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Update on Dietary Fat and Cancer[1] (42421)

DAVID M. KLURFELD AND DAVID KRITCHEVSKY

The Wistar Institute, 36th Street at Spruce Street, Philadelphia, Pennsylvania 19104

The usual response of both researchers and the lay public to the association of dietary fat and cancer is that consumption of the macronutrient leads to increased risk of the disease. It is our position that the data, while suggestive of an association with certain tumors, are not overwhelmingly in favor of this hypothesis. This review will attempt to add our perspective on this issue and will cite recent developments in both basic and epidemiologic research that are significant in relating dietary fat with cancer.

The strongest evidence for a statistical association of fat consumption and cancer incidence is derived from international comparisons. These data are based on per capita nutrient *availability,* rather than actual consumption, and on cancer mortality data that are not necessarily accurate (especially in the less affluent countries that have lower reported rates of certain cancers) or age adjusted. In any scattergram of deaths from cancer of the breast or colon versus dietary fat there are points on the graph where one can find countries whose per capita fata availabilities are identical but whose cancer mortality varies several-fold (Fig. 1) (1). Likewise, if one compares countries with similar death rates from the putatively diet-related tumors one can find countries whose fat availability differs by several hundred percent. The search for reasons behind such discrepancies may be more revealing than ignoring such "outliers" from the regression equation. While there probably are real differences in specific cancer death rates between affluent and poor countries, it is equally important to consider the life expectancy in these countries as well. All the affluent countries with the high cancer rates also have the longest life expectancies (2). Likewise, the countries with the lower rates of cancer generally have significantly shorter life expectancies. One exception to this rule that is often cited by advocates of dietary change is Japan. This country has reliable cancer and dietary data and does have very low mortality from breast and colon cancers. However, the burden of stomach cancer in Japan is so high that mortality from this disease exceeds that of stomach, breast, and colon cancers in the United States (Table I) (3). In fact, there is a strong inverse correlation between mortality from breast or colon cancer and stomach or liver cancer. Therefore, the data supporting a role of dietary fat in the etiology of breast and colon cancer can be used with equal validity to suggest protection against stomach or liver cancer by consumption of high fat diets.

Age-adjusted cancer death rates compiled by the American Cancer Society (ACS) show a 29% increase over the past 30 years for males and an 8% drop for females (4). Real increases in mortality have occurred for cancers of the lung and pancreas, with lung cancer accounting for all of the increase in total mortality (Table II). It is informative to examine similar statistics compiled by the National Center for Health Statistics (NCHS) which show a death rate from malignant neoplasms one-third less during the same time period than that reported by the ACS. Also, the NCHS data show a very small increase in total cancer mortality that is more than accounted for by the increase in lung cancer deaths (Table III) (5).

A major work by Doll and Peto is often cited as evidence for the role in a significant proportion of cancers (6). Although this paper has been used by many authors to support the position that diet is related to a significant proportion of cancers, it contains the statements that "there is no evidence of any generalized increase [in deaths due to cancer] other than that due to tobacco" and "it must be emphasized that the figure chosen [of 35% of cancers related to diet] is highly speculative and chiefly refers to dietary factors which are not yet reliably identified" (6). Despite the softness of data relating diet with cancer, dietary guidelines have been published by a va-

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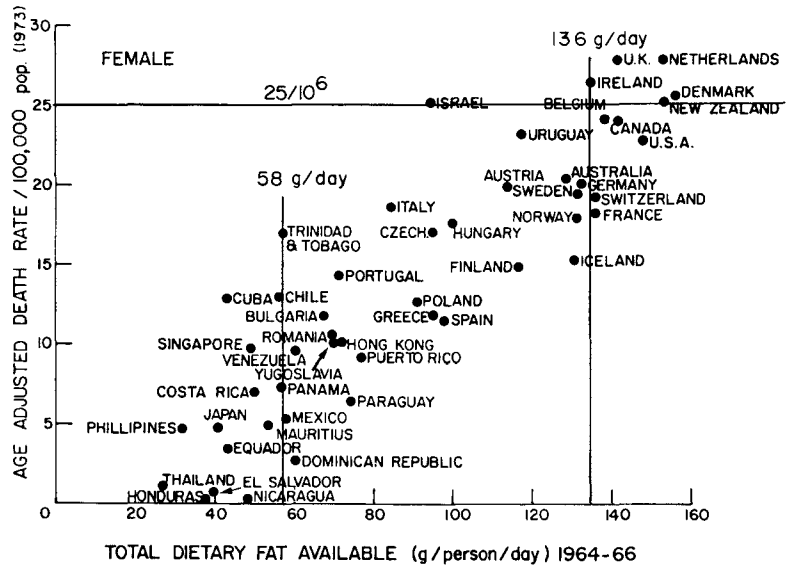

FIG. 1. Correlation between per capita fat availability and mortality from breast cancer. Note that at given fat availabilities there are marked differences in death rates in countries with either low or high fat available. The converse is true at a single death rate where fat availability varies greatly.

riety of organizations for prevention of cancer. As an example, the American Cancer Society recommends a reduction in total fat intake and points out that this is an effective way to reduce total calories. However, the same publication contains the sentence, "No concrete dietary advice can be given that will guarantee prevention of any specific human cancer" (7). Risk reduction must be differentiated from true prevention if claims for dietary modification are to have any meaure of credibility in the future. The Diet, Nutrition, and Cancer report of a National Academy of Sciences committee recommended a reduction of fat intake from 40 to 30% of calories while admitting that the scientific data do not provide a strong basis for establishing fat intake at 30% of calories (8).

Most people do not know what the fat content of their diet is or the quantitative contribution individual foods make to the various nutrient classes in their diets. Publication of the second National Health and Nutrition Examination Survey (NHANES II) data is a major step in defining more clearly the "typical American Diet." Table IV lists 12 food cate-

TABLE I. AGE-ADJUSTED CANCER DEATH RATES PER 100,000[a]

Country	Stomach	Colon and rectum	Breast	Total
USA	13	35	22	70
Netherlands	39	35	26	100
W. Germany	51	38	19	108
Chile	95	14	11	120
Japan	100	16	4	120

[a] 1968–1969, from (3).

TABLE II. 30-YEAR TRENDS IN AGE-ADJUSTED CANCER DEATH RATES PER 100,000[a]

Site	Sex	1949–1951	1979–1981	% Change
All sites	Male	168.0	217.0	+29
	Female	147.8	135.5	−8
Breast	Female	25.9	26.3	+2
Colorectal	Male	26.2	25.4	−3
	Female	25.3	18.5	−27
Lung	Male	22.0	71.2	+224
	Female	4.8	20.7	+331
Pancreas	Male	8.2	10.6	+29
	Female	5.5	7.0	+27
Stomach	Male	24.6	8.3	−66
	Female	13.5	3.9	−71
Uterus	Female	21.6	7.8	−64

[a] From (4).

TABLE III. AGE-ADJUSTED DEATH RATES FROM SELECTED CAUSES IN THE USA, 1950–1983[a]

Cause of death	1950	1960	1970	1980	1983
All causes	841.5	760.9	714.3	585.8	549.6
Diseases of heart	307.6	286.2	253.6	202.0	188.5
Cerebrovascular diseases	88.8	79.7	66.3	40.8	34.3
Malignant neoplasms	125.4	125.8	129.9	132.8	132.3
Digestive system	47.7	41.1	35.2	33.0	31.8
Breast (female only)	22.2	22.3	23.1	22.7	22.8
Respiratory system	12.8	19.8	28.4	36.4	38.1

[a] From (5).

gories that provide half of the calories in the diet. Other than the white bread, rolls and crackers category no food was reported consumed by more than 41% of the respondents (9), indicating the diversity of the "American diet." While many of the foods are high in fat, a number of them provide important amounts of protein and micronutrients. Most in this field believe that all consumers share our interests in the relationship of diet and health. Unfortunately, this is not the case. Herrmann *et al.* (10) found that 33% of households surveyed expressed a strong concern about nutrition and health; these people had the highest incomes and the most formal education. Another 22% were also concerned about nutrition but were characterized by trying to economize and were not interested in new recipes or products. The remainder were unconcerned about nutrition or were identified as having little interest in changing their food patterns. It is likely that there is a bimodal distribution of dietary lifestyles in the United States, with a sizeable minority eating according to current guidelines for health and the remainder continuing their traditional consumption habits.

Recent research developments that may be significant concerning the relationship of diet with cancer include what has come to be called metabolic epidemiology. Of specific interest in this area are studies examining fecal bile acids in populations with different degrees of risk for development of colon cancer. In general, populations with high-fat, low-fiber diets have higher concentrations of fecal bile acids than populations with lower risks of colon cancer who consume low-fat, high-fiber diets (11). However, the Finnish population is at low risk for development of colon cancer in spite of very high fat consumption in Finland. One significant difference in diet in this country is that a very high proportion of fat is de-

TABLE IV. MAJOR CONTRIBUTORS OF CALORIES IN THE U.S. DIET[a]

Rank	Description	% of total calories	% of population consuming food
1	White bread, rolls, crackers	9.59	76.66
2	Doughnuts, cookies, cake	5.70	40.85
3	Alcoholic beverages	4.72	26.63
4	Whole milk, whole milk beverages	4.72	41.39
5	Hamburgers, cheeseburgers, meat loaf	4.39	26.18
6	Beef steaks, roast	4.14	22.76
7	Regular soft drinks	3.63	39.08
8	Hot dogs, ham, lunch meats	3.19	29.59
9	Eggs	2.53	31.37
10	French fries, fried potatoes	2.53	17.30
11	Cheese, excluding cottage cheese	2.45	32.87
12	Pork, including chops, roast	2.28	14.43

[a] From (9).

rived from dairy products. Nevertheless, Finns also consume a high-fiber diet which results in a significant reduction in the concentration of fecal bile acids (12). The interaction of fat and fiber in the risk of colon cancer was pointed out in a case-control study by Dales *et al.* (13) who reported a gradient of risk progressing from a low-fat, high-fiber diet to a high-fat, low-fiber diet. While this relationship is quite appealing, it must be pointed out that the number of cases in this study is quite small (11 to 44 per diet category). Epidemiologic investigation has also demonstrated that fat consumption is inversely correlated with intake of cereals, pulses, nuts, and seeds; the more affluent countries consume more fat and fewer high-fiber foods (14).

One basis for belief in dietary influence on the development of certain types of cancer is studies of migrating populations, especially Japanese who have a low risk of breast and colon cancer in Japan but an increased risk when moving to Hawaii or the mainland USA. Two notable reports have come from studies of this population recently. The Japan–Hawaii Cancer Study followed over 7000 middle-aged men of Japanese ancestry living in Hawaii for 15 years. A statistically significant, negative association was found between colon cancer and the intake of saturated fat whether assessed on the basis of absolute intake or as a percentage of caloric intake (15). The Honolulu Heart Program studied over 8000 men of Japanese descent living in Hawaii and found that total dietary fat was significantly inversely related with 10-year age-adjusted cancer mortality. The investigators from that study concluded that their results presented a dilemma since there was a positive relationship between dietary intake of fat and cholesterol with coronary heart disease death but a low-fat diet was associated with increased mortality from other causes, particularly cancer and stroke, "indicating no overall benefit from a low fat diet" (16).

A critical conceptual development derived from recent basic research is the fact that certain tumors responsive to dietary fat demonstrate an essential fatty acid (EFA) requirement higher than that usually required by an animal for normal health. Ip *et al.* (17) used dimethylbenz[a]anthracene (DMBA)-induced mammary tumors in rats and found that in a 20% fat diet the EFA requirement for optimal tumor yield was slightly over 4%. Roebuck *et al.* (18) used the same diets in rats with azaserine-induced pancreatic tumors and found there was increased tumor yield throughout the range (up to 11.5%) of EFA fed. Although the reported EFA requirements derived from these experiments are probably true only for diets containing 20% total fat (of a highly saturated nature), the concept derived from these two studies is especially important for comparison of types and amounts of fats used to modify appearance of carcinogen-induced tumors in animal models. As examples, the observation that saturated fat is less of a tumor promoter than polyunsaturated fat may be explained by provision of an inadequate amount of EFA for maximal tumor response and the recent flurry of investigations using fish oils to reduce tumor yield may simply have fed too little EFA in the fish oil diet to get a tumor yield similar to controls who are usually fed a high-EFA diet.

There are a number of hypotheses being investigated concerning the mechanisms by which dietary fat may increase the risk of certain tumors. These include lipid peroxidation, altered metabolism of carcinogens, incorporation of dietary fatty acids into target cell membrane phospholipids, alteration of eicosanoid metabolism, changes in endocrine function, increased and/or altered fecal bile acid patterns, and excess caloric intake or net energy. Since cancer is acknowledged to be a multistage, multifactorial disease it may be unrealistic to expect only a single mechanism to be operative in tumor enhancement by dietary fat. In a test of the significance of lipid peroxidation in DMBA-induced mammary tumorigenesis, Lane *et al.* (19) found that while 20% fat significantly enhanced tumor yield over a 5% fat diet, the levels of peroxides in the mammary glands of animals fed the high-fat diet were significantly lower than in mice fed 5% fat.

An examination of the influence of caloric intake versus fat content of the diet by our laboratory has shown that even when three times as much fat is fed to rats whose calories are restricted by 40% during the promotion phase of chemical carcinogenesis, there are significant reductions of both breast and colon tumors (20, 21) (Table V). While caloric intake

TABLE V. PREDOMINANCE OF EFFECT OF DIETARY CALORIES OVER FAT IN CHEMICALLY INDUCED MAMMARY AND COLON CANCERS IN RATS[a]

	Tumor incidence (%)	Tumors/ tumor-bearing rat
3.9% fat diet fed *ad lib*[b]	58	2.8 ± 0.5
14.0% fat diet–60% of *ad lib* cal	0	0
4.0% fat diet fed *ad lib*[c]	80	4.0 ± 0.5
13.1% fat diet–60% of *ad lib* cal	20	1.0 ± 0.0
4.0% fat diet fed *ad lib*[d]	100	3.5 ± 0.4
13.1% fat diet–60% of *ad lib* cal	53	2.1 ± 0.6

[a] From (20, 21).
[b] DMBA-induced mammary tumors—primarily saturated fat.
[c] DMBA-induced mammary tumors—polyunsaturated fat.
[d] DMH-induced colon tumors—polyunsaturated fat.

may be a greater determinant than fat content for susceptibility to tumor promotion, other data reported by us showed that there is a unique fat effect that enhances tumor promotion but it can be modulated by caloric restriction (22) (Table VI). A different approach to this same question was taken by Boissonneault *et al.* (23) who found that a 30% fat diet was no more of a mammary tumor promoter than a 5% fat diet when caloric intakes of the two groups were paired. In this study, 73% of rats fed the high-fat diet developed DMBA-induced tumors while 43% of the animals fed the low-fat diet had tumors and only 7% of the animals given the high-fat diet in an amount restricted to the calories consumed by the low-fat group had tumors. These experimental data are supported by epidemiologic research that has recently reported body weight was significantly related to risk of breast cancer in women (24, 25). In fact, data compiled by the ACS showed increased body weight associated with increased risk of cancer of the colon, breast, cervix, prostate, endometrium, gall bladder, and ovary in a study of 750,000 people (26). A recently published case-control study of colorectal cancer also found significantly greater intake of calories by patients. The sources of the excess calories were carbohydrate (21% more) and fat (14% more). The extra carbohydrate was largely in the form of sugars and the extra fat as combinations of fat and sugars (27).

Although the relationship of dietary fat and cancer is the most studied of all nutrient effects on the neoplastic process, controversy continues to surround the degree of effect and the mechanism(s) by which fat alters susceptibility to the tumorigenic process. The mechanisms proposed in the literature fall short of explaining the effects of fat on cancer; clearly, new hypotheses and additional investigation are

TABLE VI. EFFECT OF 25% CALORIC RESTRICTION ON DMBA-INDUCED MAMMARY TUMORS IN RATS FED HIGH FAT DIETS[a]

Diet	Tumor incidence (%)	T/TBR[b]	Tumor wt (g)	Tumor burden (g)
Ad libitum				
5% fat	65	1.9 ± 0.3	2.0 ± 0.7	4.2 ± 1.9
15% fat	85	3.0 ± 0.6	2.3 ± 0.7	6.6 ± 2.7
20% fat	80	4.1 ± 0.6	2.9 ± 0.5	11.8 ± 3.2
Restricted				
20% fat[c]	60	1.9 ± 0.4	0.8 ± 0.2	1.5 ± 0.5
26.7% fat	30	1.5 ± 0.3	1.4 ± 1.0	2.3 ± 1.6
Statistical significance	$P < 0.005$	$P < 0.001$	$P < 0.001$	$P < 0.001$

[a] From (22).
[b] Tumors per tumor-bearing rat.
[c] Rats were fed 75% of calories consumed by *ad lib*-fed animals so fat intake in 20% restricted group was identical to 15% *ad lib* group; fat intake in 26.7% restricted group was identical to 20% *ad lib* group.

necessary. Neither basic nor clinical research in this area objectively supports recommendations to reduce fat intake to some arbitrary level in order to reduce risk of cancer. Furthermore, the long-term consequences of reductions in dietary fat are unknown. We must be sure that chronic consumption of low-fat diets has no untoward effects on other aspects of physiology nor increases the risk of cancer at other organ sites. This area is one of the great unresolved controversies facing nutrition science (28) and cannot be won by majority opinion but by the facts alone. Dietary recommendations must be based on reasonable evidence and not on conjecture, no matter how reasonable that conjecture seems.

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