutritional factors and cancer risk in humans has been impeded until recently by the necessity to restrict research to observational rather than experimental studies. Within the framework of observational studies, there are many uncertainties, the most important of which in diet and cancer research is the valid measurement of diet.

In recent years there have been several assessments of the literature of nutritional factors and cancer etiology. These essays have varied in scope, detail, and emphasis. Table I lists a selected sampling of the more recent reviews on nutrition and cancer etiology, but it is by no means a complete listing. The purpose of this article is to review critically and in more detail than previously the various observational studies of diet and cancer etiology in humans. Because of this emphasis, we will mention only briefly the pertinent experimental research which generates or tests hypotheses for human epidemiologic research. The reader who wishes more detailed information regarding experimental or metabolic studies is referred to the appropriate references in Table I. Only nutritional factors which occur prior to the onset of cancer will be discussed. The many nutritional consequences of cancer, which are extremely important in the clinical management of the cancer patient, have been addressed by other authors (Van Eys, 1979) and will not be included in this review.

TABLE I
SELECTED ESSAYS ON THE RELATIONSHIP BETWEEN DIETARY FACTORS AND CANCER

Date	Principal author	Reference
	General	
1976	Alcantra	2
1976	Wynder	266
1977	Lowenfels	158
1977	Gori	70
1977	Wynder	267
1977	Modan	187
1978	Gori	71
1979	Wynder	268
1979	Doll	48
1979	Gori	72
1979	Shils	231
1979	Wells	261
1980	Alderson	3
1980	Werther	262
1980	Masek	174
1980	McMichael	176
1980	Reddy	221
1980	Graham	75
1980	Shils	232
1980	Miller	184
1981	Doll	49
1981	Correa	35
1981	Wynder	280
1981	Kritchevsky	152
1981	Graham	82
1981	Ellison	54
1981	Silverman	234
1982	McBean	175
1982	Newell	202
1982	Enstrom	59
	Focus on gastrointestinal cancer only	
1975	Wynder	265
1975	Graham	74
1976	Walker	252
1977	Reddy	219
1977	Kritchevsky	151
1978	Cummings	38
1979	Reddy	216
1979	Graham	81
1980	Zaridze	283

(continued)

TABLE I (*Continued*)

Date	Principal author	Reference
1980	Joossens	137
1980	Hill	106
1980	Cummings	39
1981	Joossens	138
1981	Reddy	217
1982	Burkett	22
1982	Weisburger	260
	Focus on breast cancer only	
1978	Hankin	97
1979	Dickerson	47
1980	Carroll	27
1982	de Waard	46
	Focus on experimental or metabolic studies only	
1975	Carroll	26
1975	Clayson	29
1979	Roe	223
1979	Weisburger	256
1979	Wattenberg	254
1980	Weisburger	259
1981	Stout	245
1981	Vitale	250
1981	Newberne	200
1982	Weisburger	260

We will first discuss the general methods of epidemiologic inquiry, focusing on considerations of study design which are specific to the study of nutrition and cancer and on problems of the measurement of diet. We will then review the evolution of observational studies of diet and cancer over the last 50 years and will integrate, site by site, the various human observational studies with pertinent findings from experimental studies, both in human and nonhuman systems. Finally, we will provide an overall assessment of the current "state-of-the-art" of epidemiologic inquiry in nutrition and cancer, and we will outline some strategies for the future.

There are a variety of means by which dietary factors might be related to cancer risk. Specific agents contained within foods, either naturally occurring (Hilker, 1980) such as mycotoxins, added during processing such as preservatives or colorants (Fairweather, 1980; Slaga, 1981), or unintentional contaminants such as pesticides may be either carcinogenic or anticar-

cinogenic (Conney, 1982). In these cases, food acts only as a vehicle by which agents affecting risk can be delivered to the individual. Cancer causation in these ways is a conceptually simple process and one which should be empirically testable given means of measurement of carcinogens in foods. It is quite clear that there are many hundreds of mutagens in foods commonly eaten by all of us with the potential of causing DNA structural changes which could result in tumor initiation (Sugimura, *et al.*, 1981). It is extremely important that we identify these potential carcinogens and limit their quantities in the foods that we eat, but specific carcinogenic contaminants of foods may not explain much of the overall variance in cancer incidence.

More important than simple foodborne contaminants may be nutritional factors themselves. Specific nutritional deficiencies and/or excesses may lead to somatic changes in body structure or function which increase the susceptibility to cancer development, either alone or in combination with other factors. It is clear from many experimental studies that dietary deficiencies of such nutrients as vitamins or inorganic ions, as well as dietary excesses of fats or total calories, may create a variety of somatic changes which can impair proper function. The immune system is a very important bodily function not only in combating infectious disease but also perhaps in preventing cancer. There have been several reviews of the experimental evidence that a variety of alterations in immune function occur with dietary excesses and deficiencies (Axelrod, 1980; Good, 1981; Gross and Newberne, 1980; Hoffman-Goetz and Blackburn, 1981). The concept of cancer causation by dietary factors is consistent with the clinical observation that nutritional deficiencies and excesses can lead to many clinically apparent somatic changes. It is also consistent with the commonly held notion that "we are what we eat."

Either additives to foods or nutrients themselves could theoretically act to increase or decrease risk either at the initiation or the promotion stages of carcinogenesis. In animal and *in vitro* carcinogenesis literature much attention is focused on the activity of carcinogens according to the stage of their action (Farber, 1982). In the epidemiologic literature, on the other hand, we have not yet developed enough precision in our methods to be able to define the time during which dietary factors may be acting. Although our inference from animal experimental studies is that dietary factors often seem to be more active in the promotional stages of cancer development, there are many reasons to believe that they may also be important in initiation as well.

As both scientists and citizens, those of us interested in nutrition and cancer find ourselves in a difficult position. Despite considerable progress in our understanding of the possible relationship between nutrients and cancer etiology and several exciting leads for future research, we find ourselves still in the early stages of research in this field. Many hypotheses and, in particu-

lar, investigative methodologies are still in the developmental stage. Drawing firm inferences from existing data is therefore very difficult. Nonetheless, chronic degenerative diseases including cancer continue to take their toll. In most of the Western world, cancer ranks as the second leading cause of death. Thus there is understandably a large public demand for dietary "prescriptions" for cancer prevention. Some have searched for the "optimal diet" (Hegsted, 1979), while others have attempted to define a "prudent diet" (Wynder, 1976). In the absence of definitive scientific evidence, however, public demand often results in both superstitious behavior by the public (Darby, 1979; Young and Newberne, 1981) and the overinterpretation of inconclusive studies by the scientific community.

In epidemiologic inquiry, there are a number of pitfalls which make causal inference difficult to draw. Associations observed in epidemiologic studies may be a result of a number of factors, including measurement bias, sampling bias, confounding, and chance alone, particularly when multiple factors are investigated simultaneously. Causal inferences can be made only after integrating epidemiologic information with existing knowledge from other scientific disciplines, which is a very difficult process. The judgment as to whether to take or, more importantly, to recommend preventive action on the basis of inconclusive data is a very difficult and complex one. The Committee on Diet, Nutrition, and Cancer of the Assembly of Life Sciences of the National Research Council has been charged with the task of reviewing all scientific evidence, both epidemiologic and otherwise, related to nutrition and cancer risk. Based on this comprehensive review (1982), it was their judgment that there now exists sufficient evidence of a causal relationship between certain dietary factors and cancer risk to make some specific recommendations on diet alterations for the American public. Their recommendations, presented as "interim dietary guidelines" are as follows: (1) decrease fat intake to 30% of total calories, (2) include fruits, vegetables, and whole-grain cereals in the diet, (3) minimize consumption of foods preserved by salt curing or smoking, (4) attempt to minimize possibly carcinogenic nonnutritive additives to foods, (5) increase testing of foods for mutagenicity, and (6) minimize the consumption of alcohol.

These recommendations seem rational and modest enough and, fortunately, are consistent with coronary heart disease prevention and sound nutritional practices in general. Nevertheless, future research may suggest important exceptions even to these modest recommendations. Other more radical recommendations for dietary changes and nutrient supplementation which appear in the lay literature are more difficult to evaluate with regard to their risk/benefit ratio. What is becoming clear from animal experimental work is that the relationship between cancer risk and many nutrients is not a simple one. For example, some vitamins may inhibit cancers in conjunction

with some carcinogens yet promote them with others, or they may inhibit cancer in one organ and promote it in another. We need to conduct a great deal more research *in vitro*, *in vivo*, and in human population settings to shed light on such conflicting findings and to arrive at more definitive grounds for prescribing diets which can enhance the public health.

II. Methods of Inquiry

Nutritional factors in cancer etiology can be studied by epidemiologic methods, which are largely observational, or by experimental methods in the laboratory. Laboratory methodology involving animals and *in vitro* methods in nutrition and cancer research have both distinct advantages and disadvantages as compared to human observational research. In animal systems and *in vitro*, exposure to nutrients can be carefully controlled and the outcome can be precisely measured while the risk of cancer can be experimentally manipulated with known carcinogens. Many animal models have demonstrated strong relationships between nutrient intake and cancer risk. Likewise, *in vitro* systems, which more recently have included human cell culture studies, have more precisely defined the relationships between micronutrients and the morphology and function of the cell and many subcellular components. Particularly exciting and relevant to nutrition and cancer work is the growing capability of researchers to study nutrient effects on DNA and its associated proteins.

However, extrapolation from effects measured on cells grown in culture to the *in vivo* situation or from an animal model to man, or even from one species of rat to another, is often very difficult. Despite the many similarities in the various systems, it appears that the relationship between nutrients and cancer risk may be highly dependent on the specific metabolic milieu examined. Marked differences in the apparent effect of nutrient deficiencies or excesses from species to species, from organ system to organ system, and from situation to situation have been observed. Despite differences, however, there are similarities in results among animal and *in vitro* models and the human system, such that laboratory experiments are an essential component of the entire research effort in human carcinogenesis. Experimental research complements human observational research, both by uncovering new leads of inquiry and by confirming the biological importance of observed associations. Integrating findings in animal and *in vitro* experiments with human observations is an important step in the complex process of drawing valid inferences from the general body of knowledge of carcinogenesis.

Human epidemiologic studies of diet as a causal factor in cancer have been generally of four types: ecological studies, case–control studies, prospective studies, and intervention studies. In the sections which follow, we will

discuss the methodologic considerations of each type of study as it relates to diet and cancer research, and we will review selected previous studies as examples of the ways in which the study designs have been employed.

A. Ecological Studies

Ecological studies are inquiries in which cancer rates for defined populations are correlated with rates of suspected risk factors as measured in these same populations. Thus these studies are based on populations as the units of analysis. Ecological studies have been useful in generating hypotheses regarding possible human dietary factors in cancer etiology. Stavraky (1976) presented a review and critique of the role of ecological studies of disease. Although this discussion focuses specifically on colon cancer, the concepts can be generalized to most ecological studies of human cancer and diet. More recently, Morgenstern (1982) has reviewed the methodological and statistical problems encountered in ecological analysis.

Associations between cancer risk and dietary factors observed in such studies are very difficult to infer as being causal, both because of the heterogeneity of diets within any defined population and because of the problem of many potential confounding variables. As we correlate cancer rates and dietary factors for defined groups of individuals, we cannot account for what is often rather marked individual variation of diet within each group and must, by design, make the implicit assumption that everyone within each group eats the same diet in order to draw inferences about cancer causation for individuals. This may be, of course, an untenable assumption. The Health and Nutrition Examination Survey (HANES) (Department of Health, Education and Welfare, 1979) in the United States, for example, showed that there is considerable variation in the diet of Americans, as shown in Table II. Ecological studies may only by chance describe the specific diet of cancer patients.

In addition to the problem of heterogeneity of diet within a population, ecological studies also are often not able to account for important confounding variables. Because diets of countries often correlate very strongly with many other factors which may be directly or indirectly related to cancer risk, there is an immense problem of potential confounding variables in such studies. Any factor associated with the population which experiences high cancer rates might, in an ecological study design, be implicated as potentially causal. In breast cancer, for instance, where the rates are highest in developed, Western nations, ecological studies based on international statistics would likely find strong associations with factors such as the per capita use of hair dryers and aluminum foil, though there are no compelling reasons to presume that these factors are causal. In addition, there are also strong

TABLE II
NUTRIENT INTAKE BY PERCENTILES OF THE POPULATION AS MEASURED IN THE HANES SURVEY[a]

	Percentile of Population								
	5th	10th	20th	50th	75th	90th	95th	$\bar{X}$	SD
Daily protein (g)									
8813 males	36	46	62	84	114	153	179	93	45
11930 females	25	31	43	59	79	102	119	64	31
Daily vitamin A (IU)									
8813 males	801	1184	2057	3503	5951	9796	13770	5138	7245
11930 females	575	872	1548	2714	4781	8581	12625	4431	8016

[a] Ref. No. 45.

associations between various elements of diet. Cereal consumption tends to be negatively associated with meat consumption so that international correlational studies find positive correlations with cereal (Hakama and Saxen, 1967) and negative associations with meat (Gregor *et al.*, 1969). It is often difficult to be sure, on the basis of ecological studies alone, which dietary factor, if any, is the causally important one.

There is striking variability from country to country in the international mortality and incidence rates for cancers of the various sites (Doll and Waterhouse, 1970; Segi and Kurihara, 1972). This striking variation, in conjunction with the observation that migrants tend to adopt cancer risks of the area to which they moved (within one or two generations) and leave behind the cancer risks from their native land, has led to the general belief that most human cancers seem to be environmentally caused. The use of the word "environment" in this context simply means "nongenetic," rather than implying causation necessarily by factors commonly held to be environmental, such as air and water pollutants (Higginson, 1979; Higginson and Muir, 1979). Adverse health behavior such as cigarette smoking and unhealthy diets, as well as the complexities of the entire social–psychological fabric, would be considered environmental causes in this context.

Ecological studies have been conducted using countries as the units of analysis, regions within countries, or special populations such as migrant or ethnic groups. Table III summarizes selected previous studies of human cancer which have been based on an ecological design. This table is not an exhaustive enumeration of all such studies but represents the major studies which are most frequently cited, as well as studies which are representative of their type. Included in this category, for the purpose of this review, are

TABLE III

SELECTED EPIDEMIOLOGIC STUDIES OF DIETARY FACTORS AND CANCER BASED ON ECOLOGICAL DESIGNS

Date	Principal author	Cancer site(s) studied	Country	Reference number
		Studies based on international cancer and food statistics		
1967	Hakama	Stomach	Many	96
1969	Gregor	All GI	Many	86
1973	Drasar	Colon, breast	Many	52
1973	Shennan	Kidney	Many	230
1973	Irving	Colon	Many	129
1974	Howell	Many	Many	125
1975	Wogan	Liver	Many	264
1975	Armstrong	Many	Many	7
1977	Wynder	Many	Many	267
1978	Hems	Breast	Many	99
1979	Gray	Breast	Many	85
1979	Lui	Colon	Many	161
1981	van Rensburg	Esophagus	Many	249
		Studies based on cancer and food statistics for regions within a single country		
1971	Alpert	Liver	Uganda	4
1973	Peers	Liver	Kenya	208
1975	(Study group)	Esophagus	China	34
1975	Jansson	All GI	United States	133
1975	Armijo	Stomach	Chile	5
1975	Howell	Colon, rectum	United States	126
1975	Enstrom	Colon, rectum	United States	56
1976	Cuello	Stomach	Columbia	37
1976	Peers	Liver	Swaziland	209
1977	(Study group)	Esophagus	Iran	136
1977	Enstrom	Colon, rectum	United States	57
1978	Enig	Many	United States	55
1979	Hill	Colon	Hong Kong	109
1979	Gaskill	Breast	United States	68
1979	Bingham	Colon, rectum	Britain	11
1980	Pawlega	Breast	United States (Iowa)	206
1980	Rawson	Many	United States (Southwest)	215
1980	Yang	Esophagus	China	281
1980	Hems	Breast	Britain	100
1981	Armijo	Stomach	Chile	6
1981	Ziegler	Colon	United States	285
1982	Nagi	Stomach, esophagus	Japan	199