Intakes of fish and marine fatty acids and the risks of cancers of the breast and prostate and of other hormone-related cancers: a review of the epidemiologic evidence

Paul D Terry, Thomas E Rohan, and Alicja Wolk

ABSTRACT

Marine fatty acids, particularly the long-chain eicosapentaenoic and docosahexaenoic acids, have been consistently shown to inhibit the proliferation of breast and prostate cancer cell lines in vitro and to reduce the risk and progression of these tumors in animal experiments. However, whether a high consumption of marine fatty acids can reduce the risk of these cancers or other hormone-dependent cancers in human populations is unclear. Focusing primarily on the results of cohort and case-control studies, we reviewed the current epidemiologic literature on the intake of fish and marine fatty acids in relation to the major hormone-dependent cancers. Despite the many epidemiologic studies that have been published, the evidence from those studies remains unclear. Most of the studies did not show an association between fish consumption or marine fatty acid intake and the risk of hormone-related cancers. Future epidemiologic studies will probably benefit from the assessment of specific fatty acids in the diet, including eicosapentaenoic and docosahexaenoic acids, and of the ratio of these to n-6 fatty acids, dietary constituents that have not been examined individually very often. Am J Clin Nutr 2003;77:532–43.

KEY WORDS n-3 Fatty acids, n-6 fatty acids, breast cancer, prostate cancer, endometrial cancer, ovarian cancer, hormone-dependent cancers, sex hormones, prostaglandins, eicosapentaenoic acid, docosahexaenoic acid

INTRODUCTION

Environmental factors, including those related to diet, are believed to contribute significantly to the etiology of many forms of cancer. This hypothesis is often underscored by observed differences in cancer incidence rates across regions, temporal changes in incidence rates within regions, and changes in incidence rates among persons who have migrated from one region to another. On the basis of these patterns, environmental factors appear to play important roles in the development of cancers of the breast and prostate and of other hormone-dependent cancers (1–6). For example, the rising incidence rates of breast and prostate cancers in several countries that previously were considered to have low incidence rates (7–10) appear to be coincident with the adoption of a Western lifestyle in those populations, implicating factors such as low levels of physical activity, high relative body weight, and high dietary fat intake.

Dietary fat intake is among the most widely studied dietary risk factors for breast and prostate cancers; yet its roles in influencing endogenous sex hormone concentrations (11–15) and cancer risk (16, 17) remain unclear. In recent years, increasing attention has been paid to the intake of specific fatty acids (18) rather than total fat intake, and notable among these have been marine fatty acids. Long-chain eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3), which are polyunsaturated n-3 fatty acids contained primarily in fatty fish, have been shown consistently to inhibit the proliferation of breast and prostate cancer cell lines in vitro and to reduce the risk and progression of these tumors in animal experiments (19, 20). Various biological mechanisms have been proposed to explain these findings, eg, enhanced metabolism of estradiol to inactive catechol estrogens (21) in the case of breast cancer and a reduction in circulating testosterone concentrations (15) in the case of prostate cancer. However, whether a high intake of marine fatty acids can lower the risk of these cancers in human populations remains to be determined.

Our aim in the present article was to review the current epidemiologic literature on fish consumption and marine fatty acid intake and the risks of cancers of the breast and prostate and of other hormone-dependent cancers (endometrium and ovary). Toward this end, we obtained relevant articles through searches of the MEDLINE (National Library of Medicine, Bethesda, MD) and CANCERLIT (National Cancer Institute, Bethesda, MD) databases in which we used various keywords, such as “fatty acids, omega-3,” “diet,” and “prostaglandins” and terms for various malignancies. We obtained additional published reports by cross-matching the references of relevant articles. Virtually all published reports are in the English language and we restricted our review to those articles. We excluded studies in which fish consumption was reported only in terms of mean intakes (22–25).

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FISH, MARINE FATTY ACIDS, AND CANCER

TABLE 1
Prospective cohort studies of fish or fish oil consumption and breast cancer risk

<table>
<thead>
<tr>
<th>Reference</th>
<th>n Cases</th>
<th>Follow-up</th>
<th>Exposure</th>
<th>Country</th>
<th>Per capita n−3 intake</th>
<th>Per capita n−6 intake</th>
<th>Comparison</th>
<th>RR(^{4})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gertig et al (35)</td>
<td>453 [462]</td>
<td>8</td>
<td>Total fish</td>
<td>United States</td>
<td>0.10</td>
<td>0.003</td>
<td>&gt;0.5 compared with ≤0.14 servings/d</td>
<td>1.3 (0.7, 2.6)</td>
</tr>
<tr>
<td>Holmes et al (36)</td>
<td>2956 [88795]</td>
<td>14</td>
<td>n−3 Fatty acids Dietetic EPA Dietary DHA</td>
<td>United States</td>
<td>0.10</td>
<td>0.003</td>
<td>0.1% of energy/d (continuous) 0.03% of energy/d (continuous) 0.03% of energy/d (continuous)</td>
<td>1.1 (1.0, 1.1)</td>
</tr>
<tr>
<td>Key et al (37)</td>
<td>427 [34759]</td>
<td>14.1</td>
<td>Dried fish</td>
<td>Japan</td>
<td>1.5</td>
<td>0.08</td>
<td>≥5 compared with ≤1 serving/wk ≥5 compared with &lt;1 serving/wk</td>
<td>0.8 (0.6, 1.0)</td>
</tr>
<tr>
<td>Lund and Bonaa (38)</td>
<td>3995 [533276]</td>
<td>15</td>
<td>Married to a fisherman</td>
<td>Norway</td>
<td>0.40</td>
<td>0.01</td>
<td>Fishermen’s wives compared with wives of nonfishermen</td>
<td>0.7 (0.5, 0.9)</td>
</tr>
<tr>
<td>Stampfer et al (39)</td>
<td>601 [89538]</td>
<td>4</td>
<td>Total fish</td>
<td>United States</td>
<td>0.10</td>
<td>0.003</td>
<td>≥2 servings/wk compared with ≤1 serving/mo</td>
<td>1.1 (0.5, 2.4)</td>
</tr>
<tr>
<td>Toniolo et al (40)</td>
<td>180 [900]</td>
<td>3.8</td>
<td>Total fish</td>
<td>United States</td>
<td>0.10</td>
<td>0.003</td>
<td>Highest compared with lowest quintile</td>
<td>1.0 (0.6, 1.7)</td>
</tr>
<tr>
<td>Vatten et al (41)</td>
<td>152 [14500]</td>
<td>12.5</td>
<td>Fish as part of main meal Poached fish</td>
<td>Norway</td>
<td>0.40</td>
<td>0.01</td>
<td>≥2 compared with &lt;2 times/wk ≥5 compared with ≤2 servings/mo</td>
<td>1.2 (0.8, 1.7)</td>
</tr>
</tbody>
</table>

\(^{1}\)RR, relative risk; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid. \\
\(^{2}\)Total n in brackets. \\
\(^{3}\)From Hursting et al (42), on the basis of food disappearance data. \\
\(^{4}\)95% CI in parentheses. \\
\(^{5}\)A nested case-control study. \\
\(^{6}\)Significant test for trend, P < 0.05. \\
\(^{7}\)The outcome was breast cancer mortality.

In interpreting the results of epidemiologic studies to date, we focused on how exposure was measured or reported. Regarding fish consumption, the concentrations of EPA and DHA in fish oil vary between fish species (26), with relatively high concentrations found in fatty species native to cold waters, such as salmon, mackerel, sardines, and herring, and relatively low concentrations in lean fish, such as sole, halibut, and cod. The interpretation of “total fish consumption” in epidemiologic studies can therefore be problematic, because the absolute and relative amounts of fatty acids reflected in this measure vary greatly among populations.

**Ecologic studies of breast and prostate cancers**

Cross-national studies showed inverse associations between per capita consumption of fish and the incidence of and mortality rates from prostate (27, 28) and breast cancer (29–33). Within populations, such as those living in Japan (10), Iceland (7), Alaska (8), and Greenland (9), reductions over time in the relative contribution of fish to total fat intake have coincided with increased incidence rates of hormone-dependent cancers. Although not without merit, ecologic studies, which are based on comparisons between or within populations, suffer from important limitations, including the fact that variations in exposure at the population level do not always correspond to variations among persons within any given population and the lack of adjustment for potentially confounding factors (34). Hence, our focus in this review is on analytic epidemiologic studies, namely, cohort and case-control studies comparing persons with high and low consumption within populations.

**Analytic studies of hormone-related cancers**

Most of the epidemiologic studies on fish consumption or marine fatty acid intake and cancer risk that have been published to date used the case-control design. Case-control studies have several limitations, including their vulnerability to certain biases. Because participants are selected on the basis of disease status, differential participation with respect to exposure could spuriously drive a study’s results toward or away from a null association. For example, a lower degree of participation among potential control subjects who do not eat fish could bias results toward a spurious inverse association. Case-control studies are also vulnerable to recall bias, such as might occur if case subjects systematically recall less fish consumption than do control subjects, which would also bias results toward a spurious inverse association. The problems of unbiased selection and recall are minimized or avoided by using the prospective cohort study design. However, cohort studies are not without limitations. For example, changes in diet during follow-up can lead to the misclassification of long-term exposure if, as has generally been the case, exposure is not updated after the baseline assessment. Because nondifferential misclassification can attenuate any association that may exist, random changes in diet over time would tend to mask a true association between fish consumption and cancer risk. Cohort studies can also be limited by losses to follow-up, because assumptions regarding the lack of bias due to systematic losses must be made.

**BREAST CANCER**

**Prospective cohort studies**

The results of 7 prospective cohort studies (35–41) that examined the association between fish consumption or marine fatty acid intake and breast cancer risk are shown in Table 1. Of these, 4 studies in the United States, a country with relatively low per
capita intake of n-3 fatty acids (42), found no association between fish consumption (35, 39, 40) or marine fatty acid intake (36) and breast cancer risk. One study in Japan (37) found that women who consumed ≥5 servings of undried or dried fish/wk had a 10% or 20% lower risk, respectively, than did women who consumed ≤1 serving/wk. In a Norwegian study (41), women who consumed ≥5 servings of poached fish/mo (salmon is often poached) had a 30% lower risk than did those who ate poached fish ≤2 times/mo, although the latter may have consumed fish cooked by methods other than poaching. In that study, there was no association observed with total fish consumption. Finally, in another study in Norway (38), fisherman’s wives had 30% lower mortality from breast cancer than did the wives of men who were not employed as fishermen, and this finding was significant. For this finding to be consistent with an association between fat intake and breast cancer risk, however, the assumption must be made that the wives of fishermen ate more fish than did those in the comparison group, because fish consumption was not measured. The results of this study may also have been influenced by confounding; for example, the wives of the fishermen may have been different from those in the comparison group with respect to lifestyle or dietary risk factors other than fish consumption.

It is perhaps noteworthy that the 3 studies that showed an inverse association with fish consumption were in Japan and Norway, countries with relatively high consumption of n-3 fatty acids (42). In contrast, the per capita consumption of n-3 fatty acids in the United States, where the null studies were conducted, is ≈1/4th that in Norway and ≈1/15th that in Japan. It may also be noteworthy that 3 of the 4 null studies also had relatively short follow-up periods (Table 1).

Case-control studies

The results of 19 case-control studies (43–61) that examined the association between fish consumption or marine fatty acid intake and breast cancer risk are shown in Table 2. These studies were conducted in many different geographic areas, and as with the cohort studies, their results were mixed. Approximately two-thirds of these studies (43–45, 47–49, 51–55, 57, 58, 60) examined total fish or seafood consumption without accounting for the type of fish consumed. Of these, no clear association between total fish consumption and breast cancer risk was observed in 1 study in the United States (43), 2 studies in Italy (45, 60), 1 study in Uruguay (44), 1 study in China (58), and 2 studies in Singapore (53, 54). The null studies have several features in common, including a mostly (with the possible exception of China) low per capita intake of n-3 fatty acids in the studied populations and narrow or unclear ranges of exposure. Two studies in Canada, a country with a relatively low per capita intake of n-3 fatty acids (42), showed mixed results with total fish consumption (48, 49): significant inverse associations were evident only for premenopausal women (48) and women with tumors that were negative for estrogen receptors (49). These findings among subgroups defined by menopausal status and estrogen receptor status may have been due to chance. Mixed results were also observed in 2 studies in Argentina (50; both based on the same case series), suggesting an inverse association with fish, but not with seafood per se. Of the 4 remaining case-control studies that examined only total fish consumption, one small study in Switzerland (55) found that women in the highest tertile of consumption had a 30% lower risk than did those in the lowest tertile, another small study in Spain (52) found that women in the highest tertile of consumption had a 70% lower risk than did those in the lowest tertile (neither of these 2 studies included CIs), and 2 studies in Japan (47, 51) showed a weak inverse association (47) and a null association (51), respectively. Both Spain and Japan have relatively high per capita intakes of n-3 fatty acids (42).

Five case-control studies (46, 50, 57, 59, 61) examined dietary measures of exposure other than total fish consumption in relation to breast cancer risk (Table 2). Of these, 2 studies (46, 59) examined associations for lean and fatty fish consumption separately. No associations were observed in a case-control study in the United States (46), in which actual intakes were not specified. The intake of fatty fish in that study’s population was apparently low because division of the data into quartiles was only possible with lean fish consumption. In a study in Sweden (59), a country with a relatively high consumption of fatty fish (42), subjects who consumed > 3.5 servings of lean or fatty fish/wk had a 20% and 30% lower risk, respectively, than did those who consumed ≤0.5 servings/wk, although neither of these differences was significant. The age-adjusted results of that study were not appreciably altered by additional adjustment for relative body weight, height, smoking status, physical activity, consumption of various foods and alcohol, history of benign breast disease, parity, age at menarche, age at menopause, age at first delivery, and the use of exogenous hormones, suggesting that these dietary and lifestyle factors are not strong confounding variables in this association.

Two case-control studies (57, 61) examined dietary intake of n-3 fatty acids in relation to breast cancer risk (Table 2); one of these studies, which was conducted in Finland (57), reported 2 sets of results based on the same cases but different control series. In that study, intake of n-3 fatty acids was inversely associated with risk when cases were compared with controls who were sampled either from the general population or from women referred for screening; the latter comparison yielded a significant association. It is perhaps noteworthy that the inverse associations with n-3 fatty acids in this Finnish study were stronger than those with total fish consumption, which serves to highlight the limitations of studies that assessed only total fish consumption. Dietary DHA and EPA were both inversely associated with risk in a small study in Finland (61), which also found an inverse association with adipose DHA (Table 3).

Seven case-control studies examined the association between n-3 fatty acids in adipose tissue (61–65) or serum phospholipids (66, 67) and breast cancer risk (Table 3). In a study in Sweden (62), a relatively high concentration of EPA in serum phospholipids was associated with a halving of breast cancer risk (although the CIs included unity), whereas DHA and the ratio of EPA to linoleic acid (18:2n-6) both showed weaker associations with risk. Two studies in the United States (62, 64) found essentially no association between adipose tissue marine fatty acids and breast cancer risk. In a study in France (64), both adipose DHA and the ratio of total n-3 to n-6 fatty acids in adipose tissue were strongly inversely associated with risk. A study in Finland (61) found a significant inverse association with adipose tissue DHA, but not EPA, although the sample size of this study was very small. These findings are consistent with those from a small study in Norway (67), which found that women with the highest serum phospholipid DHA concentrations had a moderately but non-significantly lower risk of breast cancer than did those with the lowest concentrations, but that breast cancer risk was only weakly associated with EPA. In a multicenter study (66), total n-3 fatty acid concentrations were associated with a lower risk of breast cancer than were the individual n-3 fatty acids, consistent with the results from a recent meta-analysis (68). A significant inverse association with EPA was seen in a meta-analysis of 11 studies (69).
acid concentrations in adipose tissue were not significantly associated with breast cancer risk, and adipose EPA and DHA concentrations were inversely associated with risk, albeit only weakly. In this study, the women in the highest tertile of n-3/n-6 fatty acids had a 30% lower risk than did the women in the lowest tertile, suggesting that the intake of n-3 fatty acids relative to that of n-6 fatty acids may be a more relevant measure of exposure with respect to breast cancer risk than either group of fatty acids examined independently. Indeed, evidence from in vivo studies suggests that the modulation of eicosanoid biosynthesis depends more on the ratio of these fatty acid groups than on their absolute concentrations (19).

**PROSTATE CANCER**

**Prospective cohort studies**

The results of 8 prospective cohort studies that examined the association between either dietary intakes of fish or marine fatty acids (68–74) or serum (75) or plasma (69) fatty acid concentrations...
TABLE 3
Case-control studies of marine fatty acid concentrations in adipose tissue and serum and breast cancer risk1

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Cases</th>
<th>Controls</th>
<th>Exposure</th>
<th>Country</th>
<th>Per capita n−3 intake2</th>
<th>Per capita n−6 intake2</th>
<th>Comparison</th>
<th>OR†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>g/d</td>
<td>g/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chajes et al (62)</td>
<td>196</td>
<td>388</td>
<td>Serum phospholipid n−3</td>
<td>Sweden</td>
<td>0.50</td>
<td>0.03</td>
<td>Highest compared with lowest quartile</td>
<td>0.6 (0.3, 1.3)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Serum phospholipid EPA</td>
<td></td>
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<td></td>
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<td>Serum phospholipid DHA</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Serum phospholipid EPA/LA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>London et al (63)</td>
<td>402</td>
<td>597</td>
<td>Adipose EPA</td>
<td>United States</td>
<td>0.10</td>
<td>0.003</td>
<td>Highest compared with lowest quintile</td>
<td>0.7 (0.4, 1.1)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Adipose DHA</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Maillard et al (64)</td>
<td>241</td>
<td>88</td>
<td>Adipose DHA</td>
<td>France</td>
<td>0.28</td>
<td>0.01</td>
<td>Highest compared with lowest tertile</td>
<td>0.3 (0.1, 0.8)‡</td>
<td></td>
</tr>
<tr>
<td>Petrek et al (65)</td>
<td>154</td>
<td>125</td>
<td>Adipose n−3/n−6</td>
<td>United States</td>
<td>0.10</td>
<td>0.003</td>
<td>Highest compared with lowest quintile</td>
<td>1.2 (0.6, 2.3)</td>
<td></td>
</tr>
<tr>
<td>Simonsen et al (66)</td>
<td>291</td>
<td>351</td>
<td>Adipose total n−3</td>
<td>Multicenter</td>
<td>—</td>
<td>—</td>
<td>Highest compared with lowest tertile</td>
<td>1.1 (0.6, 2.1)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Adipose long-chain n−3</td>
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<td></td>
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<td></td>
<td>Adipose n−3/n−6</td>
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<td></td>
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<tr>
<td>Vatten et al (67)</td>
<td>87</td>
<td>235</td>
<td>Serum phospholipid n−3</td>
<td>Norway</td>
<td>0.40</td>
<td>0.01</td>
<td>Highest compared with lowest tertile</td>
<td>0.7 (0.4, 1.0)</td>
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<td></td>
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<td>Serum phospholipid EPA</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Zhu et al (61)</td>
<td>73</td>
<td>55</td>
<td>Adipose EPA</td>
<td>Finland</td>
<td>0.37</td>
<td>0.02</td>
<td>No significant differences</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adipose DHA</td>
<td></td>
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</tbody>
</table>

1 OR, odds ratio; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; LA, linoleic acid.
2 From Hursting et al (42), on the basis of food disappearance data.
3 From Hursting et al (42), on the basis of food disappearance data.
4 OR, odds ratio; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; LA, linoleic acid.
5 95% CI in parentheses.
6 Significant test for trend, P < 0.05.
7 As proportion of total fat.
8 For postmenopausal women only.

and prostate cancer risk are shown in Table 4. No clear differences between cases and controls were observed in serum concentrations of total n−3 and n−6 fatty acids in a very small study in the United States (75). In the large Health Professionals’ Follow-up Study (68), strong, significant inverse associations were observed between intake of fish and marine fatty acids and metastatic prostate cancer. In an earlier study from the same cohort (70), with considerably fewer cases, intake of n−3 fatty acids from fish was inversely associated with the risk of advanced prostate cancer, but the association was weak (P = 0.30). In a study that examined data from the Swedish Twin Registry (74), total fish consumption (presumed on the basis of national dietary patterns to contain a high proportion of fatty fish) was inversely associated with prostate cancer incidence and mortality. Although this study had a very long follow-up period (up to 30 y), the assessment of fish consumption was qualitative (no absolute intakes were obtained) and dietary information was not reassessed after the data were collected at baseline. Adjustment for the potentially confounding effects of red meat and processed meat did not alter the findings of that study, although it is important to note that increased fish consumption was inversely associated with the consumption of other meats. In contrast with the studies showing inverse associations with prostate cancer risk, a small cohort study in Hawaii found no association with total fish consumption (73); nor was an association observed with plasma EPA in a small case-control study nested within the Physicians’ Health Study (69). In the Netherlands Cohort Study, neither total fish consumption (72) nor the intake of EPA or DHA (71) was associated with risk.

Case-control studies
The results of 9 case-control studies (45, 76–83) that examined the association between prostate cancer risk and either marine fatty acid intake or marine fatty acid concentrations in adipose tissue, erythrocyte membranes, or serum are shown in Table 5. Of these, 4 studies (45, 76, 79, 83) examined a measure of total fish or total seafood consumption, and each study found a significant (76, 79) or nonsignificant (45, 83) inverse association with prostate cancer risk. One study in Poland also found significant inverse associations with the consumption of smoked fish and fried fish (82). Three studies examined EPA and DHA concentrations in erythrocyte membranes (77, 80, 81), and one of these studies, which was a small case-control study in the United States (77), also examined concentrations in adipose tissue. That study found a nonsignificant inverse association with adipose EPA but not DHA, although both erythrocyte EPA and DHA concentrations (especially the latter) were associated inversely but not significantly with risk. In contrast, erythrocyte EPA and DHA concentrations were not associated with risk in another small study in the United States (80), whereas a much larger study in New Zealand (81) found significant inverse associations with both of these measures. Serum concentrations of marine fatty acids were not clearly associated with prostate cancer risk in a small case-control study in Norway (78).

OTHER HORMONE-DEPENDENT CANCERS
Because marine fatty acids may lower the risk of cancer through sex hormone-mediated processes, the examination of fish
risk (odds ratio: 0.6; 95% CI: 0.5, 0.8; 43). Fish intake was strongly, inversely associated with endometrial cancer risk. In the most recent of these studies (90), which examined the association between fish consumption and endometrial cancer risk, consumption of fatty fish, total fish consumption was only weakly associated with risk (odds ratio: 1.0; 95% CI: 0.8, 1.3; 249). Contrast, consumption of lean fish was not associated with risk (odds ratio: 0.9; 95% CI: 0.6, 1.0; 43). Although the study population had a relatively high consumption of fatty acids, the detail and quality of the exposure, the potential for confounding by other factors, the need for separate analyses according to the type of fish consumed or examined the intake of specific marine fatty acids. The studies also vary greatly with respect to important methodologic factors, such as sample size, adjustment for potentially confounding variables, the detail and quality of the intake of marine fatty acids from fish (94, 95) and Japan (96), but no clear reduction in risk [and perhaps an increase in risk (95, 96)] was observed. However, the 2 remaining studies (92, 93), both of which were conducted in Italy, found inverse associations with total fish consumption. The larger and more recent of these 2 studies (92) found that women in the highest quintile of total fish consumption had a significantly lower (40%) risk of ovarian cancer than did those in the lowest quintile. The absolute intakes of fish represented by the quintiles were not specified.

### DISCUSSION

Many studies examined fish consumption in relation to breast and prostate cancer risk, although only a few accounted for the type of fish consumed or examined the intake of specific marine fatty acids. The studies also vary greatly with respect to important methodologic factors, such as sample size, adjustment for potentially confounding variables, the detail and quality of the intake of marine fatty acids from fish (94, 95) and Japan (96), but no clear reduction in risk [and perhaps an increase in risk (95, 96)] was observed. However, the 2 remaining studies (92, 93), both of which were conducted in Italy, found inverse associations with total fish consumption. The larger and more recent of these 2 studies (92) found that women in the highest quintile of total fish consumption had a significantly lower (40%) risk of ovarian cancer than did those in the lowest quintile. The absolute intakes of fish represented by the quintiles were not specified.

### TABLE 4

Prospective cohort studies examining the association between either fish or marine fatty acid consumption or serum or plasma fatty acid concentrations and prostate cancer risk

| Reference | n Cases | Follow-up | Exposure | Country | Per capita n−3 intake | Per capita n−6 intake | Comparison | OR
|------------|---------|-----------|----------|---------|----------------------|----------------------|------------|-----
| Alberg et al (75) | 43 [86] | — | Total serum n−3 and n−6 fatty acids | United States | 0.10 | 0.003 | No clear differences between cases and controls | — |
| Augustsson et al (68) | 249 [47780] | 10 | Total fish consumption | United States | 0.10 | 0.003 | >3 servings/wk compared with infrequent | 0.5 (0.3, 0.8) |
| Gann et al (69) | 120 [120] | 6 | Plasma EPA | United States | 0.10 | 0.003 | Highest compared with lowest quartile | 0.9 (0.4, 1.8) |
| Giovannucci et al (70) | 126 [47855] | 3.5 | Consumption of n−3 fatty acids from fish | United States | 0.10 | 0.003 | Highest compared with lowest quintile | 0.9 (0.5, 1.6) |
| Schuurman et al (72) | 642 [58279] | 6.3 | Total fish consumption | Netherlands | — | — | Median: 20 compared with 0 g/d | 1.0 (0.8, 1.3) |
| Severson et al (71) | 642 [58279] | 6.3 | Dietary EPA | Netherlands | — | — | Median: 0.10 compared with 0 g/d | 1.0 (0.7, 1.4) |
| Terry et al (74) | 174 [7999] | 17.5 | Total fish consumption | United States | — | — | Median: 0.18 compared with 0.01 g/d | 1.0 (0.8, 1.4) |
| Alberg et al (75) | 43 [86] | — | Total fish consumption | United States | — | — | Median: 0.50 compared with ≤ 1 serving/wk | 1.2 (0.7, 2.0) |

OR, odds ratio; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

1. Total n in brackets.
2. From Hursting et al (42), on the basis of food disappearance data.
3. A nested case-control study.
4. Results reported for metastatic prostate cancers only.
5. Significant test for trend, *P* < 0.05.
6. Results reported for advanced prostate cancers only.
Several mechanisms have been proposed by which the intake of marine fatty acids may lower the risk of cancer. Among the most salient of these is the inhibition of eicosanoid biosynthesis from arachidonic acid (AA; 20:4n-6), an n-6 fatty acid metabolized in the body from linoleic acid. Eicosanoids are a class of compounds derived from polyunsaturated acids and include prostaglandins, hydroxyeicosatetraenoic acids, and leukotrienes. Prostaglandins are oxygenated, unsaturated cyclic fatty acids that perform a variety of hormone-like actions. Those converted from AA by the cyclooxygenase-2 (EC 1.14.99.1) enzyme, notably AA-derived PGE2, which may impede immune system function, possibly through its role in the generation of suppressor T cells (99–101). Marine fatty acids inhibit cyclooxygenase-2 and the oxidative metabolism of AA to PGE3 (19). EPA and DHA also have shown to inhibit lipoygenase (5-, 12-, and 15-lipoxygenase; EC 1.13.11.34, 1.13.11.31, and 1.13.11.33, respectively), which metabolizes AA to hydroxyeicosatetraenoic acids and leukotrienes. 12-Hydroxyeicosatetraenoic acid has been linked to modulation of oncogene expression (19, 104), formation of cytotoxic peroxidation products (19, 105, 106), inhibition of mitosis (107), promotion of insulin resistance (108), and modification of estrogen metabolism (21). Regarding the latter, estrogen can be metabolized along 2 major pathways, to 16-hydroxyestrone or 2-hydroxyestrone. 16-hydroxyestrone is considered to be the second most important metabolite of estrogen (109). 

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Cases</th>
<th>Controls</th>
<th>Exposure</th>
<th>Country</th>
<th>EPA</th>
<th>DHA</th>
<th>Comparison</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ewings and Bowie (76)</td>
<td>159</td>
<td>164</td>
<td>Total fish consumption</td>
<td>United Kingdom</td>
<td>0.13</td>
<td>0.006</td>
<td>Type of meat usually consumed</td>
<td>0.0 (0.0, 0.6)</td>
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<tr>
<td>Fernandez et al (45)</td>
<td>127</td>
<td>7990</td>
<td>Total fish consumption</td>
<td>Italy</td>
<td>0.12</td>
<td>0.005</td>
<td>≥2 compared with &lt;1 serving/wk</td>
<td>0.7 (0.4, 1.1)</td>
<td></td>
</tr>
<tr>
<td>Godley et al (77)</td>
<td>89</td>
<td>38</td>
<td>Adipose EPA Adipose DHA</td>
<td>United States</td>
<td>0.10</td>
<td>0.003</td>
<td>Highest compared with lowest quartile</td>
<td>0.5 (0.2, 1.6)</td>
<td></td>
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<tr>
<td>Harvei et al (78)</td>
<td>141</td>
<td>141</td>
<td>Serum n-3 fatty acids</td>
<td>Norway</td>
<td>0.40</td>
<td>0.01</td>
<td>Highest compared with lowest quartile</td>
<td>1.1 (0.6, 2.1)</td>
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<tr>
<td>Mishina et al (79)</td>
<td>100</td>
<td>100</td>
<td>Total seafood consumption</td>
<td>Japan</td>
<td>1.5</td>
<td>0.08</td>
<td>Regular compared with never or occasional</td>
<td>0.4²</td>
<td></td>
</tr>
<tr>
<td>Newcomer et al (80)</td>
<td>67</td>
<td>156</td>
<td>Erythrocyte membrane EPA Erythrocyte membrane DHA</td>
<td>United States</td>
<td>0.10</td>
<td>0.003</td>
<td>Highest compared with lowest quartile</td>
<td>1.3 (0.6, 3.0)</td>
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</tr>
<tr>
<td>Norris et al (81)</td>
<td>317</td>
<td>480</td>
<td>Erythrocyte membrane EPA Erythrocyte membrane DHA</td>
<td>New Zealand</td>
<td>0.07</td>
<td>0.005</td>
<td>Highest compared with lowest quartile</td>
<td>0.6 (0.4, 1.0)²</td>
<td></td>
</tr>
<tr>
<td>Pawlega et al (82)</td>
<td>76</td>
<td>152</td>
<td>Smoked fish consumption</td>
<td>Poland</td>
<td>—</td>
<td>—</td>
<td>≥1 serving/wk compared with rarely</td>
<td>0.5 (0.2, 0.8)</td>
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<tr>
<td>Talamin et al (83)</td>
<td>271</td>
<td>685</td>
<td>Total fish consumption</td>
<td>Italy</td>
<td>0.12</td>
<td>0.005</td>
<td>Highest compared with lowest tertile</td>
<td>0.8 (0.5, 1.2)</td>
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</tr>
</tbody>
</table>

¹OR, odds ratio; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.
²From Hursting et al (42), on the basis of food disappearance data.
³95% CI in parentheses.
⁴No cases were observed among the men who most often ate fish rather than other types of meat.
⁵Significant test for trend, P < 0.05.
production ratio of 2-hydroxyestrone to 16α-hydroxyestrone and thereby increase cancer risk. However, the link between the ratio of these estrogen metabolites and cancer risk has yet to be clearly established. Nonetheless, it has been noted that even in the absence of altered hormone production or metabolism, enhanced hormonal activity can still result from alterations in the receptor binding capacity of hormones related to tumor growth (eg, prolactin) that occur because of changes in the membrane phospholipid fatty acid composition (103). Several studies focused specifically on DHA and its role in the development of breast and prostate cancers. For example, DHA may activate peroxisome-proliferator activated receptor-γ (114), ligands of which have shown antiproliferative effects in vitro on prostate cancer cell lines (115). DHA also has been shown to improve the response of breast tumors to cytotoxic agents (116).

As mentioned earlier, studies of both cross-national and intra-national secular trends have shown inverse associations between per capita consumption of marine fatty acids and the incidence of and mortality rates from prostate (27, 28) and breast cancer (29–33). Moreover, the shift toward a Western diet usually involves a concurrent decrease in n–3 fatty acid intake and increase in n–6 fatty acid intake, such that observed in Japan over the past several decades (with a concurrent rise in breast cancer incidence) (10). Whereas the intakes of these 2 classes of fatty acids were, for most of human history, similar in quantity (ie, an intake ratio near unity), modern diets now heavily favor the intake of n–6 fatty acids; for example, one cross-national study of food disappearance data (42) estimated the per capita intake ratio of n–3 to n–6 fatty acids in the United States to be ≈0.003, a ratio that is consistent with that observed in adipose tissue concentrations (77). Indeed, the results of several human and animal studies suggest that reductions in epithelial cell proliferation rates, mammary tumorigenesis, and PGE2 biosynthesis can best be achieved with a relatively high intake ratio of n–3 to n–6 fatty acids (eg, >0.5) (117–121), findings that are further supported by data from the large multicenter EURAMIC study of adipose tissue concentrations and breast cancer risk (66). Hence, the processes that ultimately modulate the concentration of tumor growth–enhancing eicosanoids may depend more on the relative concentrations of specific fatty acids in the diet than on their absolute concentrations.

The concentrations of EPA and DHA relative to those of other fatty acids contained in fish vary between species, and relatively high concentrations are found in fatty fish, such as salmon, mackerel, sardines, and herring, species that are generally native to cold waters (19, 26). Lean fish, which typically are native to warmer waters, tend to have lower concentrations of EPA and DHA and may sometimes have higher concentrations of AA (19, 122). For example, a 100-g serving of Pacific herring contains 1.0 g EPA and 0.7 g DHA (19). In contrast, a 100-g serving of haddock contains 0.1 g each of EPA and DHA (19). Thus, different types of fish may have different effects on processes related to cancer development. For studies that examined only total fish consumption in relation to cancer risk, assumptions regarding the type of fish consumed (and, therefore, EPA and DHA intake) can be made from the per capita intake of marine fatty acids (when such estimates are available). For example, total fish consumption in a Scandinavian population might reflect a greater intake of fatty fish than would the same total fish consumption in a population in the United States, because the per capita intake of n–3 fatty acids and the per capita intake ratio of n–3 to n–6 fatty acids in Scan-
In conclusion, the development and progression of breast and prostate cancers appear to be affected by processes in which EPA and DHA play important roles; yet, whether the consumption of fish containing marine fatty acids can alter the risk of these cancers or of other hormone-dependent cancers is unclear. Given the dearth of studies that examined the intake or tissue concentrations of specific marine fatty acids and the fact that most studies of fish consumption did not account for the type of fish consumed, there are still too few data from epidemiologic studies to evaluate the strength, consistency, and dose response of the relation between marine fatty acid intake and human cancer. Although there is ample evidence from in vitro and animal studies that these essential fats can inhibit the progression of tumors in various organs, particularly the breast and prostate, the evidence from epidemiologic studies is less clear. Although most of the studies did not show an association between fish consumption or marine fatty acid intake and the risk of hormone-related cancers, the results of the few studies from populations with a generally high intake of marine fatty acids are encouraging. Future epidemiologic investigations will probably benefit from the assessment of specific fatty acids in the diet, including EPA and DHA, and of the ratio of these to n–6 fatty acids, dietary constituents that have been examined infrequently in humans.

The identification of clinically relevant endpoints as biomarkers of cancer risk may help avoid the time and cost of long-term cohort studies and randomized trials of cancer risk. For example, mammographic parenchymal patterns with respect to breast cancer (19) may prove to be useful in this regard (19). Parenchymal patterns refer to the relative amount and configuration of breast tissue as it appears on a mammogram, with fat appearing dark (radiolucent) and epithelial and stromal tissues appearing light (radiodense) (132). Given the positive associations between breast density and breast cancer risk (132) and between estrogen concentrations and breast density (133), parenchymal patterns may be a useful biological marker for estrogen-mediated effects of marine fatty acids on the growth and development of breast cancer. In addition, the recent observation that the inhibitory effect of DHA on human breast cancer cell growth in vitro was proportional to the expression by those cells of mammary gland–derived growth inhibitor–related genes (134), which encode fatty acid binding proteins, is worthy of further exploration. More generally, as has been noted recently (135), the recommendation of the American Heart Association (136) to eat 2 servings of fish/wk, especially fatty fish, for the prevention of sudden cardiac death may have additional benefits, including those related to blood triacylglycerol concentrations, clotting mechanisms, blood pressure, the immune system, and the developing central nervous system. The potential benefits of an increased intake of marine fatty acids with respect to cancer prevention have yet to be established clearly, but they may be important.

REFERENCES


