Fish Intake Is Positively Associated with Breast Cancer Incidence Rate[1]

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ABSTRACT Animal studies have, in general, been supportive of a protective effect of fish and fish (n-3) PUFA against breast cancer risk; but the epidemiologic evidence of such a relationship is limited. Case-control and cohort studies have rarely shown significant associations. The association between total fish intake and the effect of fat content and preparation method of the fish, in relation to the incidence rate ratios of breast cancer, were investigated among postmenopausal women. We also investigated the effect of fish intake with respect to estrogen receptor expression of breast cancer tumors. A total of 23,693 postmenopausal women from the prospective study "Diet, Cancer and Health" were included in the study. During follow-up, 424 women were diagnosed with breast cancer. The incidence rate ratio (IRR) and 95% CI per each additional 25 g of mean daily intake of fish were 1.13 (CI, 1.03–1.23). Analysis of fatty fish gave IRR of 1.11 (CI, 0.91–1.34), and the result for lean fish was 1.13 (CI, 0.99–1.29). When fish intake was stratified into three types of preparation methods, the IRR for fried fish was 1.09 (CI, 0.95–1.25), for boiled fish 1.09 (CI, 0.85–1.42), and for processed fish 1.12 (CI, 0.93–1.34). The IRR per additional 25 g of mean daily intake of fish was 1.14 (CI, 1.03–1.26) for estrogen receptor–positive (ER+) and 1.00 (CI, 0.81–1.24) for estrogen receptor–negative (ER−) breast cancer. In conclusion, this study showed that higher intakes of fish were significantly associated with higher incidence rates of breast cancer. The association was present only for development of ER+ breast cancer. J. Nutr. 133: 3664–3669, 2003.

KEY WORDS: • *breast neoplasms* • *fish* • *estrogen receptors* • *cohort study*

Fish is a major food group worldwide. It is a source of high quality protein and contains all essential amino acids, while contributing to the intake of fat-soluble vitamins such as A and D, and trace elements such as selenium and iodine. In many countries, health authorities advise the population to eat more fish; the Danish population, for instance, is advised to eat 200–300 g of fish per week (1). In addition, a high proportion of the population takes supplements containing fish (n-3) PUFA.

Epidemiologic investigations studying how intake of fish and fish PUFA influences the occurrence of cancer, however, have not been conclusive. A report by the World Cancer Research Fund in 1997 concluded that fish may be protective against cancers of the colon, rectum, breast and ovary; but the evidence was considered insufficient (2). Long-chain (n-3) fatty acids, of which fish oil is a rich source, have consistently been shown to inhibit the growth of human breast cancer cells both in culture and in explants in immunosuppressed mice (3); but the epidemiological evidence of a protective effect comes mainly from ecological studies of breast cancer incidence and mortality (4–7). Most case-control and cohort studies have focused on fish intake rather than the intake of fish PUFA. We identified 20 case-control studies relating fish intake to breast cancer. Although the majority of these showed no significant relationship (8–23), three showed a significant reduction in the risk of breast cancer with increasing fish intake (24–26); in the study of Hirose et al. (26), this was the case only among postmenopausal women. One study actually showed a significant increase in risk with increasing fish intake (27). A recent pooled analysis of eight cohort studies, including 7379 women who were diagnosed with breast cancer during up to 15 y of follow-up, found an incidence rate of 1.01 for a 100 g/d increment in fish consumption (28). In a recent review of the epidemiologic literature on intake of fish and marine fatty acids and the risks of hormone-related cancers, the authors concluded that although the development and progression of breast cancer appears to be affected by processes in which eicosapentaenoic acid (EPA)[3] and docosahexaenoic acids (DHA) play important roles, it remains unclear whether the consumption of fish containing marine fatty acids can alter the risk of these cancers (29).

Given the clinical relevance of hormone receptors, there has been interest in determining whether epidemiologic risk factors for breast cancer differ by estrogen and progesterone

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[3] Abbreviations used: DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ER+, estrogen receptor positive; ER−, estrogen receptor negative; FFQ, food frequency questionnaire; HA, heterocyclic amines; HRT, hormone replacement therapy; IRR, incidence rate ratio.

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receptor status (30). Some studies have investigated dietary risk factors and estrogen receptor (ER)-specific breast cancer (31–36). One of these addressed the intake of fish and found that, among postmenopausal women, a frequent (weekly) consumption of fish was associated with an increased risk of ER+ tumors and a reduced risk of ER− tumors (32).

The aim of this study was to investigate the association of fish intake and breast cancer among postmenopausal women, and to evaluate whether a possible association was influenced by fat content or preparation method of the fish. Further, we wanted to investigate possible effects of fish intake on ER-specific breast cancer.

SUBJECTS AND METHODS

In the prospective study "Diet, Cancer and Health," we invited all individuals who lived in two selected geographical areas (greater Copenhagen and Aarhus) and who fulfilled the following criteria: age between 50 and 64 y; born in Denmark; and not registered with a cancer diagnosis in the Danish Cancer Registry. A total of 29,875 women participated in the study between December 1993 and May 1997. This corresponds to 37% of the women invited. The study "Diet, Cancer and Health" and the substudy reported here were approved by the Regional Ethical Committees on human studies in Copenhagen and Aarhus, and by the Danish Data Protection Agency.

Dietary information. Dietary information was obtained from a detailed, 192-item food frequency questionnaire (FFQ), which study participants received by mail before a visit to one of the two study clinics. A description of the development and validation of the questionnaire was published previously (37,38). The FFQ was developed to obtain information on the subjects' habitual diet during the preceding year. Answers to questions on intake of different foods and dishes were given in 12 different categories, ranging from never to 8 or more times a day. For foods that come in natural units, such as slices of bread, cups or glasses of different beverages, and pieces of fruit, participants were asked to average their daily intake of the relevant unit. For other foods, such as mixed dishes, a sex-specific portion size was calculated by using the results from a calibration study (39). A mean daily intake of foods and nutrients was calculated by multiplying the frequencies of intake by the portion size, using the software program FoodCalc (40). A total of 24 of the 192 foods and recipes in the FFQ covered intakes of different types of fish, and questions were specified according to preparation method. A biomarker study was carried out to validate the information on dietary intake of fatty acids, including fish PUFA (41).

Background information and anthropometrical measurements. During their visit, participants also completed a lifestyle questionnaire, including questions about reproductive factors, health status, social factors and lifestyle habits. Both the FFQ and the lifestyle questionnaire were processed during the visit by optical scanning, and checked so that missing or unclear information could be clarified with the participant before she left the study clinic. A few missing values were accepted in the lifestyle questionnaire, but not in the FFQ. From the lifestyle questionnaire, we obtained information about school education (short: ≤7 y, medium: 8–10 y, or long: >10 y), parity, age at birth of first child, history of benign breast tumor surgery (yes/no), use of hormone replacement therapy (HRT; never, past, or current) and duration of HRT. Furthermore, professional staff members at the study clinics collected biological material and obtained anthropometrical measurements including height and weight. The BMI was calculated as weight (kg) per height squared (m^2).

A total of 6076 women were excluded from the analysis because they were later reported to have had a cancer diagnosis before invitation or were premenopausal (had reported at least one menstruation no > 12 mo before entry and no use of HRT); or because they did not provide complete information on either the exposure variables or the potential confounding variables. Furthermore, we excluded 106 women including one case who never ate fish, both because they comprised a selected group, which may differ in an unknown way, and because this group by definition cannot contribute any information on how the breast cancer incidence rate differs by the different amounts of fish intake, by the fat content of the fish, or by the preparation methods of the fish. Thus a total of 23,693 women were included in this study, including 5229 women with a history of oophorectomy, hysterectomy or both (**Fig. 1**).

Follow-up. Cohort members were identified by the personal, 10-digit identification number, comprising date of birth and a four-digit running number, which is allocated to every Danish citizen by the Central Population Register.

All 23,693 cohort members were linked to the Central Population Register for information on vital status and migration. Information on cancer occurrence was obtained through record linkage to the Danish Cancer Register (42), which collects information on all individuals with cancer in Denmark. Linkage was performed by use of the personal identification number. Each cohort member was followed-up for breast cancer occurrence from the date of entry (i.e., date of visit to the study center) until the date of diagnosis of any cancer (except for nonmelanoma skin cancer), the date of death, the date of emigration or 31 December 2000, whichever came first.

In addition to the general Danish Cancer Register, a register exclusively concerning breast cancer has been established in Denmark. Information on ER status was obtained from The Danish Breast Cancer Co-operative Group, which holds records on a range of details (e.g., ER status) for ~90% of breast cancers diagnosed in Denmark (43). Although several medical centers were involved, a standardized immunohistological method was used. The cut-off level used to define positive receptor status was 10% or more positive cells. Linkage to the

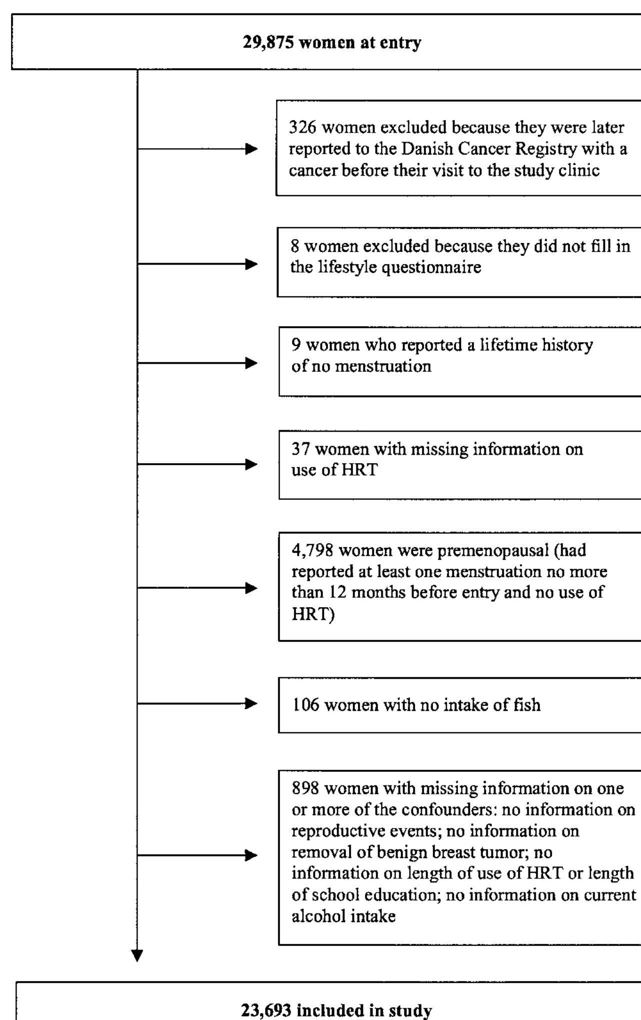

FIGURE 1 Flow chart indicating the reasons for the exclusion of 6182 women from the study of the association of fish intake and breast cancer among postmenopausal women.

Danish Breast Cancer Co-operative Group register was performed by use of the personal identification number as well.

Statistical analyses. The analyses of the relation between the exposure variables and breast cancer rates were based on the Cox proportional hazard model (including time-dependent variables) using age as the time axis to ensure that the estimation procedure was based on comparisons of individuals at the same age. The other time variable, "time under study," was included as a time-dependent variable, modeled by a linear spline with a boundary at 1 y after entry into the study cohort, to allow for a possible "healthy-participants" effect. In analyses considering ER status, the two types of breast cancer defined by the receptor status were treated as competing causes of failure, i.e., in separate analyses, in which breast cancers of the opposite type were censored by the age at the time of cancer diagnosis. Breast cancers with unknown receptor status were censored at the cancer diagnosis in both analyses. All models were adjusted for baseline values of established risk factors for breast cancer, such as parity (entered as two variables; the categorical variable parous/nulliparous and the quantitative variable number of births); age at first birth; previous benign breast tumor surgery (yes/no); length of school education (low, medium, high); use of HRT (never, former, current); duration of HRT; BMI; and alcohol intake. Two-sided 95% CI for the incidence rate ratio (IRR) were calculated based on Wald's test of the Cox regression parameter, i.e., on the log rate ratio scale. The procedure PHREG in SAS (release 6.12; SAS Institute, Cary, NC) on a Unix platform, was used for statistical analyses.

All quantitative variables were entered linearly in the Cox model. This is biologically more reasonable than the step functions corresponding to categorization; furthermore, it increases the power of the analyses (44). The hypothesis of a linear association was evaluated using a linear spline with three boundaries as covariates in the Cox model (45). For the continuous variables, the three boundaries were placed at the quartile cut points of fish intake among cases (see Table 2 for placement of boundaries). The linearity was evaluated graphically as well as by a numerical test using the likelihood ratio test statistic to compare the model assuming linearity with the linear spline model. We found no significant departure from linearity.

In the analyses, fish intake was divided according to fat content (lean fish with ≤8 g fat/100 g fish and fatty fish with >8 g fat/100 g fish) and preparation method [fried (8 different questions), boiled (5 different questions) and processed fish (11 different questions)]. Processed fish was considered a separate group because this type of preparation differs from the two others by including fish prepared by other methods, e.g., pickling, salting and smoking. In the analysis comparing intake of fatty and lean fish (Table 2), women with intake of only one type were excluded. Total energy intake was evaluated in all models, but did not influence the estimates, and thus was not included in the final model.

RESULTS

The median age at entry for the 23,693 postmenopausal women included was 57 y (range, 50–65 y). The median length of follow-up was 4.8 y (1st-99th percentiles: 1.1–6.8), during which time 424 cases of a primary breast cancer were diagnosed. Information about ER status of the tumors was obtained for 394 (93%) cases of breast cancer. Of these, 303 (77%) tumors were reported to be ER+ and 91 (23%) tumors ER−. For the remaining 30 tumors, it was not possible to determine ER status on 10 in situ tumors; the remaining 20 tumors could not be located in the register.

The fish intake varied between 11 and 86 g (5th and 95th percentiles) for the total cohort with a higher intake of lean fish than fat fish. Most of the fish were fried, fresh fish or

TABLE 1

Observed percentiles of the distribution of intake of fish according to fat content and preparation method, as well as occurrence of previously established risk factors for breast cancer, among breast cancer cases and all postmenopausal cohort members in the Danish study "Diet, Cancer and Health" (1993–2000)

	Cases (n = 424)[1]					Total cohort (n = 23,693)[1]				
	Median	5%	25%	75%	95%	Median	5%	25%	75%	95%
Total intake of fish, *g/d*	39	12	26	58	87	36	11	24	52	86
Fish according to fat content, *g/d*										
Fatty fish	12	2	6	21	39	11	2	6	19	39
Lean fish	24	8	16	36	64	23	7	16	32	56
Fish according to preparation method, *g/d*										
Fried fish	21	5	13	33	55	20	5	13	30	55
Boiled fish	8	0	4	12	26	6	0	4	11	23
Processed fish	11	3	6	21	43	11	2	6	19	40
Age at baseline, *y*	57	51	54	60	64	57	51	53	61	64
Duration of HRT use,[2] *y*	6	1	2	10	20	4	1	1	10	18
Age at first birth, *y*	23	18	20	27	32	23	18	21	26	31
Number of births,[3] *n*	2	0	1	2	3	2	0	1	3	4
BMI, *kg/m²*	25	20	23	28	34	25	20	23	28	34
Alcohol intake, *g/d*	11	0	3	22	44	9	0	3	17	42
School education, %										
Low	30					34				
Medium	47					49				
High	22					17				
Use of HRT, %										
Never	34					50				
Past	13					16				
Current	53					35				
Parous, %	86					88				
Benign breast tumor surgery, %	21					13				

1 Values are medians (5th, 25th, 75th, 95th percentiles) or as fraction (%) in each category.
2 Among ever users of hormone replacement therapy (HRT).
3 Among parous.

processed, but intake of boiled fish was relatively low (**Table 1**). The associations between confounding variables and the breast cancer incidence were all in the expected directions. That is, the incidence rates decreased with number of children, but increased with increasing values of age at first birth, use of HRT, duration of HRT use, length of education, intake of alcohol and history of benign breast tumor surgery.

Total fish intake was associated with a significant increase in the breast cancer incidence rate per 25 g daily intake [IRR = 1.13 (CI, 1.04–1.22); **Table 2**]. Adjustment for established risk factors did not change the result. To illustrate this relationship further, the total fish intake was divided according to quartiles. When the upper quartile group was compared with the lower quartile group, there was an increase of 47% in the incidence rate of breast cancer. To explore whether the elevated IRR was related to the fat content, we divided the fish intake according to fat content. This resulted in IRR of 1.11 (CI, 0.91–1.34) for fatty fish and 1.13 (CI, 0.99–1.29) for lean fish, both per 25 g mean daily intake. Analyzing fish intake according to the three different types of preparation method gave almost identical IRR when adjusted for established risk factors. These results indicate that high total fish intake rather than fat content or preparation method is associated with an increased incidence of breast cancer.

High total fish intake was associated with a significantly increased incidence rate of ER+ breast cancer with an IRR of 1.14 (CI, 1.03–1.25) per mean intake of 25g/d. For ER− breast cancer, no association was present, i.e., IRR = 1.01 (CI, 0.83–1.24). Adjustment for established risk factors did not change the result (**Table 3**).

DISCUSSION

This prospective study found that higher intakes of fish were associated with higher incidence rates of breast cancer. The association was independent of fat content and preparation method of the fish. The incidence of ER+ tumors was increased for higher intakes of fish, whereas no increase was seen for ER− tumors.

Our study has several strengths. The FFQ used in this study had 24 specific questions on fish, making this study very comprehensive on this relationship, and providing the possibility of studying the specific associations with fish according to fat content or preparation method. Our FFQ was validated (38). Also, a biomarker study comparing fatty acid profiles in adipose tissue biopsies with dietary intake was carried out and showed correlations between the fish PUFA measured in the adipose tissue and in the FFQ of 0.58 for EPA and 0.49 for DHA (41). The correlations for these specific fatty acids were higher compared with other types of fatty acids, and comparable to results from other studies (46). Danish women have the third highest mean intake of fish among European populations participating in the European Prospective Investigation into Cancer and Nutrition study, and the second highest mean intake of fatty fish (47). Together with a high interindividual variation in fish intake, it provides a unique opportunity to study the significance of different types of fish, including fat content and preparation methods.

Because the data were collected in a prospective design, differential recall for cases is highly unlikely. Follow-up rate was nearly complete (99.8%). Adjustment for known risk factors changed the estimates only slightly; thus, it is not likely that residual confounding from those factors affected the estimates considerably.

To our knowledge, no prospective study has examined the significance of fat content in fish in relation to development of breast cancer. If the protective effect of fish PUFA shown in experimental models could be applied to humans, we would expect a protective effect most pronounced for fatty fish, which was not the case in our study. Another hypothesis is that fish might be contaminated with substances present in the environment, such as heavy metals and pesticides, which may have estrogenic effects. Because these agents accumulate in fat tissue, one would expect the elevated risk to be more pronounced with higher intakes of fatty fish compared with lean fish, which was not the case in our study. The influence of pesticides on breast cancer risk was evaluated in a recent review of human epidemiologic studies (48). Studies on the organochlorine pesticides dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) did not find that these pesticides predict breast cancer risk in Caucasian Western women. For another persistent organochlorine pesticide, dieldrin, a relationship was found in Danish but not in American women, with a doubling of the breast cancer risk

TABLE 2

Incidence rate ratio (IRR) and 95% CI for breast cancer per mean intake of 25 g/d of total fish, fish according to fat content or preparation method and for categorization according to quartiles of daily intake among cases

	IRR (95% CI)	IRR (95% CI)[1]
Total fish intake	1.13 (1.04–1.22)	1.13 (1.03–1.23)
Fish according to fat content[2,3]		
Fatty fish	1.08 (0.89–1.30)	1.11 (0.91–1.34)
Lean fish	1.15 (1.01–1.31)	1.13 (0.99–1.29)
Fish according to preparation method[3]		
Fried fish	1.04 (0.91–1.19)	1.09 (0.95–1.25)
Boiled fish	1.21 (0.96–1.52)	1.09 (0.85–1.42)
Processed fish	1.12 (0.94–1.34)	1.12 (0.93–1.34)
Total fish intake in quartiles		
Quartile 1 (0–26 g/d)	1	1
Quartile 2 (27–39 g/d)	1.01 (0.77–1.32)	0.99 (0.76–1.30)
Quartile 3 (40–58 g/d)	1.17 (0.89–1.53)	1.12 (0.85–1.47)
Quartile 4 (>58 g/d)	1.54 (1.18–2.02)	1.47 (1.10–1.98)

[1] Estimates are adjusted for parity (parous/nulliparous, number of births and age at first birth), benign breast tumor, years of school, use of hormone replacement therapy (HRT), duration of HRT use, BMI and alcohol.

[2] From this analysis, 225 women were excluded including one case who did not have an intake of both fatty and lean fish.

[3] Mutually adjusted.

TABLE 3

Incidence rate ratio (IRR) and 95% CI for breast cancer, per mean intake of 25 g/d of total fish, for estrogen receptor positive (ER+) breast cancer (303 cases) and estrogen receptor negative (ER−) breast cancer (91 cases)

	Total fish intake IRR (95% CI)	Total fish intake[1] IRR (95% CI)
(ER+) breast cancer	1.14 (1.03–1.25)	1.14 (1.03–1.26)
(ER−) breast cancer	1.01 (0.83–1.24)	1.00 (0.81–1.24)

[1] IRR were adjusted for baseline values of parity (parous/nulliparous, number of births and age at first birth), previous benign breast tumour surgery, school education, use of hormone replacement therapy (HRT), duration of HRT use, intake of alcohol and BMI.

for women in the highest quartile group compared with women in the lowest quartile group (49,50). The concentrations of dieldrin were comparable in the two studies.

There are considerable discrepancies between the results from experimental studies and epidemiologic studies, with experimental studies exclusively showing a preventive effect of fish oil on the development and progression of breast cancer. The epidemiologic literature has not shown similar results, when excluding the ecologic studies. An explanation of this discrepancy could be that the fish oils and fatty acids used in experimental models differ from those eaten by humans, e.g., with regard to content of contaminating substances. If this is true, there might be a true beneficial effect of fish PUFA but it might be obscured by opposite effects of other substances found in the fish being eaten.

If the association between fish intake and breast cancer incidence was caused by the fat content of the fish, then a higher rate ratio per 25 g fish should be seen for the fat fish types. Thus, the almost identical estimates for fat fish and lean fish indicate that the associations may be caused by other substances that are present in equal amounts in fat fish and lean fish. Although a recent study (51) showed that associations with dietary fat in general may be underestimated because of imprecise measurement methods, this is not applicable for the present study because there is very little measurement uncertainty on the type of fish.

Cooking at high temperatures has been shown to form carcinogenic substances such as heterocyclic amines (HA) in both animal and in vitro studies; several studies have investigated how preparation methods of meat and fish affect breast cancer risk. A prospective study with extensive information on preparation practices found an almost five times higher risk of breast cancer among women who consumed overcooked meats than among women who consumed rare- or medium-cooked meats (52). Whether this result is applicable to fish is not clear, but it has been hypothesized that the HA content might be even higher in well-done fish than in other meats (53). Only one study reported on the specific relationship of fish preparation and breast cancer risk, finding an inverse relation with the frequency of main meals containing fish in poached form (54). In our study, we did not find any association with preparation method. Our questionnaire distinguished among preparation methods by separate questions on fried, boiled and processed fish, and also questions on the appearance of the surface of prepared meat, including fish, at four different levels. There were no differences between cases and the cohort in answers to the questions on doneness; however, our questions might have been too unspecific to explain the degree of exposure to HA, and factors other than the exposure itself might be of importance. The risk of breast cancer has been evaluated according to differential sensitivity toward HA, due to genetic variations; one study reported that exposure to HA may be a risk factor only among women with the high acetylating *N*-acetyltransferase 2 polymorphism (55).

To our knowledge, only one epidemiologic study previously examined the relationship between fish intake and breast cancer risk according to ER status of the breast cancer tissue (32). This case-control study had results similar to ours. The present study found no association for ER− tumors but with wide confidence limits leaving the possibilities of adverse or protective effect of fish intake on ER− tumors.

Because this is the first prospective study analyzing the association between dietary fish intake and ER status–specific breast cancer, the results have to be interpreted with caution, especially because the number of ER− tumors was relatively small. In a review on pesticides and breast cancer, it was noted that out of several studies investigating the relation of ER status of breast tumors to body burdens of DDT or DDE, only one found a relationship between receptor status and tissue levels of DDE, showing that women with ER+ breast tumors had substantially higher concentrations of DDE in breast adipose tissue than women with ER− breast tumors; the other studies found no relationship (56).

Because the estimated associations for fat fish and lean fish are almost identical, even very narrow confidence limits would lead to the same conclusion; thus, lack of statistical power of the study cannot explain the lack of difference between the two associations. Similarly, the estimated incidence rate ratio for ER− tumors per 25 g average daily intake of fish was very close to one, indicating that lack of statistical power in itself cannot explain the null result.

The present study indicates that the observed association between fish intake and incident breast cancer among postmenopausal women cannot be ascribed to the fat content. Furthermore, the adverse effect of fish intake was observed for ER+ tumors only. Further studies are warranted to examine which other substances in fish or other risk factors related to fish intake may explain the observed association for ER+ tumors, and to evaluate a possible difference in the association for ER+ breast cancer and ER− breast cancer.

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