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Diet, Nutrition, and Avoidable Cancer

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In a 1981 review, Doll and Peto estimated that approximately 35% of cancer deaths in the United States were potentially avoidable by the modification of diet but that this percentage might be as low as 10% or as high as 70%. Since that time, the epidemiologic literature on diet and cancer has grown greatly, as has understanding of the mechanisms of carcinogenesis. In general, this expanded literature has not provided reason to alter the Doll and Peto estimate substantially. For colon cancer, evidence has accumulated that some of the international differences that were attributed to diet are probably due to physical activity. For breast cancer, the concept that fat intake per se is the primary reason for differences in rates among countries has not been supported by prospective studies. Although several lines of evidence suggest that caloric restriction and slow growth rates may contribute importantly to the low rates of breast cancer found outside Western countries, this may not translate directly to practical means of prevention. In contrast to breast cancer, more recent data have supported a causative role for red meat in the development of colon and prostate cancers, although perhaps not entirely due to its fat content. Whereas earlier thinking about nutrition and cancer emphasized the adverse effects of fat and other components in the diet, the most compelling evidence of the last decade has indicated the importance of protective factors, largely unidentified, in fruits and vegetables. Considering the more recent evidence, it is roughly estimated that about 32% of cancer may be avoidable by changes in diet; however, it now seems unlikely that less than 20% or more than 42% of cancer deaths would be avoidable by dietary change. — Environ Health Perspect 103(Suppl 8):165–170 (1995)

Key words: diet, nutrition, cancer, fat, fiber

Introduction

Over the years we have learned a great deal about diet in the cause and prevention of cancer, and in a brief review one can only superficially address the large and rapidly growing literature on this topic. While much remains to be learned, evidence is sufficient to draw several practical and important conclusions. As a starting point, this overview will use Doll and Peto's 1981 summary of the causes of cancer deaths in the United States (*1*). These epidemiologists estimated that 35% of all cancer deaths are potentially avoidable by dietary change, with a range of 10 to 70%. I will consider how we might modify these numbers in light of what we have learned since that time. The increment of knowledge since the time of the Doll-Peto report is large; there has been a manyfold increase in the number of relevant studies since their report.

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Abbreviations used: *r*, coefficient of correlation; RR, relative risk.

The method Doll and Peto used to arrive at their estimate is not totally clear, but they invoked the approach of *guesstimation*, which is still an appropriate technology at this time for this issue. Doll and Peto considered possible dietary relationships with the main site-specific cancers, and then presumably used some sort of weighting by the number of specific cancer deaths to obtain their estimate. The method by which they derived their confidence interval is considerably less clear.

To begin with, I will review the state of knowledge regarding diet in relationship to the major causes of cancer death, since this is where the greatest quantitative impact is likely to exist.

Colon Cancer

For colon cancer, a large—at least 60-fold—variation in rates exists among countries (*2*). Also, the international correlations with dietary factors are extremely strong; the correlation is high for fat but is even stronger ($r = 0.9$) for meat consumption (Figure 1). Vegetable fat, however, is not associated with colon cancer rates internationally (*3*). These correlations have been a major source of hypotheses and have generated considerable research on dietary fat and meat consumption in relation to colon cancer. Howe et al. (*4*) have summarized data from 13 case–control studies and found a clear positive association between total energy intake and risk of colon cancer, which was also quite apparent from the individual studies. However, when adjusted for total energy intake, total fat and specific types of fat essentially had no relationships with colon cancer (G Howe, personal communication). Thus, the fat composition of the diet, in case–control studies overall, does not appear to be associated with risk of colon cancer.

The relationship between diet and colon cancer has now also been examined in several prospective studies (Table 1). In none of them has there been any suggestion of a positive association with total energy intake, which can be interpreted as evidence for recall bias in the case–control studies. Also, total fat intake has not been clearly related to colon cancer risk in the prospective studies. We reported a relative risk of nearly two for high, compared with low, animal fat intake in the Nurses' Health Study (*5*), but when adjusted for red meat, the association with animal fat disappeared,

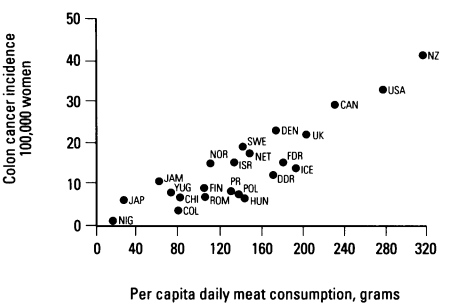


Figure 1. Correlation between per capita meat intake and incidence of colon cancer in women in 23 countries. Reproduced from Armstrong and Doll, (*2*) with permission.

Table 1. Prospective studies of colon cancer: energy, fat, and meat.

Study and reference	RR, for high vs low		
	Energy	Total fat	Meat
NHS (*5*)	0.94	2.00	2.52–beef, main dish 1.21–processed
Iowa (*12*)	0.60	0.88	1.21–beef, main dish 1.51–processed
Dutch (*7*)	0.74	1.07	1.72–processed
HPFS (*8*)	0.94	1.19	3.57–beef, main dish
American Cancer Society (*13*)	M	1.14	—
	F	0.85	—

Abbreviations: NHS, Nurses' Health Study; HPFS, Health Professionals Follow-Up Study; RR, relative risk; M, male; F, female.

whereas the red meat association remained (W Willett, unpublished data).

There has been more evidence that meat consumption is related to risk of colon cancer. Among women in the Nurses' Health Study, we found a rather strong association with beef, pork, or lamb consumption (*5*), and an almost significant trend with processed meat was seen in the Iowa Women's Study (*6*). In Holland, colon cancer risk was associated with processed, although not with fresh, meat (*7*). In the Health Professionals Follow-Up Study, a strong relationship was seen between red meat consumption and risk of colon cancer (*8*), but there was no association with animal fat or total fat intake. A similar association with red meat consumption was also seen in relationship to risk of large bowel adenoma in this same group of men (*9*). Thus, the evidence seems fairly strong that there is not a strong association between fat composition of the diet per se and risk of colon cancer. There is much more evidence that some component of red meat—and a number of hypotheses have been proposed—is related to risk of colon cancer.

The relationship of vegetable and fruit consumption or fiber intake to colon cancer risk has been examined in many studies (*10*). Many of these studies were conducted under the hypothesis that fiber intake is protective and, indeed, the results from case–control studies have been impressively consistent. Collectively, they suggest that something in fruit and vegetables is protective; however, consumption of grains has not generally been related to reduced risk (*11*). Again, in the pooled analyses of 13 case–control studies by Howe et al., there were inverse associations with fiber, vitamin C, and beta-carotene, but, adjusted for one another, fiber intake appeared to be the primary protective factor (*4*).

Table 2. Prospective studies of fiber and colon cancer.

Study and reference	Cases	RR, high vs low
NHS (*5*)	150	0.90 (0.54–1.49)
Iowa (*12*)	212	0.80 (0.49–1.31)
American Cancer Society[a] (*13*)	M–611	0.76 (0.57–1.02)
	F–539	0.62 (0.45–0.86)
HPFS (*8*)	203	1.08 (0.68–1.70)

Abbreviations: NHS, Nurses' Health Study; HPFS, Health Professionals Follow-Up Study; RR, relative risk; M, male; F, female. [a]A composite score for fruits, vegetables and grains.

The prospective studies of fiber and colon cancer are not as impressive as the case–control studies (Table 2). In general, the relative risks have been less than one for higher intake of fiber, but they are not as markedly reduced as in the case–control studies. In our cohort of men, in fact, we saw no protective relationship at all with fiber (*8*), and in the Nurses' Health Study, the relationship was quite weak (*5*). In the Iowa Women's Study, the association was also weak and was not statistically significant (*12*). Although a stronger inverse association was seen in the American Cancer Society cohort (*13*), only fatal cases were included and this may have resulted in bias if persons with higher fiber intake were more likely to seek regular screening, an association we have observed in our cohort of men. Thus, in studies less subject to methodologic artifact, it has become less clear that fiber has a major protective effect against colon cancer.

One area of major recent interest has been a possible protective effect of folic acid intake against colon cancer. Moreover, there is evidence that risk may be particularly elevated when low folate intake is combined with alcohol consumption, which does appear related to risk of large bowel cancer. In a case–control study by Freudenheim et al. (*14*), high intake of folic acid was apparently protective, and the combination of low folic acid and high alcohol intake was particularly deleterious. In analyses conducted by Giovannucci et al., inverse relationships with intake of folic acid and methionine (the main methyl donor) and a positive association with alcohol intake were seen for both colon cancers (*15*) and adenomas (*16*). Emerging evidence from research on congenital malformations (*17*) and cardiovascular disease (*18*) suggests that U.S. diets are inadequate in folic acid, and colon cancer may be another consequence.

Another hypothesis that has received much attention is that high intake of dietary calcium protects against colon cancer. The cohort studies and the case–control studies generally suggest a fairly consistent inverse association with higher intake of calcium (*19*). However, this relationship illustrates the importance of examining foods as well as nutrients and noting the nature of the dose–response relationship; otherwise, the findings may be misleading. The temptation is, of course, to advise drinking four glasses of milk a day, given the data on calcium intake. However, in data from both the Health Professionals Follow-Up Study (Kearney et al., unpublished data) and the Iowa Women's Study (*19*), there was little overall trend with calcium intake. Moreover, there was not a substantially reduced risk with higher intake; if anything, the only association was with a slightly increased risk at low calcium intake. And, when we examined milk itself, there was no suggestion of any beneficial effect. The slight protective association with calcium intake seemed to be coming from the nondairy sources, which are largely vegetables and grains. Therefore, support for a substantial effect of calcium against colon cancer is weak but needs further examination.

In their review, Doll and Peto attributed 90% of colon cancer mortality to dietary factors. Presumably, their assumption was that most of the international variation was accounted for by diet. This now appears questionable because a large literature suggests quite strongly that physical activity protects against colon cancer (*20–23*), which obviously confounds the international associations in an important way.

Breast Cancer

Several years ago Howe et al. published a pooled analysis of case–control studies indicating an overall positive association with fat intake (*24*). Although the relative risks (RR) appeared somewhat impressive (RR = 1.35 for 100 g of fat per day, an unrealistic change for virtually all women), in the scale of percent of energy, the relative risk is only about 1.06 for 40% of energy compared with 30% of energy. Thus, although it was statistically significant, this was a weak association for a change in fat intake that has been widely advocated.

The prospective studies on fat and breast cancer, again less subject to methodologic bias, seem to be providing a different answer. Comparing the highest and lowest categories of fat intake, there were no significant increases in risk, and the

Table 3. Prospective studies of the association between total fat intake and risk of breast cancer.

Study and reference	Population	Total cohort	Follow up, years	Cases	Range of total fat intake, % of calories from fat	RR, high vs low intake[a]	95% CI
Jones et al. (*49*)	U.S.	5,485	10	99	<30–≥42	0.62	0.33–1.19
NHS 4-year (*50*)	U.S.	89,538	4	601	32–44	0.82	0.64–1.05
Mills et al. (*51*)	California	20,341	6	193	NA	1.21[b]	0.81–1.81
Knekt et al. (*52*)	Finland	3,988	20	54	NA	1.72	0.61–4.82
Howe et al. (*53*)	Canada	56,837	5	519	31–47	1.30	0.90–1.88
Kushi et al. (*54*)	U.S.	32,080	4	408	27–41	1.13	0.84–1.51
NHS 8-year (*26*)	U.S.	89,494	8	1,439	29–>49	0.86	0.67–1.08
Graham et al. (*55*)	New York State	17,401	7	344	<26–>37	1.00	0.59–1.70
Byrne et al. (*56*)	U.S.	6,122	4	53	NA	1.10	0.5–2.40
Van den Brandt (*57*)	Netherlands	62,573	3	471	NA	1.08	0.73–1.59
Toniolo et al. (*58*)	U.S.	14,291	6	180	NA	1.49	0.89–2.48

Abbreviations: NNHS; Nurses Health Study; RR, relative risk; CI, confidence interval; NA, not available. [a]For most studies categories are quintiles of the intake distribution; in some studies quartiles or tertiles are used. [b]Estimate for animal fat intake only.

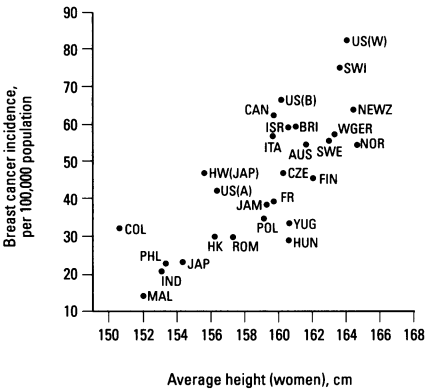


Figure 2. Correlation of average adult height in women with breast cancer incidence for 30 countries (r=0.8). Reproduced from Micozzi (*3*), with permission.

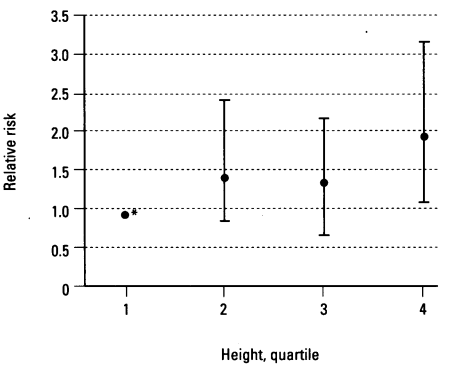


Figure 3. Relative risk of breast cancer by quartiles of height in the NHANES (*33*). The reference point is designated by an asterisk (*).

summary relative risk is only 1.03 (*25*) with a very tight confidence interval (0.91–1.18) (Table 3). Thus, there is little suggestion of a positive association between total fat intake and breast cancer in the prospective data.

Based largely on the international correlations, many have hypothesized that breast cancer is specifically related to saturated fat intake. Again, however, the relative risks have all been close to one in the prospective studies; no studies found the risk to be significantly greater for the highest compared with the lowest categories (Table 4).

The possibility exists that measurement error may contribute to a lack of positive association with fat intake, but in analyses that have taken measurement error into account, this could not explain the failure to see the association expected on the basis of international correlations (*26*). Also, when we used a more detailed questionnaire in the Nurses' Health Study in 1984, and then looked at the next 4 years of breast cancer incidence, we found a significant inverse association, driven mainly by an inverse relationship with monounsaturated fat (*26*). This finding raises interesting questions, particularly since reduced risks of breast cancer with higher olive oil intake have been seen in two recent case–control studies conducted in the Mediterranean countries (*27,28*). Thus, the relationship between fat intake and breast cancer may be much more complicated than we had originally believed.

Table 4. Saturated fat and breast cancer risk.

	RR (high vs low)
Nurses' Health Study (*50*)	0.86 (0.67–1.11)
Nurses' Health Study (*26*)	0.86 (0.67–1.10)
Canadian Study (*53*)	1.08 (0.73–1.59)
Iowa Womens' Study (*54*)	1.10 (0.83–1.46)
Dutch Health Study (*57*)	1.39 (0.94–2.06)
New York State Cohort[a] (*55*)	1.12 (0.78–1.61)
Adventists Health Study[a] (*51*)	1.21 (0.81–1.81)

RR, relative risk. [a]Animal fat.

In contrast to dietary fat, the evidence is strong that energy restriction and reduced growth rates reduce breast cancer incidence. For over 60 years, it has been known that animals restricted in energy intake experience a dramatic reduction in mammary tumors (*29*). In animal studies, even a 20% restriction in energy intake causes a 70% reduction in the occurrence of mammary tumors (*30*). The effect of energy restriction has been seen in many models and is a highly reproducible finding.

But does the relationship between energy restriction and breast cancer also apply to humans? The evidence is now compelling. Micozzi has compiled international data using height as an indicator of energy balance during growth and development (*31*). Height is obviously a crude indicator for this purpose because it reflects genetic predisposition; nevertheless, a strong positive international correlation exists (Figure 2). From studies of migrants and secular changes of height within Japan, we know that the short stature seen in populations with low breast cancer incidence is related to nutritional factors, as these groups increase dramatically in height when better sanitation and nutrition become available (*32*). Reduced growth rates due to limited intake of protein, linoleic acid, or other essential nutrients might also contribute to reduced risk. In many case–control and cohort studies, a positive association between height and breast cancer risk has been seen (*25*). For example, in data from National Health and Nutrition Examination Survey (NHANES) (*33*), there was a 2-fold elevation in risk of breast cancer among taller women (Figure 3). Energy restriction and reduced growth rates almost certainly operate in part by delaying age at menarche (*34*), which has long been known to decrease the risk of breast cancer. Additional mechanisms are also likely to operate, as energy restriction reduces the incidence of many tumors in animals, and reduced stature has also been associated with lower risk of other human cancers (*33,35*).

Alcohol, discussed elsewhere in this symposium, is the other well-established dietary risk factor for breast cancer (*25,36*). Accumulating evidence suggests that this effect is likely to be mediated by increased endogenous estrogen levels (*37*).

Considerable evidence also suggests that vitamin A intake is inversely associated with breast cancer risk; this has been seen in multiple case–control studies and now also in cohort studies. Reduced risks

among women with higher vitamin A intake were seen in both the Nurses' Health Study (*38*) and the Canadian Prospective Breast Cancer Study (*39*). Interestingly, and in contrast to virtually all other cancers, this association seemed to be strongest when intake included vitamin A both from animal and vegetable sources, suggesting that protective effects were not due only to carotenoid or a antioxidant actions. An effect of vitamin A per se would be consistent with a tumor–suppressing action seen in animal models of mammary carcinogenesis (*40*).

Prostate Cancer

The third major cancer to be addressed here is prostate cancer. Again, large differences in prostate cancer rates are seen internationally, and strong positive correlations exist with fat intake and red meat consumption (*2*). As for breast and colon cancer, this has led to hypotheses that dietary fat might be important in the etiology of prostate cancer.

The relationship between dietary fat and prostate cancer risk has been examined in a few case–control studies, and most of them have suggested some association in one subgroup or another. However, findings have not been consistent regarding the subgroups in which these associations exist. In prospective data from our cohort of men, we found evidence that fat, particularly animal fat, was important (*41*). This association was only with the advanced stages of prostate cancer, which is the form that varies among countries. The more benign type of prostate cancer is distributed rather equally around the world, so dietary factors may be particularly important in the transition from the relatively benign to the more aggressive form of prostate cancer. When we examined associations with specific fatty acids, alpha-linolenic acid was mostly strongly associated with risk; in this population, this essential polyunsaturated fat was obtained mainly from red meat. The association between diet and prostate cancer has recently been examined in a prospective study in Hawaii. Again, positive associations with animal fat and beef consumption were seen (*42*). Although additional data are clearly needed, present evidence does suggest that animal fat may be an important cause of prostate cancer.

Lung Cancer

Approximately two dozen case–control and cohort studies have examined the relationship between vitamin A-containing foods and risk of lung cancer (*43*). In these studies, there is highly consistent evidence of an inverse association with carotenoid intake but not with intake of preformed vitamin A. The relative risks have generally been about 0.7 or 0.6 for high compared with low intakes. This evidence has raised the hypothesis that beta-carotene is a specific protective factor for lung cancer (*44*). Studies using prospectively collected blood have consistently found an inverse association between serum beta-carotene levels and subsequent risk of lung cancer (*43*). Taken together, evidence is strong that a phytochemical in fruits and vegetables, possibly a carotenoid or something associated closely with beta-carotene in the diet, protects against lung cancer.

Steinmetz and Potter (*45*) and Block et al. (*46*) have reviewed the substantial amount of evidence that higher intakes of fruits and vegetables protect against many other cancer sites. Questions remain about the amount of fruit and vegetable consumption that is optimal, what kinds of fruits and vegetables are critical, and what it is in them that is anticarcinogenic.

Cancer Deaths Avoidable by Dietary Change

Returning to the task of assigning a number for the estimated percent of cancer deaths avoidable by dietary change, I have attempted to do this by site (Table 5). An attempt has also been made to assign reasonable estimated upper and lower bounds on the percent avoidable by diet for each cancer site. Making quantitative estimates at this time is treacherous, as the available evidence can only be interpreted roughly. Methods of dietary assessment are sufficiently informative to identify consistent associations for a number of diet and cancer relationships, but their imprecision will tend to underestimate the magnitude of these relationships. For typical degrees of measurement error, the underestimation is roughly 2-fold (*47*), but this may be larger if dietary intake during the most relevant time period of exposure (which is not known with any precision) was not assessed. Further, much of the available evidence is based on case–control studies, and methodologic biases due to differential recall of diet and selective participation of controls could distort associations in either direction. For this reason, formal correction for measurement error cannot be applied to the overall literature. Another approach to quantitative estimation is to assume that the international differences are due to diet once a reasonable amount of evidence for a causal effect of diet exists from case–control and cohort studies, metabolic investigations, and animal experiments. A fundamental problem with this approach is that nondietary factors, such as smoking habits, reproductive experiences, physical activity, and infectious agents, may also contribute to international differences. In light of these complexities, I have adopted the guesstimation method used by Doll and Peto, relying mainly on case–control and cohort data, but also on international comparisons when the case–control and cohort evidence diet contributes to the international differences was strong.

For lung cancer, the estimate of 20% used by Doll and Peto remains consistent with the many subsequent studies. It also seems unlikely that more than 30% of lung cancer is avoidable with dietary change, as few studies have suggested larger differences between the highest and the lowest intakes of protective factors.

For colon cancer, Doll and Peto estimated that 90% was avoidable by dietary

Table 5. Cancer deaths avoidable by dietary change, 1994.

Type of cancer	Deaths,[a] %	Percent avoidable		
		Doll-Peto	Current	Range
Lung	28	20	20	10–30
Colon/rectum	11	90	70	50–80
Breast	8	50	50	20–80
Prostate	7	(with other)	75	20–80
Pancreas	5	50	50	10–50
Stomach	5	35	35	30–70
Endometrium	1	50	50	50–80
Gall bladder	1	50	50	50–80
Larynx, bladder, cervix, mouth, pharynx, esophagus	6	20	20	10–30
Other types	28	10	10	—
Overall estimate		35	32	20–42

[a]Percent estimated deaths, 1993.

change, largely on the basis of international comparisons. I think we have to reduce this estimate because of the clear evidence that physical activity is important and almost surely explains some of the international variation. Therefore, I used 50%, but this may still be high.

For breast cancer, I have left the estimate at 50%, but the confidence interval here reflects whether or not the estimate includes energy restriction as a dietary change. An effect of energy balance, and possibly protein intake at the point at which it limits growth, is highly likely to be real and large, but this knowledge may not result in a practical intervention that can reduce breast cancer incidence. If we only include practical interventions and attainable dietary changes, the percentage of breast cancer avoidable by dietary change may be considerably smaller.

Doll and Peto did not provide a specific number for prostate cancer, but there is now considerable evidence that diet is probably an important contributor to prostate cancer mortality. But, again, here I have left a wide confidence interval, as we are just beginning to develop a solid body of evidence regarding the relationship of diet to this disease.

I found no reason to change the Doll and Peto estimates for pancreatic (for which considerable evidence suggests that fruit and vegetable consumption may have a modest protective effect) (*48*) and endometrial cancers (for which data remain meager), or most of the other cancers. In some instances, however, the confidence intervals are tightened up a bit. Weighting the percentages of site-specific cancers avoidable by dietary change by the percent of deaths in 1993 due to specific cancers, an estimate of about 32% is obtained for cancers avoidable by diet, just slightly less than that of Doll and Peto. However, assuming that all of the maximal estimates are true (which is quite unlikely), an estimate of about 42% is obtained as the maximum percentage avoidable by dietary changes.

Again, all these estimates are very rough, and one can argue with any one of them. Nevertheless, the collective data provide evidence that diet does play an important role in the cause and prevention of cancers, and, coupled with evidence for cardiovascular disease, one can sensibly recommend an abundant consumption of fruits and vegetables and low intake of red meat. Further research to identify the optimal amounts and types of fruits and vegetables in the diet and the factors in these foods and meat that account for their relationships with cancer incidence is likely to be fruitful.

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