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[1–3]

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

Reference	*n* Cases[2]	Follow-up time	Exposure	Country	Per capita n−3 intake[3]	Per capita n−3 intake/ n−6 intake[3]	Comparison	RR[4]
		y			*g/d*	*g/d*		
Gertig et al (35)[5]	453 [462]	8	Total fish	United States	0.10	0.003	>0.5 compared with ≤0.14 servings/d	1.3 (0.7, 2.6)
Holmes et al (36)	2956 [88 795]	14	n−3 Fatty acids Dietary EPA Dietary DHA	United States	0.10	0.003	0.1% of energy/d (continuous) 0.03% of energy/d (continuous) 0.03% of energy/d (continuous)	1.1 (1.0, 1.1) 1.1 (1.0, 1.1) 1.0 (1.0, 1.1)
Key et al (37)	427 [34 759]	14.1	Dried fish Undried fish	Japan	1.5	0.08	≥5 compared with ≤1 serving/wk >5 compared with <1 serving/wk	0.8 (0.6, 1.0)[6] 0.9 (0.7, 1.3)
Lund and Bonaa (38)[7]	3995 [533 276]	15	Married to a fisherman	Norway	0.40	0.01	Fishermen's wives compared with wives of nonfishermen	0.7 (0.5, 0.9)
Stampfer et al (39)	601 [89 538]	4	Total fish	United States	0.10	0.003	≥2 servings/wk compared with ≤1 serving/mo	1.1 (0.5, 2.4)
Toniolo et al (40)[5]	180 [900]	3.8	Total fish	United States	0.10	0.003	Highest compared with lowest quintile	1.0 (0.6, 1.7)
Vatten et al (41)	152 [14 500]	12.5	Fish as part of main meal Poached fish	Norway	0.40	0.01	≥2 compared with <2 times/wk ≥5 compared with ≤2 servings/mo	1.2 (0.8, 1.7) 0.7 (0.4, 1.0)

[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), fishermen'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

TABLE 2
Case-control studies of fish or fish oil consumption and breast cancer risk[1]

Reference	*n*		Exposure	Country	Per capita n−3 intake[2]	Per capita n−3 intake/ n−6 intake[2]	Comparison	OR[3]
	Cases	Controls			*g/d*	*g/d*		
Ambrosone et al (43)	301	316	Total fish	United States	0.10	0.003	>38 compared with <15 g/d	0.9 (0.6, 1.5)
De Stefani et al (44)	352	382	Total fish	Uruguay	—	—	≥53 compared with <12 servings/y	0.6 (0.4, 1.1)[4]
Fernandez et al (45)	3412	7990	Total fish	Italy	0.12	0.005	≥2 compared with <1 serving/wk	1.0 (0.8, 1.1)
Goodman et al (46)	272	296	Lean fish	United States	0.10	0.003	≥90 compared with 0 g/wk	1.2
			Fatty fish				> 60 compared with 0 g/wk	1.0
Hirose et al (47)	606	14 864	Total fish	Japan	1.5	0.08	≥3 compared with ≤0.75 serving/wk	0.8 (0.6, 1.0)
Hislop et al (48)	846	862	Total fish	Canada	0.04	0.002	Weekly compared with less than weekly	0.8 (0.7, 1.0)
							Premenopausal women	0.3 (0.5, 0.9)[4]
							Postmenopausal women	1.0 (0.8, 1.3)
Hislop et al (49)	493	527	Total fish	Canada	0.04	0.002	Weekly compared with less than weekly	
							Tumors negative for ER	0.6 (0.4, 0.9)[4]
							Tumors positive for ER	1.1 (0.8, 1.5)
Iscovich et al (50)	150	150[5]	Seafood	Argentina	—	—	Highest compared with lowest quartile	2.2
			Freshwater fish				Highest compared with lowest quartile	0.1[4]
			Preserved fish				Highest compared with lowest tertile	0.1[4]
Iscovich et al (50)	150	150[6]	Seafood	Argentina	—	—	Highest compared with lowest quartile	1.6
			Freshwater fish				Highest compared with lowest quartile	0.6
			Preserved fish				Highest compared with lowest tertile	0.5
Kato et al (51)	889	889	Total fish	Japan	1.5	0.08	Daily compared with ≤1–2 servings/wk	1.2 (0.8, 1.7)
Landa et al (52)	100	100	Total fish	Spain	0.38	0.01	Highest compared with lowest tertile	0.3[4]
Lee et al (53)	200	420	Total fish	Singapore	—	—	Highest compared with lowest tertile	1.0 (0.6, 1.9)
Lee et al (54)	91	213	Total fish	Singapore	—	—	≥51.4 compared with <29.4 g/d	1.2 (0.6, 2.3)
Levi et al (55)	107	318	Total fish	Switzerland	0.12	0.004	Highest compared with lowest tertile	0.7
Malik et al (56)	80	80	Total fish	Pakistan	—	—	Controls more likely to consume >1 serving of fish/wk[4]	
Mannisto et al (57)	310	454[7]	Total fish	Finland	0.37	0.02	55 compared with 21 g/d (means)	1.0 (0.4, 2.3)
			Dietary n−3				2.3 compared with 1.3 g/d (means)	0.7 (0.3, 1.7)
Mannisto et al (57)	310	506[8]	Total fish	Finland	0.37	0.02	55 compared with 21 g/d (means)	0.7 (0.3, 1.7)
			Dietary n−3				2.3 compared with 1.3 g/d (means)	0.3 (0.1, 0.6)
Shu et al (58)	1459	1556	Seafood	China	0.50	0.03[9]	Highest compared with lowest quintile	0.9 (0.7, 1.2)
Terry et al (59)	2085	2000	Fatty fish	Sweden	0.50	0.03	>3.5 compared with ≤0.5 servings/wk	0.7 (0.5, 1.1)
			Lean fish				>3.5 compared with ≤0.5 servings/wk	0.8 (0.5, 1.2)
Toniolo et al (60)	250	499	Total fish	Italy	0.12	0.005	Highest compared with lowest quartile	1.0
Zhu et al (61)	73	55	Dietary EPA	Finland	0.37	0.02	Significantly lower among cases than among controls[10]	—
			Dietary DHA				Significantly lower among cases than among controls[10]	—

[1] OR, odds ratio; ER, estrogen receptors; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.
[2] From Hursting et al (42), on the basis of food disappearance data.
[3] 95% CI in parentheses.
[4] Significant test for trend, $P < 0.05$.
[5] Neighbor controls.
[6] Hospital controls.
[7] Population controls.
[8] Referral controls.
[9] Value for Hong Kong.
[10] For postmenopausal women only.

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 risk[1]

Reference	*n*		Exposure	Country	Per capita n−3 intake[2]	Per capita n−3 intake/ n−6 intake[2]	Comparison	OR[3]
	Cases	Controls			*g/d*	*g/d*		
Chajes et al (62)	196	388	Serum phospholipid n−3	Sweden	0.50	0.03	Highest compared with lowest quartile	0.6 (0.3, 1.3)
			Serum phospholipid EPA				Highest compared with lowest quartile	0.5 (0.3, 1.0)
			Serum phospholipid DHA				Highest compared with lowest quartile	0.9 (0.4, 2.0)
			Serum phospholipid EPA/LA				Highest compared with lowest quartile	0.9 (0.4, 1.9)
London et al (63)	402	597	Adipose EPA	United States	0.10	0.003	Highest compared with lowest quintile	0.7 (0.4, 1.1)
			Adipose DHA				Highest compared with lowest quintile	1.1 (0.6, 1.7)
Maillard et al (64)	241	88	Adipose DHA	France	0.28	0.01	Highest compared with lowest tertile	0.3 (0.1, 0.8)[4]
			Adipose n−3/n−6				Highest compared with lowest tertile	0.3 (0.2, 0.7)[4]
Petrek et al (65)	154	125	Adipose n−3[5]	United States	0.10	0.003	Highest compared with lowest quartile	1.2 (0.6, 2.3)
Simonsen et al (66)	291	351	Adipose total n−3	Multicenter	—	—	Highest compared with lowest tertile	1.1 (0.6, 2.1)
			Adipose long-chain n−3				Highest compared with lowest tertile	0.9 (0.5, 1.7)
			Adipose n−3/n−6				Highest compared with lowest tertile	0.7 (0.4, 1.0)
Vatten et al (67)	87	235	Serum phospholipid n−3	Norway	0.40	0.01	Median: 142 compared with 74 mg/L	0.7 (0.3, 1.6)
			Serum phospholipid EPA				Median: 35.2 compared with 18 mg/L	0.9 (0.4, 2.0)
			Serum phospholipid DHA				Median: 90 compared with 57 mg/L	0.6 (0.3, 1.3)
			Serum phospholipid n−3/n−6				Median: 0.36 compared with 0.24	1.0 (0.4, 2.1)
Zhu et al (61)	73	55	Adipose EPA	Finland	0.37	0.02	No significant differences	—
			Adipose DHA				Significantly lower among cases than among controls[6]	—

[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] 95% CI in parentheses.
[4] Significant test for trend, $P < 0.05$.
[5] As proportion of total fat.
[6] 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

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[1]

Reference	*n* Cases[2]	Follow-up time	Exposure	Country	Per capita n−3 intake[3]	Per capita n−3 intake/ n−6 intake[3]	Comparison	OR[4]
		y			*g/d*	*g/d*		
Alberg et al (75)[5]	43 [86]	—	Total serum n−3 and n−6	United States	0.10	0.003	No clear differences between cases and controls	—
Augustsson et al (68)[6]	249 [47 780]	10	Total fish consumption	United States	0.10	0.003	>3 servings/wk compared with infrequent	0.5 (0.3, 0.8)
			Marine fatty acid consumption				0.5 g/d (continuous)	25% reduced risk[7]
Gann et al (69)[5]	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)[8]	126 [47 855]	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 [58 279]	6.3	Total fish consumption	Netherlands	—	—	Median: 20 compared with 0 g/d	1.0 (0.8, 1.3)
Schuurman et al (71)	642 [58 279]	6.3	Dietary EPA	Netherlands	—	—	Median: 0.10 compared with 0 g/d	1.0 (0.7, 1.4)
			Dietary DHA				Median: 0.18 compared with 0.01 g/d	1.0 (0.8, 1.4)
Severson et al (73)	174 [7999]	17.5	Total fish consumption	Hawaii	—	—	≥5 compared with ≤1 serving/wk	1.2 (0.7, 2.0)
Terry et al (74)	466 [6272]	21.4	Total fish consumption	Sweden	0.50	0.03	Moderate compared with small part of diet (incidence)	0.4 (0.2, 0.8)[7]
	340 [6272]		Total fish consumption				Prostate cancer mortality	0.3 (0.2, 0.6)[7]

[1] OR, odds ratio; 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] Results reported for metastatic prostate cancers only.
[7] Significant test for trend, $P < 0.05$.
[8] Results reported for advanced prostate cancers only.

consumption in relation to other hormone-dependent cancers, such as those of the endometrium and ovary, is warranted. However, studies of diet and cancers of the endometrium and ovary are relatively few, and none examined the intake of specific fatty acids. The results of these studies are briefly summarized below.

Endometrial cancer

One cohort study (84) and 7 case-control studies (45, 85–90) examined the association between fish consumption and endometrial cancer risk. In the most recent of these studies (90), which was a large case-control study in Sweden, consumption of fatty fish was strongly, inversely associated with endometrial cancer risk (odds ratio: 0.6; 95% CI: 0.5, 0.8; *P* for trend = 0.0002). Statistical adjustment for relative body weight, smoking status, physical activity, consumption of alcohol, multivitamin use, and prevalence of diabetes slightly strengthened the inverse association that was observed in a model in which only age was adjusted for. In contrast, consumption of lean fish was not associated with risk (odds ratio: 1.0; 95% CI: 0.8, 1.3; *P* for trend = 0.72). Even though the study population had a relatively high consumption of fatty fish, total fish consumption was only weakly associated with risk (odds ratio: 0.9; 95% CI: 0.6, 1.0; *P* for trend = 0.05), which underscores the need for separate analyses according to the type of fish consumed. Perhaps the generally low per capita intake of n−3 fatty acids in countries where the remaining studies were conducted, or the fact that these studies did not account for the type of fish consumed, explains why only 1 (45) of the remaining 7 studies (45, 84, 85, 87–89, 91) found a significant inverse association between total fish consumption and endometrial cancer risk.

Ovarian cancer

Five case-control studies (92–96) examined the association between total fish or seafood consumption and ovarian cancer risk. Three of those studies (94–96) were conducted in countries with relatively high per capita intakes of n−3 fatty acids [China (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 varied greatly with respect to important methodologic factors, such as sample size, adjustment for potentially confounding variables, the detail and quality of the

TABLE 5
Case-control studies examining the association between prostate cancer risk and either fish or seafood consumption or fatty acid concentrations in adipose tissue, erythrocyte membranes, or serum[1]

Reference	*n*		Exposure	Country	Per capita n−3 intake[2]	Per capita n−3 intake/ n−6 intake[2]	Comparison	OR[3]
	Cases	Controls			*g/d*	*g/d*		
Ewings and Bowie (76)	159	164	Total fish consumption	United Kingdom	0.13	0.006	Type of meat usually consumed	0.0 (0.0, 0.6)[4]
Fernandez et al (45)	127	7990	Total fish consumption	Italy	0.12	0.005	≥2 compared with <1 serving/wk	0.7 (0.4, 1.1)
Godley et al (77)	89	38	Adipose EPA	United States	0.10	0.003	Highest compared with lowest quartile	0.5 (0.2, 1.6)
			Adipose DHA				Highest compared with lowest quartile	1.1 (0.3, 4.4)
			Erythrocyte membrane EPA				Highest compared with lowest quartile	0.7 (0.2, 2.3)
			Erythrocyte membrane DHA				Highest compared with lowest quartile	0.4 (0.1, 1.3)
Harvei et al (78)	141	141	Serum n−3 fatty acids	Norway	0.40	0.01	Highest compared with lowest quartile	1.1 (0.6, 2.1)
			Serum n−6/n−3 fatty acids				Highest compared with lowest quartile	0.8 (0.4, 1.6)
			Serum EPA				Highest compared with lowest quartile	1.2 (0.6, 2.1)
			Serum DHA				Highest compared with lowest quartile	1.0 (0.5, 1.8)
Mishina et al (79)	100	100	Total seafood consumption	Japan	1.5	0.08	Regular compared with never or occasional	0.4[5]
Newcomer et al (80)	67	156	Erythrocyte membrane EPA	United States	0.10	0.003	Highest compared with lowest quartile	1.3 (0.6, 3.0)
			Erythrocyte membrane DHA				Highest compared with lowest quartile	1.0 (0.4, 2.3)
Norrish et al (81)	317	480	Erythrocyte membrane EPA	New Zealand	0.07	0.005	Highest compared with lowest quartile	0.6 (0.4, 1.0)[5]
			Erythrocyte membrane DHA				Highest compared with lowest quartile	0.6 (0.4, 1.0)[5]
Pawlega et al (82)	76	152	Smoked fish consumption	Poland	—	—	≥1 serving/wk compared with rarely	0.5 (0.2, 0.8)
			Fried fish consumption				≥1 serving/wk compared with rarely	0.5 (0.2, 0.9)
Talamini et al (83)	271	685	Total fish consumption	Italy	0.12	0.005	Highest compared with lowest tertile	0.8 (0.5, 1.2)

[1] OR, odds ratio; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.
[2] From Hursting et al (42), on the basis of food disappearance data.
[3] 95% CI in parentheses.
[4] No cases were observed among the men who most often ate fish rather than other types of meat.
[5] Significant test for trend, $P < 0.05$.

dietary assessment, and the duration of follow-up (in the cohort studies). In addition, epidemiologic studies to date have not examined intakes of specific fatty acids in relation to endometrial and ovarian cancers. Clinical and experimental studies of these cancers also have been scarce. Only one epidemiologic study to date considered the type of fish consumed in relation to endometrial cancer risk (90), and its results support an inverse association for the consumption of fatty fish but not other types of fish. There have been no similar studies with respect to ovarian cancer.

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 prostaglandin E_2 (PGE_2), have been linked to carcinogenesis in several types of studies: animal experiments of mammary tumor development, studies of the proliferation of breast and prostate cancer cell lines in vitro, and human studies of fish oil intake, epithelial cell proliferation rates, and PGE_2 biosynthesis [reviewed in detail by Rose and Connolly (19), Bougnoux (97), and Galli and Butrum (98)]. Tumor cells typically produce large amounts of AA-derived PGE_2, 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 PGE_2 (19). EPA and DHA also have been shown to inhibit lipoxygenase (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 the suppression of apoptosis, the stimulation of angiogenesis, stimulation of tumor cell adhesion, and expression of the invasive phenotype (19). Lipoxygenase inhibitors have been discussed recently as a potentially important class of chemopreventive agents (102).

Eiocosanoids derived from AA also may be involved in other processes related to cancer progression, as well as cancer initiation. These include alteration of tumor cell membranes (103), 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-α-hydroxyestrone or to 2-hydroxyestrone. 16-α-Hydroxyestrone is considered to be the more biologically active of the 2 estrogen metabolites and has been observed to increase mammary epithelial cell proliferation rates in experimental studies (109). In contrast, 2-hydroxyestrone may decrease proliferation and has been associated in some (109–112), but not all (113), studies with reduced breast cancer risk. Thus, "Western" diets that are rich in linoleic acid may decrease the

production ratio of 2-hydroxyestrone to 16-α-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 intranational 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 as 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 PGE_2 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 Scandinavia are up to 5- and 10-fold, respectively, those in the United States (42). Of the 12 epidemiologic studies of breast cancer risk conducted in areas with a relatively high intake of n−3 fatty acids (eg, >0.25 g/d) (37, 38, 41, 47, 51, 52, 57–59, 61, 64, 67), 5 showed significant inverse associations with fish or marine fatty acids (37, 38, 52, 61, 64), 6 showed inverse associations that were not significant (41, 47, 57, 59, 67, 123), and 1 in Japan (51) showed a slightly but nonsignificantly increased risk. In contrast (as can be seen in Tables 1–3), most of the studies conducted in areas with a relatively low intake of n−3 fatty acids showed no association. Similarly, 2 (74, 79) of 3 (74, 78, 79) studies of prostate cancer risk from areas with a relatively high intake of n−3 fatty acids found a significant inverse association with fish consumption, whereas 1 (78) found essentially no association with serum fatty acid concentrations. Somewhat surprisingly, nearly half (68, 76, 77, 81, 82) of the remaining 11 studies (45, 68, 69, 71–73, 75–77, 80–83) [excluding an earlier study that was recently updated (70)] in countries with a relatively low per capita intake of marine fatty acids (and a relatively high n−6 fatty acid intake) also found that men who had a "high" intake of fish or marine fatty acids had a significantly lower (moderate to strong difference) risk of prostate cancer than did men who had a "low" intake.

Data from a few experimental studies (124–126) suggest that the strength of the association with marine fatty acids may be reduced in the presence of high antioxidant intake, because both the former and the latter inhibit the formation of AA-derived peroxidation products (97, 127). This has been put forth as a potential reason for the largely null results of studies in the United States, where supplementation with antioxidants is widespread. However, this explanation is not entirely convincing because the formation of cytotoxic peroxidation products is only one of several mechanisms that may underlie the association between marine fatty acids and cancer risk (19, 105). Nevertheless, adjustment for dietary antioxidants in ecologic and analytic studies of n−3 fatty acids to date has been infrequent.

Interpretation of the results of the prospective cohort studies according to the duration of follow-up also may help to reconcile their differences. For example, the studies that showed the strongest inverse associations with prostate cancer risk (68, 74) were among those with the longest follow-up periods (see Table 4). However, it is unclear whether shorter-term studies (and case-control studies) failed to account for the relevant latency period between exposure and outcome, given the presumably greater role of AA-derived eicosanoids in tumor progression than in tumor initiation (103, 128). Indeed, metastatic prostate cancers in the Health Professionals' Follow-up Study (68) and fatal prostate cancers in the Swedish Twin Registry (74) had a stronger inverse association with marine fatty acid intake than did advanced (70) and incident (68, 74) prostate cancer in the respective cohorts. These results are consistent with the notions that fatty acids act primarily in tumor promotion and progression rather than in initiation and that dietary fats are more strongly associated with aggressive prostate cancer types than with indolent types (129). Intake of marine fatty acids also has been observed to inhibit the metastasis of human breast cancer cell lines growing as solid tumors in animal models (130, 131). Hence, the association between fatty acids and cancer risk may be clarified further through the analysis of epidemiologic data that take into account various follow-up (or induction) periods, that are from studies with repeated assessment of diet during the follow-up period, and that provide information on cancer at various stages of growth and progression.

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 shown 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.

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