Linoleic acid intake and cancer risk: a review and meta-analysis

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. Am J Clin Nutr 1998;68:142–53.

KEY WORDS  Linoleic acid, n–6 polyunsaturated fat, carcinogenesis, tumors, breast cancer, colon cancer, rectal cancer, prostate cancer, risk factors, humans, meta-analysis

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 concentra-

See corresponding editorial on page 5.

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acid (cancer risk, risk was not increased with high intakes of linoleic fat). We were able to extract a quantitative estimate of breast cancer risk for each extra 45 g/d. In a model that included all 3 types of fat, the relative risks for high compared with low polyunsaturated fat intake were 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

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 buttock 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

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.
Cancer incidence or mortality (69–73). Some studies suggest that
Ecologic comparisons between populations

data are limited.

1.69 (95% CI: 1.02, 2.78) for each 5-g/d increase in intake of
59). The new analysis applied a mutual adjustment for intakes of
of the Swedish Mammography Screening cohort (68). An earlier

tumor progression, but the

In an Australian study (65), the relative risk of death of 412

relatively high intakes of linoleic acid in prospective cohort studies. The pooled
study by Willett et al (58) refers to estimates from the Nurses’
77) estimated that a 50% reduction in both saturated

FIGURE 2. Relative risks of breast cancer with high compared with
low intakes of linoleic acid in prospective cohort studies. The pooled
estimate was derived from the study by Hunter et al (59). Bars are 95% Cis. The study by Willett et al (58) refers to estimates from the Nurses’
Health study: A, follow-up from 1980 to 1986; B, follow-up from 1986 to

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 polysaturated 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 polysaturated 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 polysaturated 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
polysaturated 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 polysatur-
ated 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 corre-
lations 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 satu-
rated fats rather than to the use of vegetables or polysaturated
fats (72, 74–76), but others show positive associations of breast
cancer rates with the use of polysaturated 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 polysaturated fat; in contrast, Pre-
tice et al (3, 77) estimated that a 50% reduction in both saturated
and polysaturated 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 north-
ern Europe, whose intakes were probably 4–7% of energy.
The breast cancer rate in the Israeli women may have been addi-
tionally 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 pro-
motion stage, but less so during the initiation stage (for a review
see reference 82). In rats, a diet rich in polysaturated 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
polysaturated fats (87–90). On the other hand, in experiments

FIGURE 3. Breast cancer incidence in 11 European regions and
Israel by the average linoleic acid content of adipose tissue in 40–164
healthy subjects in the corresponding regions [control subjects from the
EURAMIC (European Community Multicenter Study on Antioxidants,
Myocardial Infarction, and Breast Cancer) study (79)].
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 by 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-
nations. Bars are 95% CIs.

Average linoleic acid intake ranged from 8 g/d in Japan, Rome, and eastern Finland to 22 g/d in Belgrade, Serbia (Figure 6). Mortality from colorectal cancer was not associated with linoleic acid intake. Adjustment for dietary fiber and energy intakes did not change this result. Mortality from all cancers was also not associated with linoleic acid intake. Adjustment for dietary fiber and energy intakes did not change this result. Mortality from all cancers was also not associated with linoleic acid intake.

Animal studies

Results from animal experiments that studied the effect of dietary fat on artificially induced colon cancer varied with the model and methods used (for review see references 128 and 129). Diets high in polyunsaturated fat promoted tumor growth in rats after initiation of the tumors, but not during the initiation stage (130). Some studies in rats indicated that polyunsaturated n-6 fatty acids promote the growth of chemically induced colon tumors more so than do saturated fatty acids (23, 131, 132), but others showed no difference (133) or found that n-6 fatty acids promote tumor growth less so than do saturated fatty acids (134). In a meta-analysis of 14 rat studies (135), total fat intake adjusted for energy intake increased tumor growth in Fischer 344 rats, but not in Sprague-Dawley rats. In Fischer 344 rats, both n-6 polyunsaturated and saturated fats increased tumor growth more so than did monounsaturated or n-3 polyunsaturated fats (135). The minimum amount of dietary essential fatty acids needed to induce colon tumors in rats is ≈1% of energy (136), which is much lower than the 4.5% of energy needed to induce breast tumors (88). In mice, increasing amounts of dietary linoleic acid stimulated growth of transplanted colonic adenocarcinoma tumors up to 4% of energy intake, but not at higher intakes (137). Thus, there is some evidence that n-6 polyunsaturated fat promotes the growth of artificially induced colorectal tumors in rodents, but the data are inconsistent.

Prostate cancer

Analytic studies within populations

Case-control studies. Case-control studies of the relation between dietary fat and prostate cancer generally show a positive relation with total fat intake (for review see reference 138), but few studies collected data on specific fatty acids. For the 3 case-control studies from which we were able to extract quantitative estimates of risk (139–141), involving a total of 654 cases and 924 control subjects, we calculated a combined relative risk of prostate cancer of 1.27 (95% CI: 0.97, 1.66) with high compared with low intakes of polyunsaturated fat (Figure 7). One study found an increased risk with high polyunsaturated fat intake in older men, but not in younger men (139). Another study found an increased risk with a 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 according to a food-frequency questionnaire, but not according to the proportion of linoleic acid in red blood cells (115). Thus, the limited amount of data from case-control studies show either no or positive associations between linoleic acid intake and prostate cancer risk.

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
of ies found an increased risk of prostate cancer with higher intakes 62 771 men, was 0.83 (95% CI: 0.56, 1.24). However, both stud-

risk, involving a total of 399 cases of prostate cancer among 62 771 men, was 0.83 (95% CI: 0.56, 1.24). However, both stud-
ies found an increased risk of prostate cancer with higher intakes of α-linolenic acid (18.3 n−3). Thus, these cohort studies suggest that prostate cancer risk may be associated with α-linolenic acid, but not with linoleic acid.

**Ecologic comparisons between populations**

Population comparisons show positive associations between total fat disappearance and mortality or incidence rates of prostate cancer (3, 71, 78, 147, 148). One study suggested that this association was due to animal rather than to vegetable fat (75), but others showed positive associations with both saturated and polyunsaturated fats (3, 78). Thus, there is some, but inconsistent, evidence from population comparisons that linoleic acid may be associated with prostate cancer risk.

**Animal studies**

There are few animal models for the study of prostate cancer (149). In 1 study of a genetically susceptible strain of rats treated with testosterone, animals consuming a diet to which corn oil had been added up to a level of 40% of energy from total fat spontaneously developed prostate tumors, whereas animals consuming a control diet with 10% of energy from fat did not (150). In another study of chemically induced prostate tumors in testosterone-treated rats, the amount or type of fat in the diet had no effect on tumor growth (151). Thus, animal experiments do not provide much evidence for a possible link between linoleic acid and prostate cancer risk.

**Cancer cases in controlled trials of diets high in linoleic acid**

Diets high in linoleic acid (> 12% of energy intake) have been used in intervention trials to determine their possible relation to CAD (Table 1). These trials may show whether a higher than normal incidence of cancer occurs when people consume high amounts of linoleic acid for 1–7 y.

Men in the Los Angeles Veterans Administration trial (17, 157) who consumed a diet high in linoleic acid (14% of total energy) for 6.5 y had higher cancer mortality than men who consumed the standard institutional diet, which was high in satu-

**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 underre-
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 $\approx 5$ 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

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**TABLE 1**

Cancer incidence in clinical trials of high–linoleic acid diets and coronary artery disease in men

<table>
<thead>
<tr>
<th>Study</th>
<th>Linoleic acid intake</th>
<th>Duration of study (diet + follow-up)</th>
<th>Number of cancer cases</th>
<th>Relative risk (95% Cl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of energy</td>
<td></td>
<td>Experimental</td>
<td>Control</td>
</tr>
<tr>
<td>Oslo Diet-Heart Study (153)</td>
<td>20.7</td>
<td>5 + 6</td>
<td>10/206</td>
<td>7/206</td>
</tr>
<tr>
<td>Medical Research Council soybean oil (154)</td>
<td>17.0</td>
<td>4.5 + 3</td>
<td>2/199</td>
<td>8/194</td>
</tr>
<tr>
<td>Finnish Mental Hospital (155)</td>
<td>12.0</td>
<td>6</td>
<td>4/327</td>
<td>4/254</td>
</tr>
<tr>
<td>Faribault (156)</td>
<td>17.4</td>
<td>1.5 + 5</td>
<td>1/167</td>
<td>1/57</td>
</tr>
<tr>
<td>Los Angeles Veterans (157)</td>
<td>13.8</td>
<td>6.5 + 2</td>
<td>67/424</td>
<td>52/422</td>
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<tr>
<td>Combined</td>
<td>16.2</td>
<td>5 + 3</td>
<td>84/1323</td>
<td>72/1133</td>
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</tbody>
</table>

1 Adapted from the study by Ederer et al (152), who estimated a combined relative risk of 1.15 (95% CI: 0.81, 1.63) by the method of Gart (158).
2 High compared with low linoleic acid intakes.
3 Mean.
4 Crude risk ratio of the pooled data.

**Crude risk ratio of the pooled data.**
dietary fat than were those induced by chemicals (176), and certain conditions and in certain models (129, 175). For example, linoleic acid promotes tumor growth in rodents only under certain conditions and in certain models (129, 175). Nevertheless, except for 1 trial (17), the findings do not support the hypothesis that a high linoleic acid intake increases breast cancer risk. 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 breast 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.

We thank E Feskens, D Kromhout, and M Jansen for providing data from the Seven Countries Study, and N Boyd, L Holmberg, G Howe, D Hunter, R Kaaks, P Toniolo, and A Wolk for supplying additional information about their studies.

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**TABLE 2**

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

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<td>Within-population studies (combined relative risk)</td>
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</tr>
<tr>
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1 +/-, inconsistent positive association; =, no association; NA, not available.

**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.

**Implications**

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