Linoleic acid intake and cancer risk: a review and meta-analysis¹⁻³

Peter L Zock and Martijn B Katan

ABSTRACT  Replacement of saturated fat by the major dietary polyunsaturated fat linoleic acid reduces blood cholesterol concentrations and the risk of coronary artery disease. However, there is concern that long-term consumption of large amounts of linoleic acid might increase cancer risk. We reviewed the epidemiologic and experimental literature on linoleic acid intake and cancer risk and performed additional meta-analyses of risk estimates from case-control and prospective cohort studies. None of the combined estimates from within-population studies indicated a significantly increased risk of cancer with high compared with low intakes of linoleic acid or polyunsaturated fat. For case-control studies, the combined relative risks were 0.84 (95% CI: 0.71, 1.00) for breast, 0.92 (95% CI: 0.85, 1.08) for colorectal, and 1.27 (95% CI: 0.97, 1.66) for prostate cancer. For prospective cohort studies, combined relative risks were 1.05 (95% CI: 0.83, 1.34) for breast, 0.92 (95% CI: 0.70, 1.22) for colon, and 0.83 (95% CI: 0.56, 1.24) for prostate cancer. Ecologic comparisons of populations showed positive associations between cancer rates and per capita use of animal or saturated fat, but less so with per capita use of vegetable oil or polyunsaturated fat. Controlled studies of coronary artery disease in men did not, except for 1 study, show an increased cancer incidence after consumption of diets with a very high linoleic acid content for several years. Animal experiments indicated that a minimum amount of linoleic acid is required to promote growth of artificially induced tumors in rodents; but above this threshold, linoleic acid did not appear to have a specific tumor-promoting effect. Although current evidence cannot exclude a small increase in risk, it seems unlikely that a high intake of linoleic acid substantially raises the risks of breast, colorectal, or prostate cancer in humans.

See corresponding editorial on page 5.

INTRODUCTION  Cancer risk in humans may be linked to the composition of the diet (1). In particular, dietary fat intake is often thought to be involved in the etiology of breast and colon cancer (2); both saturated and polyunsaturated fats have been implicated (3, 4). An increased intake of polyunsaturated fat is considered favorable because of its beneficial effects on blood cholesterol concentrations. However, the possible adverse effects of a high polyunsaturated fat intake require scrutiny.

The major polyunsaturated fatty acid in most diets is linoleic acid (cis, cis-18:2n−6). Linoleic acid is an essential fatty acid; it is required for the biosynthesis of eicosanoids but cannot be synthesized by the human body. An intake of 2–3% of dietary energy is probably enough to prevent deficiency (5). The average linoleic acid intake in the United States and Western Europe has risen from ≈3% of energy in the 1950s to 6–7% at present, with a commensurate decrease in saturated fat (6–8). A few populations (Northern Belgium and Israel) habitually consume 8–12% of their total energy intake as linoleic acid (9–12).

Replacement of saturated fat with linoleic acid is advocated to improve serum lipoprotein profiles and reduce the risk of coronary artery disease (CAD) (5, 13, 14). Replacement of saturated fat with unsaturated fat does not cause a decrease in HDL cholesterol as occurs when saturated fat is replaced with carbohydrates (15, 16). Some experts have recommended that linoleic acid consumption be raised to 10% of energy intake (5, 13, 14). However, over the past 25 y the wisdom of recommending high intakes of polyunsaturated fatty acids has been increasingly questioned (17–22). The major concern is whether diets high in polyunsaturated fatty acids increase cancer risk because linoleic acid has been linked to the development of cancer in animals (23, 24), and some population comparisons report positive associations with per capita use of polyunsaturated fatty acids (3, 4). An added concern is that polyunsaturated fat may be prone to oxidation, which may play a role in carcinogenesis (25, 26) and may increase the susceptibility of LDL particles to oxidative modification (27). Such concerns led to the current recommendations that the average intake of polyunsaturated fats remain at 7% of total energy and that individual intake should not exceed 10% of total energy intake (28, 29).

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METHODS

To identify studies of the relation between diet and cancers of the breast, colon and rectum, and prostate we searched the MEDLINE database (National Library of Medicine, Bethesda, MD) for the years 1966-1996 and BIOLOGICAL ABSTRACTS for the years 1989-1996 using the following key words: diet, fat, fatty acid, cancer, neoplasm, malignancy, carcinogenesis, tumor, carcinoma, and adenoma. We also checked citations in the identified articles. In vitro studies were not considered.

We specifically selected epidemiologic studies that provided quantitative estimates of cancer risk and its SE with high compared with low intakes of linoleic acid or polyunsaturated fat. For combined estimates across studies, we used results of published meta-analyses and performed additional meta-analyses when necessary. To this end, we extracted from individual studies the risk estimate that referred to the largest difference in intake and that reflected the greatest degree of control for other environmental and dietary risk factors. When studies provided estimates of risk for subgroups of subjects, eg, older and younger subjects, we used or calculated the risk estimate for all subjects.

For combining risk estimates, we used a random-effects model (30) to take into account both the sampling variance within studies and the variation in the true underlying effects across the studies being combined. Such variation in underlying effects (heterogeneity) seemed plausible because of the differences in populations, designs, and methods among studies. A model assuming equal sampling variances for each study, ie, each study having equal weight, and a fixed-effects model assuming the same underlying effect across studies (homogeneity) yielded similar results.

RESULTS

Breast cancer

Analytic studies within populations

Case-control studies. In the 16 case-control studies from which we were able to extract a quantitative estimate of breast cancer risk, risk was not increased with high intakes of linoleic acid (Figure 1). The combined relative risk, involving a total of 6910 cases and 8536 control subjects, was 0.84 (95% CI: 0.71, 1.00). This outcome agrees with results of previous meta-analyses. Boyd et al (47) calculated a combined relative risk of 0.92 (95% CI: 0.79, 1.08) from 9 case-control studies published before 1993. Two of these 9 studies (36, 37) showed a lower breast cancer risk with higher polyunsaturated fat intake and the other 7 studies (31–35, 38, 39) showed no significant effect (Figure 1). Howe et al (48) pooled the results of 8 studies that provided data on polyunsaturated fat. Among 5167 postmenopausal cases and control subjects, the univariate relative risks for each extra 45 g/d were 1.25 for polyunsaturated, 1.46 for saturated, and 1.41 for monounsaturated fat. In a model that included all 3 types of fat, the relative risk for polyunsaturated fat was 0.78 (95% CI: 0.51, 1.17). In 4 recent studies not included in previous meta-analyses (40–43), the relative risks for high compared with low polyunsaturated fat intakes ranged from 0.7 to 1.3 (Figure 1).

The studies mentioned above all assessed fat intake by self-report of subjects. Biomarkers of intake have also been used. One study measured the fatty acid composition of erythrocyte phospholipids in 46 breast cancer cases and 53 control women in Moscow and found a significantly reduced risk of breast cancer associated with a high proportion of linoleic acid in phospholipids (44) (Figure 1). Erythrocyte phospholipids reflect diet in the past weeks or months (49) and it is possible that patients changed their diets because of their disease or that the disease affected the proportion of linoleic acid in their erythrocytes. A better long-term biomarker is the fatty acid composition of adipose tissue (50). A study among Boston women found no associations between breast cancer risk and n-6 polyunsaturated fatty acids in buttok fat from 380 breast cancer cases and 397 control subjects (45). Similar findings were reported for women in New York (46) (Figure 1).

Several case-control studies reported results in terms other than relative risk. A study in Hawaii (51) showed no difference in self-reported linoleic acid intake between breast cancer cases and control subjects. In studies from Finland (52) and Israel (53) there were no significant differences in the linoleic acid content of breast adipose tissue between cases and control subjects. In summary, the case-control studies analyzed showed either no or negative associations between linoleic acid intake and breast cancer risk.

Prospective cohort studies. The prospective cohort studies analyzed also did not show positive associations between linoleic acid intake and breast cancer risk (Figure 2). Hunter et al (59) conducted a pooled analysis on standardized data from 7 major cohort studies of fat intake and breast cancer involving a total of 4980 cases among 337 819 women (41, 54–58, 66). The pooled relative risk, corrected for dietary measurement error, was 1.05 (95% CI: 0.83, 1.34) for each 10-g/d increase in polyunsaturated fat intake (Figure 2). In 3 cohort studies (60–62) that did not meet the criteria of Hunter et al (59), the relative risks for high compared with low polyunsaturated fat intake ranged from 0.73 to 1.23 (Figure 2). In a cohort from California, intake of all types of fat, including linoleic acid, was higher in 15
cases than in 575 women who did not develop breast cancer. These differences disappeared after adjustment for total energy intake (67). In a biomarker study that measured phospholipid fatty acids in blood sampled 0.5–16 y before the onset of breast cancer, a high proportion of linoleic acid was associated with reduced risk in women younger than 55 y (Figure 2), but not in those older than 55 y (63).

Two studies investigated the effect of dietary fat intake after diagnosis on cancer survival. In a study of 161 white and 182 Japanese breast cancer patients in Hawaii (64), the white women with a high polyunsaturated fat intake, not adjusted for energy intake, had a greater risk of death (Figure 2; relative risk: 1.72). In an Australian study (65), the relative risk of death of 412 breast cancer patients was 1.57 at a high compared with a low intake of polyunsaturated fat and 1.14 at a high compared with a low linoleic acid intake (Figure 2).

In summary, longitudinal epidemiologic studies (Figure 2) do not suggest that linoleic acid intake has a marked effect on the development of breast cancer. The 1 exception is a new analysis of the Swedish Mammography Screening cohort (68). An earlier analysis showed no relation with polyunsaturated fat intake (41, 59). The new analysis applied a mutual adjustment for intakes of different types of fat and found a relative risk of breast cancer of 1.69 (95% CI: 1.02, 2.78) for each 5-g/d increase in intake of polyunsaturated fat (68). However, other studies also adjusted for mutual confounding among the various types of fat and found no increased risk of breast cancer with higher intakes of polyunsaturated fat (40, 58). Thus, the bulk of the data still suggest that linoleic acid does not have a marked effect on the risk of breast cancer. The findings on survival in breast cancer patients suggest a possible adverse effect on mammary tumor progression, but the data are limited.

Ecologic comparisons between populations

Comparisons between countries generally show positive correlations between per capita disappearance of total fat and breast cancer incidence or mortality (69–73). Some studies suggest that these associations are mainly due to the use of animal and saturated fats rather than to the use of vegetables or polyunsaturated fats (72, 74–76), but others show positive associations of breast cancer rates with the use of polyunsaturated fat (3, 4, 77, 78). Carroll (76) reported that mortality from breast cancer is strongly associated with intakes of fat from animal sources but not with the percentage of energy as polyunsaturated fat; in contrast, Prentice et al (3, 77) estimated that a 50% reduction in both saturated and polyunsaturated fats would reduce breast cancer risk by half. Thus, results from ecologic comparisons are not consistent.

In view of the uncertainties concerning food disappearance data, population comparisons that use biomarkers of intake may be more reliable. One study assessed intake from linoleic acid in the adipose tissue of subjects from 10 European regions and Israel (79) (Figure 3). Incidence in the Israeli women, whose linoleic acid intakes have been some 10–12% of energy for the past decades (11, 12), was not higher than in women from northwestern Europe, whose intakes were probably 4–7% of energy. The breast cancer rate in the Israeli women may have been additionally inflated by the high frequency of BRCA1 and BRCA2 mutations in Ashkenazi Jews (80).

Animal studies

The hypothesis that dietary fat or specific fatty acids can cause breast cancer originates from studies in rodents by Tannenbaum in 1942 (81). Since then, a large number of animal experiments showed that the amount and type of fat can markedly influence the growth of induced breast tumors in rodents during the promotion stage, but less so during the initiation stage (for a review see reference 82). In rats, a diet rich in polyunsaturated fat promoted growth of chemically induced (dimethylbenz[a]anthracene or N-nitrosomethylurea) or transplanted tumors more than did a diet rich in saturated fat (24, 83–86). Other studies showed that up to 4–5% of dietary linoleic acid in the diet promotes artificial mammary tumorogenesis in rats but that higher amounts have no additional effects; once the diet contained 4–5% of energy as linoleic acid, tumor yield and growth increased with the total amount of dietary fat, but saturated fats had the same effect as polyunsaturated fats (87–90). On the other hand, in experiments...
with athymic nude mice that were injected with human breast cancer cells, diets containing 16% or 24% of energy as linoleic acid increased tumor weight and pulmonary metastasis compared with a diet containing the same amount of total fat but only 4% of energy as linoleic acid (91, 92).

One study addressed the effect of long-term polyunsaturated fat intake on spontaneous breast tumors in rats and mice (93, 94). In a set of experiments, 3578 female rats and mice received diet 10% of energy as fat and 2200 animals received by gavage additional corn oil that increased fat intake to 30% of energy. The 2-y incidence of spontaneous breast tumors was the same or somewhat higher with the low-fat diet (2.5% in the rats and 1.7% in the mice) than with the diet high in corn oil (1.5% in rats and 1.3% in mice).

In summary, short-term experiments show that a minimum amount of linoleic acid is required to stimulate the growth of artificially induced mammary tumors in rats. Above this threshold, it appears to be the total amount of fat, or dietary energy (95–97), that promotes tumorigenesis, and that linoleic acid is as effective as other types of fatty acids. A high linoleic acid intake did stimulate carcinogenesis in 1 particular mouse model but a long-term high intake of linoleic acid did not increase spontaneous development of breast tumors in rats and mice (93, 94).

**Colorectal cancer**

**Analytic studies within populations**

**Case-control studies.** The case-control studies from which we were able to extract quantitative estimates of risk showed no consistent association between intake of linoleic acid or polyunsaturated fat and colorectal cancer risk (Figure 4). Howe et al (108) combined the results of 13 studies on colorectal cancer and diet. Eleven studies involving a total of 5287 cases and 10 470 control subjects provided intake data on polyunsaturated fat; 2 studies (103, 104) found a positive association and the other 9 studies (98–102, 105–107) showed no or weakly inverse associations. The pooled odds ratio per 21.3 g polyunsaturated fat/d was 0.92 (95% CI: 0.85, 1.08) for all subjects, 1.05 (95% CI: 0.90, 1.23) for the men, and 0.80 (95% CI: 0.66, 0.98) for the women.

Case-control studies not included in the meta-analysis by Howe showed relative risks of colorectal cancer (109–111) or adenomatous polyps (112) ranging from 0.29 to 1.63 with high compared with low polyunsaturated fat intakes (Figure 4). In case-control studies that did not report estimates of risk, colorectal cancer patients and control subjects consumed the same amount of polyunsaturated fat (113, 114).

Three case-control studies used biomarkers to assess linoleic acid intake (11, 114, 115). These studies are not represented in Figure 4 because no estimates of relative risk were given. A small study from Scotland reported a somewhat lower proportion of linoleic acid in red blood cells of 20 colon cancer patients than in 20 control subjects (115); in other studies there were no differences between cases and control subjects in the proportion of linoleic acid in adipose tissue (11, 114) or red blood cells (114). Thus, the case-control studies analyzed showed no consistent association between linoleic acid intake and colorectal cancer risk.

**Prospective cohort studies.** Prospective data on fat and colorectal cancer risk are limited; the relative risks (Figure 5) of colorectal cancer or adenomatous polyps in subjects with high compared with low intakes of linoleic acid were measured in 3 large cohorts from the United States (116, 117, 119–121) and 1 from the Netherlands (118). In these 4 studies involving a total of 782 patients with colorectal cancer among 292 768 persons, the risk of developing colon cancer during 3–6 y of follow-up was not associated with previously reported intakes of linoleic acid or polyunsaturated fat (116–119). We calculated a combined relative risk of 0.92 (95% CI: 0.70, 1.22).

Risk of adenomatous colorectal polyps in male health professionals who underwent endoscopy was nonsignificantly increased with a high polyunsaturated fatty acid intake (120) (Figure 5). Risk of hyperplastic colorectal polyps in the same population was nonsignificantly decreased with a high polyunsaturated fatty acid intake, as was the risk of hyperplastic colorectal polyps in the Nurses’ Health Study (121). The combined risk of adenomatous and hyperplastic colorectal polyps with high compared with low polyunsaturated fat intakes, based on a total of 564 cases among 35 545 persons, was 1.06 (95% CI: 0.55, 2.05). Thus, these prospective cohort studies showed no association of polyunsaturated fat intake with the risk of colorectal cancer.

**Ecologic comparisons between populations**

International comparisons showed strong associations between per capita use of total fat and incidence or mortality from colorectal cancer (70, 71, 122–124). However, unlike breast cancer, the association was consistently limited to saturated or animal fats; there was no association with polyunsaturated or vegetable fats (3, 75, 78, 122–124).

This finding agrees with hitherto unpublished prospective data from the Seven Countries Study. Between 1958 and 1964, 12 763 men from 16 cohorts were enrolled in this study (125). Dietary information was collected at baseline from random samples of 8–49 men from each cohort. In 1987, food composites representing intake at baseline were collected locally and analyzed for fatty acids (126). The vital status of all men was verified after 25 y of follow-up (127). Linear regression analysis was used to relate average linoleic acid intake in the 16 cohorts with age-adjusted mortality rates from colorectal cancer [Interna-
Prospective cohort studies. Several prospective cohort studies have investigated dietary factors in relation to prostate cancer (for review see reference 138), but only 2 (142, 143) have investigated the relation between prostate cancer and polyunsaturated fat intake (Figure 7). In 2 cohorts, 1 of US health professionals (142) and 1 of US physicians (143), linoleic acid showed no or a weakly negative association with prostate cancer. The combined relative risk with high polyunsaturated fat intake in older men, but not in younger men (139). Another study found an increased risk with high proportion of linoleic acid in erythrocyte membranes and fat tissue (141).

A few studies measured polyunsaturated fat intake, but did not report estimates of risk. In 1 study (144, 145), prostate cancer patients consumed the same (144) or somewhat lower amounts of linoleic acid than did control subjects (145). Another study found no association between polyunsaturated fat intake and prostate cancer (146). In a study from Scotland, the polyunsaturated fat intake of 20 patients was higher than that of 20 control subjects (145). Another study found an increased risk with high proportion of linoleic acid in erythrocyte membranes and fat tissue (141).
of the 31 deaths from carcinoma during the diet phase in the experimental group occurred in men who did not adhere closely to the diet (adherence score of < 50%). Ederer et al (152) combined the Los Angeles cancer data with those of 4 other trials that studied the effects of diets with a high content of linoleic acid (153–156) (Table 1). When data from the Veterans Administration trials were excluded, the relative risks in the groups with a high linoleic acid intake as compared with the control groups were 0.75 for cancer incidence and 0.62 for cancer mortality. When data from the Veterans Administration trial were included, the relative risk became 1.15 for cancer incidence and 1.08 for cancer mortality.

In a more recent, large, 4.5-y trial with institutionalized men and women, 23 cancer deaths occurred among 4541 participants who consumed a diet containing 15% of energy as linoleic acid, whereas 20 of the 4516 subjects consuming a diet containing 5% of energy as linoleic acid died of cancer (159). Thus, cancer mortality was not higher in the high–linoleic acid group than in the control group. However, unlike in previous trials, in this trial there was no effect of linoleic acid intake on the incidence of CAD. This finding sheds some doubt on whether the duration and the intensity of the dietary treatment were sufficient.

In summary, 1 trial of diet and CAD showed an increased incidence of cancers with a very high intake of linoleic acid during several years, whereas 5 other trials of diet and CAD did not. However, each of these trials had serious methodologic limitations in terms of adherence, duration, and small number of cancer cases.

DISCUSSION

A definitive answer to the question of whether high intakes of linoleic acid increase the risk of cancer requires a randomized, controlled trial in which thousands of people consume a diet either high or low in linoleic acid for their entire lives. Because such a trial is obviously not feasible, one has to rely on other sources of evidence for the answer. Current evidence is summarized in Table 2. We found no strong evidence indicating that a diet high in linoleic acid or polyunsaturated fat increases the risk of breast, colorectal, or prostate cancer. Analytic studies within populations showed no consistent relation between linoleic acid intake and cancer risk. Some ecologic comparisons between populations showed associations between vegetable or polyunsaturated fat intake and incidence or mortality rates for breast and prostate cancers, but not for colorectal cancer. With 1 exception, trials studying the effect of linoleic acid on incidence of CAD in men do not suggest that a high linoleic acid intake for 1–7 y raises cancer risk. Several, but not all, animal experiments have indicated that linoleic acid promotes the growth of artificially induced breast and colorectal tumors in rodents.

Evidence from analytic studies within populations

The findings from case-control and prospective cohort studies do not categorically exclude an influence of linoleic acid on cancer risk. There are several reasons why true underlying effects may have been missed or obscured. Recall bias may occur in case-control studies. For example, if patients underreported their linoleic acid intake, a positive association between linoleic acid intake and cancer incidence may have been obscured. However, case-control studies that objectively assessed intake by examining tissue fatty acid contents also
found no associations between linoleic acid intake and cancer risk. Furthermore, prospective cohort studies, which are not subject to recall bias, also showed no associations. Thus, recall bias is not the most likely explanation for the absence of associations in case-control studies.

Errors in measurements of dietary intake in epidemiologic studies are generally large. Random (nondifferential) measurement error attenuates estimates of relative risk toward 1. Most of the studies reviewed here did not correct risk estimates for this type of error, but Hunter et al (59) found that correction had little effect on the outcome of their pooled analysis of cohort studies on breast cancer. This suggests that this type of error cannot totally explain the absence of associations. However, Prentice (160) criticized the existing methods for correction and argued that dietary measurement error may also be systematic (ie, not random). He concluded that dietary self-report instruments may be inadequate for analytic studies. On the other hand, assessment of dietary intake with biomarkers avoids such systematic error, and, except for 1 study (141), studies that used biomarkers also found no (45, 46) or negative (44, 63, 161) associations between linoleic acid intake and cancer incidence. It is unclear to what extent dietary measurement error may have affected the estimates of risk in studies that relied on self-reported intake.

A narrow range of linoleic acid intake in the population may be another reason why associations were not found. In the studies reviewed here, linoleic acid intake in the highest category was typically twice that in the lowest category of intake, with differences ranging from ∼5 to 25 g/d. This is comparable with the normal range of intake of 4–10% of daily energy. However, it cannot be excluded that cancer risk within populations would be affected by larger differences in linoleic acid intake. Yet another reason for not finding a significant association in an individual epidemiologic study is the limited number of subjects, which results in low statistical power. However, the combined risk estimates presented here, involving large numbers of patients, also did not show associations between linoleic acid intake and cancer risk.

Confounding must also be considered. For example, people who consume high amounts of linoleic acid may also consume high amounts of vegetables and fruit, which might obscure increases in colorectal cancer risk caused by a high linoleic acid intake. Possible confounders in studies of breast cancer are body weight and intake of total energy or of other fatty acids. Such confounders are often not taken into account or cannot be completely adjusted for. Thus, bias of risk estimates by confounding factors cannot be excluded. Also, linoleic acid intake reflects the use of vegetable oils such as rapeseed and soybean oils. It remains possible that associations reported for linoleic acid or polyunsaturated fat are affected by other substances from these oils. Publication bias is not plausible because studies showing positive associations between linoleic acid intake and cancer risk would be more likely to be published than would studies showing negative associations.

Many of the analytic studies reviewed measured the intake of all polyunsaturated fats and not linoleic acid intake per se. Polyunsaturated fat in human diets consists mainly of linoleic acid, but it also includes α-linolenic acid and long-chain n-3 fatty acids from fish oil. It has been suggested that these n-3 fatty acids may have specific effects on cancer risk (162–164). If so, then a risk estimate for polyunsaturated fat would not be the same as a risk estimate for linoleic acid. However, studies that measured polyunsaturated fat intake and studies that specifically measured linoleic acid intake showed no consistent associations with cancer risk. Therefore, it is plausible that differences in polyunsaturated fat intake reflected differences in linoleic acid intake, and that n-3 fatty acids did not materially affect the risk estimates for polyunsaturated fat.

Thus, there are several methodologic reasons analytic studies within populations may have missed a possible association between linoleic acid intake and cancer risk. The question becomes whether such studies, when applying similar methods in similar populations, can at all detect associations between fatty acid intake and disease risk. For example, do within-population studies reveal the expected relation between linoleic acid intake and the risk of CAD? Indeed, a substantial proportion of prospective cohort studies did show inverse associations between polyunsaturated fat intake and the risk of CAD (165–169), although the remainder of the studies did not (170–174). Thus, epidemiologic studies of this type should be able to detect an association between linoleic acid intake and disease risk, if one exists. In addition, several of the studies described above showed associations between cancer risk and food components other than linoleic acid, such as animal fat and red meat (107, 116). Therefore, if a substantial association between linoleic acid intake and cancer risk exists, it is unlikely that virtually all analytic studies would fail to find such an association purely because of methodologic limitations. However, the evidence from these analytic studies cannot exclude the possibility of a small increase in cancer risk with high intakes of linoleic acid.

### Evidence from other types of studies

**Ecologic comparisons**

Ecologic studies compare average cancer rates of countries or regions rather than risks of individuals. Such studies have major
limitations. There are multiple differences between populations that may affect cancer risk and there is no or only a limited possibility to adjust for these confounders. Also, the use of per capita use data to assess dietary intake is questionable, and the quality of mortality or incidence data from national cancer registrations may be different for different countries, which may bias the associations. Nevertheless, ecologic comparisons offer the advantage of involving large differences in intake between populations. Furthermore, some ecologic comparisons assess intake by aggregating individual intake data and in this way eliminate random dietary measurement error. Two ecologic comparisons that assessed intake by aggregating individual intake or biomarker data showed no association between linoleic acid and cancer risk despite large differences in linoleic acid intake (79) (Figures 3 and 6). Studies that assessed linoleic acid intake from per capita use data indicated that saturated and animal fats rather than polyunsaturated fat or linoleic acid may play a role in increased cancer risk. Thus, the ecologic comparisons we analyzed did not suggest a major influence of linoleic acid on the risk of breast or colorectal cancer.

**Controlled trials of high–linoleic acid diets**

Controlled trials that were designed to study the effects of linoleic acid on CAD did not show an increased number of cancer cases in groups of subjects that consumed high amounts of linoleic acid (16% of energy intake) for 1–7 y. These trials involved mostly men and therefore provide no information on breast cancer. Also, the number of cases was small and the exposure period may have been too short to show any effect of linoleic acid intake on cancer incidence. Thus, the strength of the evidence from controlled trials of high–linoleic acid diets is limited. Nevertheless, except for 1 trial (17), the findings do not support the hypothesis that a high linoleic acid intake increases cancer risk.

**Animal experiments**

The relevance of short-term experiments in animals with artificially induced tumors to the development of human cancers over decades is unclear. Profound and consistent effects of linoleic acid on initiation of tumorigenesis have not been shown (82). Linoleic acid promotes tumor growth in rodents only under certain conditions and in certain models (129, 175). For example, breast tumors induced by hormones were less responsive to dietary fat than were those induced by chemicals (176), and dietary fat increased colorectal tumor growth in 1 strain of laboratory rats but not in another (135). Nevertheless, there appears to be a minimum required intake of linoleic acid for tumor development in rodents. However, this requirement is about as low or lower than intakes recommended to prevent deficiency of essential fatty acids, and reducing linoleic acid intake to below these amounts is neither realistic nor desirable. We feel that experiments in rodents are of limited value for addressing the question of whether a life-long high intake of linoleic acid increases the risk of spontaneous cancers in humans.

**Implications**

The available evidence does not suggest that a high intake of linoleic acid substantially raises the risk of breast, colorectal, or prostate cancer. Nevertheless, a small increase in risk cannot be excluded. When applied to the total population, a small increase in risk may still have a large effect on public health. For example, an increase in breast cancer risk of 10% would increase the number of breast cancer cases occurring in the United States each year by ~18 000 (177). A relevant question for public health policy is whether a possible adverse effect of linoleic acid would be outweighed by beneficial effects on CAD risk. Replacement of saturated fatty acids with oleic acid instead of linoleic acid would also reduce CAD risk and at the same time avoid worries about any possible increase in cancer risk; however, it is not clear whether oleic acid is as effective as linoleic acid in improving the serum lipid profile and reducing CAD risk (15, 178). Therefore, future studies should determine the benefit of linoleic acid compared with that of oleic acid on CAD risk. If such studies show that linoleic acid and oleic acid have similar effects on CAD risk, then it may still be prudent to restrict linoleic acid intake. However, the currently available evidence does not provide a compelling argument for such a restriction.

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**REFERENCES**


**TABLE 2**

Summary of the evidence concerning the relation between linoleic acid intake and cancer risk

<table>
<thead>
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<th>Cancer site</th>
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<td>Cohort study</td>
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<td>Controlled clinical trials on</td>
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<td>Animal studies</td>
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*+, inconsistent positive association; =, no association; NA, not available.

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