British Journal of Nutrition (2007), **98**, 576–582
doi: 10.1017/S0007114507721487

Consumption of fish and risk of colon cancer in the Norwegian Women and Cancer (NOWAC) study

Dagrun Engeset[1]*, Vegard Andersen[1], Anette Hjartåker[2] and Eiliv Lund[1]

[1]*Institute of Community Medicine, University of Tromsø, Tromsø, Norway*
[2]*Cancer Registry of Norway, Oslo, Norway*

(Received 13 November 2006 – Revised 18 February 2007 – Accepted 20 February 2007)

Recent studies have shown a decreased risk of colon cancer with consumption of fish. However, most studies on fish consumption do not distinguish between lean and fatty fish, or between poached and fried fish. The aim of this study was to investigate any association between fish consumption and colon cancer in The Norwegian Women and Cancer (NOWAC) study. We focused mainly on lean fish, which was further divided into poached and fried fish. A total of 63 914 women were included in the analysis, 254 of whom were found to have colon cancer during follow-up. Since fish consumption was one of the main topics of interest in the NOWAC study, there is a predominance of women from northern Norway due to higher fish intake in this area; hence the study is not representative of the whole of Norway. The participants completed a semi-quantitative FFQ between 1996 and 1999, and were followed-up for incidence of colon cancer until 2004. No association between fish consumption and risk of colon cancer was seen, except for the third tertile of poached lean fish consumption (relative risk (RR) 1·46, 95 % CI 1·04, 2·06). This association disappeared when excluding women with less than 1 year of follow-up. In conclusion, the present study does not support the hypothesis of a protective effect of fish against colon cancer risk.

Fish consumption: Colon cancer: NOWAC: Diet

Colon cancer is the second most common cancer among women in Norway, with 1217 new cases in 2004 (age-adjusted incidence rates per 100 000 women was 23·9), and colorectal cancer is the most common cancer in men and women combined (3482 new cases in 2004)[1]. Norway has the highest incidence of colorectal cancer of the Nordic countries[2]. It is estimated that a third to half of colon cancers may possibly be avoided if different diet-related factors were controlled for[3].

Norway has a long coastline, and thus a long tradition in harvesting fish, and using fish in the diet. Lean, white fish such as cod, haddock and saithe, and fish products made from these, are most commonly eaten[4]. Fish products, such as fish balls, puddings and cakes, are mainly made of minced lean fish, starch, milk and spices. Fish served for dinner is prepared from fresh/frozen, smoked, salted and/or dried fish, and is often served with melted fat or fatty sauces[4].

Recently, results from the European Prospective Investigation into Cancer and Nutrition (EPIC) showed a decrease in colon cancer risk with higher intake of fish[5]. However, like most studies on fish consumption and cancer risk, only total fish consumption was analysed. No distinction was made between lean and fatty fish. It is also quite common in analyses of fish consumption to combine intake of fish and poultry (white meat), or fish and meat[6]. Fatty fish has been analysed in terms of *n*-3 fatty acids, but lean fish has not been investigated as much[6].

Heterocyclic amines and polycyclic aromatic hydrocarbons formed during preparation of the fish at high temperatures cause cancer in rodents[7], and may also be harmful for humans. It is therefore of interest to investigate the association between fried fish and colon cancer.

The aim of this study was to investigate any association between fish consumption and colon cancer in The Norwegian Women and Cancer (NOWAC) study. Rectal cancers were not included due to their low incidence. The main focus was on lean fish, which constitutes the majority of the fish consumed in Norway. Lean fish was further divided into poached and fried fish.

Subjects and methods

The NOWAC study is a large population-based cohort study designed to examine cancer-related factors. About 165 000 Norwegian women have been included in the cohort from 1991 to 2006. The women all returned a questionnaire about different lifestyle habits. The questionnaires were sent in series; the first questionnaires from 1991 to 1997, and the second questionnaires from 1998 to 1999. A new series of first, second and third questionnaires have been sent after 1999 but they are not included in the analyses due to the short follow-up time. The questions in the different series have varied depending on which age group they were aimed

Abbreviations: NOWAC, Norwegian Women and Cancer; RR, relative risk.

* **Corresponding author:** Dr D. Engeset, fax +47-22-85-13-13, email dagrun.engeset@ism.uit.no

at and the hypotheses tested, but some core questions have been common in all series. Only series containing dietary questions are included in the present analyses.

The NOWAC study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

The study design, material, internal validity and external validity have been described in detail elsewhere[8–11].

Study population

This study includes eleven series of six- to eight-page questionnaires about different lifestyle habits, including a semi-quantitative FFQ, that were mailed to randomly selected women all over the country during the period 1996–1999. Since fish consumption and health was one of the main topics for the NOWAC study, two questionnaire series (eight pages) were distributed randomly to women in northern Norway only (1996–1997) (*n* 13 670), due to higher fish consumption in this area. The study sample is therefore skewed towards northern Norway, and not representative for women of the particular age group in the whole of Norway as such. The total response rate was approximately 52 %. The analysis in the present report is based on a sample of 68 517 women, aged 40–71. Excluded from the analyses were women with prevalent cancer at any site at the time of enrolment (*n* 2908 women). Data for individuals in the lower and upper 1 % of the ratio of energy intake to estimated energy requirement (calculated from age, sex and body weight) (corresponding to <2200 kJ and $>15\,200$ kJ) were excluded from the analyses to reduce the effect of implausible extreme values (*n* 1414 women)[12]. We also excluded women reporting more than 60 hot meals per month (*n* 281 women)[8]. After the exclusions, 63 914 women were included in the analysis.

Diet and FFQ

For the FFQ, food items asked for, frequency and amounts consumed have been reported previously[10]. Briefly, the participants were asked to record how often, on average, they had consumed each food item during the previous year. Four to six fixed frequency choices were given for each item. For fish, the women also had to indicate in what season they normally ate different types of fish, due to seasonal variation. There were in total 11–14 questions about fish consumption, including questions about fats and sauces added to fish dishes. Added fats and sauces were defined as melted butter or margarine, full-fat and low-fat sour cream, and white or brown sauces with or without fat. Five different frequencies were specified, ranging from never to twice a week. Questions about fish in sandwiches had six frequencies, ranging from never to ten times per week. Fish for dinner had six frequencies, ranging from never to three times per week, according to season. Fish products had five frequencies, ranging from never to twice a week. Roe and fish liver had five frequencies, ranging from never to ten times a year, and crustaceans had four frequencies in the range never to once a week. In addition, there were questions about use of cod liver oil (liquid and capsules), with six frequencies from never to daily use. The portion size per consumption was asked for in natural or household units. A Norwegian weight and measurement table[13] was used to calculate the weights in grams for each food item. Daily intake of energy and nutrients was computed based on the Norwegian Food Composition table[14].

The questionnaires with fourteen fish questions included, in addition to the above-mentioned questions, questions about consumption of fresh or frozen fish and the women's perception about fish (why they are not eating more fish). These questions were not included in the present analyses, but have been dealt with previously[15].

We examined total fish consumption (whole fish, fish products, crustaceans, roe and fish liver), whole lean fish consumption, whole fatty fish consumption and consumption of fish products. Lean fish was classified as fish with less than 4 % fat (e.g. cod, haddock and saithe), and fatty fish as fish with 4 % fat and above (e.g. salmon, trout, herring and mackerel). Fish products included fish fingers (coated in bread crumbs), preserved fish (e.g. canned mackerel, smoked salmon, canned tuna), fish casseroles and minced fish products (e.g. fish balls, fish cakes). Fish products are mainly made from lean fish and contain only about 30–50 % fish on average, except for preserved fish, which mainly comprise fatty fish. However, preserved fish is mainly used in sandwiches, and the consumption was rather limited. For lean fish, we also distinguished between poached and fried fish. We could not do this for fatty fish since this information was not available. We did not examine further consumption of crustaceans or roe separately, since the consumption of these products was limited. Consumption of fish liver in relation to cancer risk has been examined separately in another paper[16].

End-points

Follow-up was based on the Cancer Registry of Norway[1]. The women were followed from enrolment (1996–1999) until first colon cancer diagnosis, death, emigration or the end of the follow-up period. By the end of 2004, 254 cancer cases were reported, all histologically verified. The 10th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD) was used, with colon cancer defined as C18.

Statistical methods

The statistical software program R (version 2.1.1.) was used for the statistical analysis. The hazard ratios and their corresponding 95 % CI were estimated using Cox proportional hazards regression, and interpreted as relative risks (RR). The counting process formulation of Andersen and Gill[17] was used, meaning the follow-up time of each subject was an interval spanned by age at enrolment as entry time and age at diagnosis or censoring (death, emigration or diagnosis of other cancers) as exit time. In this way, adjustment for age was incorporated into the baseline hazard. Known risk factors for colon cancer were included in the model and adjusted for in the analysis (see tables for details). Fatty fish and lean fish were mutually adjusted for, as were poached and fried lean fish. In addition, we adjusted for fats and sauces eaten together with the fish. Fish intake was divided in tertiles, with the lowest tertile as the reference group.

Fully adjusted models for total fish and for fish products were adjusted for age, daily intake of energy (kJ/d), ever smoking, fish liver (g/d), fruit and vegetables (g/d), fibre (g/d) and added fats and sauces (g/d). Fully adjusted models for lean and fatty fish, and for fried and poached fish, were adjusted for the same variables as total fish and fish products, but in addition we adjusted for fatty fish (g/d) and lean fish (g/d), respectively, and for poached fish (g/d) and fried fish (g/d), respectively. Age, energy, fibre, and fruit and vegetables were treated as continuous variables. Lean and fatty fish, poached and fried fish, and added fats and sauces were divided into tertiles and treated as categorical variables. Fish liver was dichotomised into users and non-users, and smokers into never smokers and ever smokers.

Red meat and meat products (g/d), alcohol (g/d), cod liver oil (g/d), folate (μg/d), calcium (mg/d), BMI (explained as body weight in kilograms divided by the square of height in metres, kg/m^2, and assembled into three categories; <25, 25–30, >30), physical activity (recorded in the questionnaire on a scale ranging from 1 to 10 and assembled into three categories; 'low' (1–3), 'moderate' (4–7) and 'high' (8–10)) and ever use of hormone replacement therapy and oral contraceptives were adjusted for in the preliminary analyses, but were not included in the final model as they did not make any significant contribution to the risk estimates.

The assumption of proportional hazards for the Cox regression model was tested for each covariate[18]. We did this by use of the *cox.zph* function in R, which uses scaled Schoenfeld residuals and a transformation of time based on the Kaplan–Meier estimate of the survival function. Except for the medium level of lean fish, the test of proportionality did not indicate any time violations of the proportional hazards assumption. A plot of the estimated coefficients as a function of time (age) indicates a slight decrease in risk over time for those with a medium consumption of lean fish. All other slopes did not differ significantly from zero. Plotting the Martingale residuals against covariates did not indicate non-linearity issues for any of the covariates.

Results

Characteristics of the study population

A description of the study population is given in Table 1. The mean age of the women at enrolment was 51·3 years (SD 6·8) with the lowest age 40·8 and highest 70·4 years. BMI, calculated from self-reported weight and height, was 24·6 kg/m^2 (SD 3·9). Sixty-two percent of the women had BMI lower than 25. The women had 11·7 years of education on average (including primary school). A higher percentage of women with a low level of education (57·8 *v.* 43·4), and a slightly higher percentage of ever smokers (64·3 *v.* 61·8) were seen among cases. Cases also had a higher percentage of overweight and obese women (41·4) compared with the total cohort (38·0).

Table 2 gives an overview of mean intake of different foods and nutrients within each tertile of the total amount of fish consumed for the total cohort and for the cases. The highest number of cases is found in the third tertile. A lower intake of meat and meat products, and a higher intake of lean fish and of added fats and sauces are seen among cases in all tertiles, and lower intake of fruit and vegetables in the third tertile. When dividing lean fish into poached and fried fish, cases have a higher consumption of poached fish than the total cohort. The cases also consumed higher amounts of cod liver oil and vitamin D.

Table 1. Characteristics of the NOWAC study participants: total cohort and colon cancer cases

Characteristics	Total cohort (*n* 63 914)	Colon cancer cases (*n* 254)
Mean age at enrolment (years)	51·3 (SD 6·8)	57·1 (SD 7·3)
Mean energy intake (kJ/d)	6741(SD 1720)	6447 (SD 1623)
BMI (%)		
< 25	62·0 (*n* 38 903)	58·7 (*n* 143)
25–30	29·3 (*n* 18 352)	32·8 (*n* 80)
> 30	8·7 (*n* 5460)	8·6 (*n* 21)
Years of education (%)		
< 10	43·4 (*n* 26 171)	57·8 (*n* 134)
10–12	28·0 (*n* 16 907)	22·0 (*n* 51)
> 12	28·6 (*n* 17 250)	20·3 (*n* 47)
Smoking (%)		
Never	38·3 (*n* 24 043)	35·7 (*n* 89)
Ever	61·8 (*n* 38 822)	64·3 (*n* 160)
Physical activity (%)		
Low	13·7 (*n* 7940)	15·8 (*n* 35)
Moderate	73·3 (*n* 42 361)	71·9 (*n* 157)
High	13·0 (*n* 7·495)	12·2 (*n* 27)
Use of HRT (%)		
Never	69·1 (*n* 42 620)	60·3 (*n* 146)
Ever	31·0 (*n* 19 099)	39·7 (*n* 96)
Use of OC (%)		
Never	46·8 (*n* 28 952)	60·1 (*n* 143)
Ever	53·2 (*n* 32 953)	40·0 (*n* 95)
Alcohol (mean g/d)	44·7 (SD 65·0)	40·5 (SD 67·2)

SD, standard deviation; HRT, hormone replacement therapy; OC, oral contraceptives.

Table 2. Mean intake of different fish items and other important foods and nutrients, distributed on tertiles (T) of total fish consumption in the total cohort, and among colon cancer cases (in parentheses)

(Mean values and standard deviation)

	T1		T2		T3	
	n 21 305 (*n* 71)		*n* 21 304 (*n* 73)		*n* 21 305 (*n* 110)	
	Mean	SD	Mean	SD	Mean	SD
Total fish	46·2 (44·1)	17·5 (17·8)	92·6 (92·9)	13·0 (12·5)	167·2 (172·2)	48·2 (56·0)
Lean fish (g/d)	12·9 (15·2)	10·9 (14·3)	29·2 (31·9)	16·9 (18·2)	59·8 (67·9)	35·6 (42·4)
Fatty fish (g/d)	8·1 (6·7)	8·1 (6·5)	16·1 (15·8)	14·3 (10·8)	30·5 (28·1)	24·9 (22·7)
Fish products (g/d)	17·6 (15·6)	11·7 (12·4)	35·2 (33·2)	16·9 (17·1)	59·5 (59·8)	28·4 (33·5)
Poached lean fish (g/d)	7·9 (9·3)	7·9 (10·4)	17·5 (22·1)	12·7 (14·4)	36·4 (44·1)	25·5 (27·5)
Fried lean fish (g/d)	4·9 (5·9)	6·5 (9·2)	11·7 (9·9)	10·2 (9·3)	23·5 (23·8)	19·2 (23·2)
Added fats and sauces (g/d)	5·8 (6·2)	6·8 (6·8)	9·1 (11·7)	8·6 (11·5)	13·0 (14·0)	11·8 (11·8)
Red meat and meat products (g/d)	88·9 (76·6)	47·8 (39·7)	95·3 (77·8)	46·0 (37·8)	97·5 (87·7)	48·5 (41·4)
Fruit and vegetables (g/d)	387·1 (389·1)	193·4 (179·9)	447·6 (467·8)	192·2 (210·0)	504·0 (484·7)	213·0 (233·5)
Chicken (g/d)	11·0 (7·2)	10·5 (8·8)	11·6 (9·5)	10·1 (10·2)	11·4 (9·1)	10·7 (8·3)
Fish liver (g/d)	0·2 (0·1)	0·4 (0·3)	0·2 (0·2)	0·4 (0·4)	0·2 (0·5)	0·5 (0·7)
Cod liver oil (g/d)	1·9 (1·4)	3·2 (2·8)	1·8 (2·4)	3·2 (3·8)	1·9 (2·4)	3·3 (3·5)
Fibre (g/d)	21·3 (18·1)	6·8 (5·9)	21·3 (21·1)	6·9 (5·9)	21·3 (21·9)	6·8 (6·3)
Calcium (mg/d)	688·2 (587·5)	276·9 (236·8)	690·3 (640·1)	277·6 (245·5)	689·7 (712·6)	279·7 (255·4)
Folate (μg/d)	170·1 (138·6)	53·5 (37·0)	170·0 (165·5)	53·8 (48·7)	168·9 (179·3)	53·4 (51·5)
Vitamin D (μg/d)	9·4 (6·1)	6·5 (6·3)	9·3 (10·0)	6·4 (8·3)	9·6 (13·0)	6·6 (8·7)
Total energy (kJ/d)	6059 (5428)	1594 (1438)	6722 (6358)	1579 (1421)	7442 (7164)	1699 (1501)

Colon cancer

Intakes of total fish, of fish products, and of lean and fatty fish, respectively, in relation to colon cancer risk are listed in Table 3. We found no association between any of the fish items in this table and risk of colon cancer. However, there was a significantly higher risk of colon cancer for those in the highest tertile of poached fish consumption (RR 1·46, 95 % CI 1·04, 2·06) (Table 4). The association did not disappear after adjusting for added fats and sauces, but it became slightly reduced. The *P*-value for trend was 0·02. When examining fried fish, we found no such association.

High consumption of added fats and sauces was significantly associated with risk of colon cancer. Risk estimate for added fats and sauces in the highest tertile (> 10 g/d), compared with the lowest tertile (> 4·2 g/d), was 1·44, 95 % CI 1·03, 2·02 (adjusted for age, daily intake of energy, ever smoking, total fish, fish liver, fruit and vegetables, and fibre). Mean consumption of fats and sauces in the highest tertile was 9·3 g/d (SD 9·8).

Women diagnosed with cancer shortly after enrolment may have changed their diet due to early symptoms of disease. Therefore, to avoid biased data, we excluded all women with less than 1 year of follow-up, and repeated the analyses. This left 63 482 women for analysis, which included 225 cases of colon cancer. This changed the estimates to some degree; all estimates were slightly diminished, and there was no longer a statistically significant association between consumption of poached fish and colon cancer (RR 1·31, 95 % CI 0·91, 1·88). When excluding women with less than 2 or 3 years of follow-up, the estimates did not change notably (data not shown). However, the 95 % CI became wider due to fewer cases.

Discussion

Our results do not support previous findings of a preventive effect on colon cancer with high consumption of fish[5,19]. On the contrary, our results show a somewhat higher, although not statistically significant, risk of developing colon cancer with higher intake of fish. This is in accordance with the results from two case–control studies; one multicentre study from the USA that found an increased, borderline significant,

Table 3. Colon cancer risk in relation to fish consumption

	T1	T2	T3	*P* for trend
Total fish·(g/d)	<70·8	70·8–117	>117	
RR*	1	0·96 (0·69, 1·33)	1·25 (0·93, 1·69)	
RR†	1	0·98 (0·70, 1·37)	1·38 (0·98, 1·95)	
RR†,¶	1	0·93 (0·66, 1·31)	1·28 (0·90, 1·81)	0·14
Fish product (g/d)	<29·1	29·1–53·4	>53·4	
RR*	1	0·79 (0·57, 1·08)	1·02 (0·76, 1·36)	
RR†	1	0·80 (0·58, 1·10)	1·02 (0·74, 1·40)	
RR†,¶	1	0·76 (0·55, 1·05)	0·96 (0·69, 1·32)	0·81
Fatty fish (g/d)	<6·6	6·6–20·4	>20·4	
RR*	1	1·21 (0·89, 1·66)	1·29 (0·94, 1·75)	
RR‡	1	1·23 (0·90, 1·69)	1·25 (0·89, 1·74)	
RR‡,¶	1	1·21 (0·88, 1·66)	1·22 (0·88, 1·71)	0·24
Lean fish (g/d)	<16·5	16·5–40·8	>40·8	
RR*	1	1·15 (0·83, 1·61)	1·25 (0·92, 1·70)	
RR§	1	1·09 (0·78, 1·54)	1·30 (0·94, 1·81)	
RR§,¶	1	1·05 (0·75, 1·49)	1·23 (0·88, 1·71)	0·22

95 % CI are given in parentheses.
RR, relative risk.
* Age adjusted
† Adjusted for age, daily intake of energy, ever smoking, fish liver, fruit and vegetables, and fibre.
‡ Adjusted for age, daily intake of energy, ever smoking, lean fish, fish liver, fruit and vegetables, and fibre.
§ Adjusted for age, daily intake of energy, ever smoking, fatty fish, fish liver, fruit and vegetables, and fibre.
¶ Adjusted for added fats and sauces.

risk of colon cancer in men[20], and another study from Shanghai that found a statistically significant increase of colon cancer in men, and a non-significant increase in women with high fish consumption[21]. However, most studies have found no association between fish consumption and colon cancer[6,22–25].

Surprisingly, we found an increased risk of colon cancer with high consumption of poached fish, but not of fried fish. This was the opposite to what we expected to find. However, the risk estimate was no longer statistically significant after excluding women with less than 1 year follow-up (432 women including 29 women diagnosed with colon cancer). The different estimates may indicate that preclinical symptoms of colon cancer or other serious illness have influenced dietary habits before diagnosis, or that the number of cases is too small to discover any effect. In any case, one should be careful in drawing conclusions. A Norwegian study on the association between fish and breast cancer risk found an inverse association with consumption of poached fish[26]. It has been postulated that fried fish may be carcinogenic due to the heterocyclic amines formed in the frying process. However, in the present study, the RR for fried fish was close to unity, and more in favour of a reduced risk, which may indicate that heterocyclic amines formed in fried fish do not increase the risk of colon cancer. These findings are supported by a Swedish case–control study on dietary heterocyclic amines and colon cancer[27].

Table 4. Colon cancer risk in relation to consumption of poached and fried lean fish

	T1	T2	T3	*P* for trend
Fried fish (g/d)	<4·7	4·7–15·8	>15·8	
RR*	1	0·91 (0·66, 1·26)	0·94 (0·71, 1·25)	
RR†	1	0·90 (0·64, 1·25)	0·85 (0·62, 1·16)	
RR†,§	1	0·88 (0·63, 1·23)	0·82 (0·59, 1·13)	0·22
Poached fish (g/d)	<9·4	9·4–20·4	>20·4	
RR*	1	1·01 (0·69, 1·47)	1·37 (1·01, 1·85)	
RR‡	1	1·04 (0·70, 1·53)	1·54 (1·09, 2·16)	
RR‡,§	1	1·00 (0·68, 1·49)	1·46 (1·04, 2·06)	0·02

95 % CI are given in parentheses.
RR, relative risk.
* Age adjusted.
† Adjusted for age, daily intake of energy, ever smoking, poached fish, fish liver, fruit and vegetables, and fibre.
‡ Adjusted for age, daily intake of energy, ever smoking, fried fish, fish liver, fruit and vegetables, and fibre.
§ Adjusted for added fats and sauces.

There may be several reasons why we found an increased risk with poached fish. While fried fish normally is prepared from fresh (fresh frozen) fish, poached fish can be made from fresh, smoked, salted and dried fish. A Finnish cohort study, with a follow-up period up to 24 years, revealed a significantly higher risk of colorectal cancer with intake of smoked and salted fish[28]. Similarly, a Chinese case–control study found an increased risk of colon cancer with consumption of salted fish in both men and women[21], and a Japanese study found an increased risk of rectal cancer with salted fish for women only, but no association with colon cancer[29]. The mechanism is thought to be via nitrosamines formed during preservation of the food, which have caused mutagenity and carcinogenity in laboratory animals[21]. Unfortunately, we do not have access to information on whether the fish was fresh, smoked or salted before poaching.

One cannot disregard a possible influence from contaminants in fish. Known contaminants in fish are methyl mercury[30], dioxins and polychlorinated biphenyls[31]. The amount and type of contaminants differ according to where the fish is caught, the fish species and methods of preparation. Dioxins and polychlorinated biphenyls accumulate in the fat, and are therefore more likely to be found in fatty fish, but may also, to some extent, be present in lean fish. Methyl mercury is found in small amounts in many fish species. It accumulates

in the food chain, and is therefore found in the highest amount in carnivorous fishes. The amount increases with age and size. However, methyl mercury is not known to cause cancer in humans or animals[4].

Our results show that the risk decreases when adjusting for added fats and sauces. This indicates that consumption of fish itself may not be the reason for a higher risk, but rather the combination of the fish meal. What you serve, and eat, together in a meal may be of more importance than the consumption of one particular food. Different nutrients in different foods, eaten together, may have antagonistic or synergistic effects on each other, and thus influence the cancer risk in different ways. Studies on fish consumption and health have reported a healthier lifestyle among fish consumers than others[32,33]. Probably due to the long tradition of fish in the Norwegian diet, this is not seen among high fish consumers in Norway[8]. The total diet and lifestyle may be the cause of the higher risk of colon cancer among high consumers than among low consumers, rather than the fish itself.

Consideration must be given to the potential limitations in the present study. First, the follow-up time was relatively short. Secondly, we know from the EPIC calibration study that fish consumption is over-reported in our questionnaires[34]. However, there is no reason to believe that the distribution of the fish consumption is wrong, even if the exact amount of fish consumed may be lower than reported. Women in the highest tertile probably do eat more fish than women in the lower tertiles. The consumption of fish has been relatively stable since 1995[35]. However, data on fish consumption are uncertain, and difficult to measure due to traditionally high amounts of self-harvested fish. Consumer studies are showing an increased consumption of fish, whereas diet surveys show a slight decrease[35].

It is difficult to compare our study with other studies on fish consumption and risk of colon cancer as Norway has a higher consumption of fish compared with many other countries, and the proportion of lean, white fish is high[4,34]. However, it may be plausible to make a comparison with Japanese studies since consumption of fish is also high in Japan[24]. On the other hand, the fish consumed most in Japan are fatty fish such as salmon, trout, eel and mackerel[29], which again makes comparison difficult.

The advantages of the study are that it is a large cohort covering the whole country, and the unique person-number system in Norway makes it possible to make a valid linkage between exposure data collected in the study and data on cancer incidence through the Norwegian Cancer Registry. Also, the detailed questionnaire with information on diet and other lifestyle variables, and the special focus on fish, made it possible to study different fish items, and to adjust for known risk factors for colon cancer. Both the external validity[9] and the internal validity[11] of the NOWAC study have been examined previously and found acceptable.

In summary, the present study does not support the hypothesis of a protective effect of fish on colon cancer risk. An increased risk was seen for high consumption of poached lean fish. The mechanisms for this are unknown.

Further investigations of whole diets, such as analysing dietary patterns, are required to understand better the complexity of food and risk of colon cancer.

Acknowledgements

D.E. is supported by a PhD scholarship from the Norwegian Cancer Society.

References

1. Cancer Registry of Norway (2006) *Cancer in Norway 2004/ Kreft i Norge* 2004. 2006.
2. Cancer Registry of Norway (2006) http://www.kreftregisteret.no/ramme.htm?fakta/kreft.htm
3. Marques-Vidal P, Ravasco P & Ermelinda CM (2006) Foodstuffs and colorectal cancer risk: a review. *Clin Nutr* **25**, 14–36.
4. Alexander J, Frøyland L, Hemre G-I, *et al.* (2006) *Et helhetssyn på fisk og annen sjømat i norsk kosthold*. Norwegian Scientific Committee for Food Safety.
5. Norat T, Bingham S, Ferrari P, Slimani M, Jenab M, Mazuir M, *et al.* (2005) Meat, fish, and colorectal cancer risk: The European prospective investigation into cancer and nutrition. *J Natl Cancer Inst* **97**, 906–916.
6. Hjartaker A (2003) Fish consumption and risk of breast, colorectal and prostate cancer: a critical evaluation of epidemiological studies. *Scand J Food Nutr* **47**, 111–122.
7. Sugimura T, Wakabayashi K, Nakagama H & Nagao M (2004) Heterocyclic amines: mutagens/carcinogens produced during cooking of meat and fish. *Cancer Sci* **95**, 290–299.
8. Engeset D, Alsaker E, Ciampi A & Lund E (2005) Dietary patterns and lifestyle factors in the Norwegian EPIC cohort: the Norwegian Women and Cancer (NOWAC) study. *Eur J Clin Nutr* **59**, 675–684.
9. Lund E, Kumle M, Braaten T, Hjartaker A, Bakken K, Eggen E, *et al.* (2003) External validity in a population-based national prospective study – the Norwegian Women and Cancer Study (NOWAC). *Cancer Causes Control* **14**, 1001–1008.
10. Parr CL, Veierod MB, Laake P, Lund E & Hjartaker A (2006) Test–retest reproducibility of a food frequency questionnaire (FFQ) and estimated effects on disease risk in the Norwegian Women and Cancer Study (NOWAC). *Nutr J* **5**, 4.
11. Hjartaker A, Lund E & Bjerve KS (1997) Serum phospholipid fatty acid composition and habitual intake of marine foods registered by a semi-quantitative food frequency questionnaire. *Eur J Clin Nutr* **51**, 736–742.
12. Ferrari P, Slimani N, Ciampi A, Trichopoulou A, Naska A, Lauria C, *et al.* (2002) Evaluation of under- and overreporting of energy intake in the 24-hour diet recalls in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Public Health Nutr* **5**, 1329–1345.
13. Blaker B & Aarsland M, Landsforeningen for kosthold og helse (1989) *Mål og vekt for matvarer*. Oslo: Landsforeningen for kosthold & helse.
14. Rimestad AH, Statens næringsmiddeltilsyn, Statens råd for ernæring og fysisk aktivitet, Universitetet i Oslo, Institutt for ernæringsforskning (2001). *Matvaretabellen*. 2. utg ed. Oslo: Gyldendal undervisning.
15. Trondsen T, Scholderer J, Lund E, *et al.* (2003) Perceived barriers to consumption of fish among Norwegian women. *Appetite* **41**, 301–314.
16. Brustad M, Manning T, Andersen V & Lund E (In the press) POP exposure from fish liver consumption and risk of cancer - The Norwegian Women and Cancer Study.
17. Andersen P & Gill R (1982) Cox's regression model for counting processes, a large sample study. *Ann Statistics* **10**, 1100–1120.
18. Grambsch PM & Therneau TM (1994) Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* **81**, 515–526.

19. Franceschi S, Favero A, La Vecchia C, Negri E, Conti E, Montella M, *et al.* (1997) Food groups and risk of colorectal cancer in Italy. *Int J Cancer* **72**, 56–61.
20. Kampman E, Slattery ML, Bigler J, Leppert M, Samowitz W, Caan BJ, *et al.* (1999) Meat consumption, genetic susceptibility, and colon cancer risk: a United States multicenter case–control study. *Cancer Epidemiol Biomarkers Prev* **8**, 15–24.
21. Chiu BC, Ji BT, Dai Q, Gridley G, McLaughlin JK, Gao YT, *et al.* (2003) Dietary factors and risk of colon cancer in Shanghai, China. *Cancer Epidemiol Biomarkers Prev* **12**, 201–208.
22. Brink M, Weijenberg MP, de Goeij AF, Roemen GM, Lentjes MH, de Bruine AP, *et al.* (2005) Meat consumption and K-ras mutations in sporadic colon and rectal cancer in The Netherlands Cohort Study. *Br J Cancer* **92**, 1310–1320.
23. English DR, MacInnis RJ, Hodge AM, Hopper JL, Haydon AM & Giles GG (2004) Red meat, chicken, and fish consumption and risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev* **13**, 1509–1514.
24. Kobayashi M, Tsubono Y, Otani T, Hanaoka T, Sobue T & Tsugane SJPHC Study Group (2004) Fish, long-chain n-3 polyunsaturated fatty acids, and risk of colorectal cancer in middle-aged Japanese: the JPHC study. *Nutr Cancer* **49**, 32–40.
25. Larsson SC, Rafter J, Holmberg L, Bergkvist L & Wolk A (2005) Red meat consumption and risk of cancers of the proximal colon, distal colon and rectum: the Swedish Mammography Cohort. *Int J Cancer* **113**, 829–834.
26. Vatten LJ, Solvoll K & Loken EB (1990) Frequency of meat and fish intake and risk of breast cancer in a prospective study of 14,500 Norwegian women. *Int J Cancer* **46**, 12–15.
27. Augustsson K, Skog K, Jagerstad M, Dickman PW & Steineck G (1999) Dietary heterocyclic amines and cancer of the colon, rectum, bladder, and kidney: a population-based study. *Lancet* **353**, 703–707.
28. Knekt P, Jarvinen R, Dich J & Hakulinen T (1999) Risk of colorectal and other gastro-intestinal cancers after exposure to nitrate, nitrite and N-nitroso compounds: a follow-up study. *Int J Cancer* **80**, 852–856.
29. Yang CX, Takezaki T, Hirose K, Inoue M, Huang XE & Tajima K (2003) Fish consumption and colorectal cancer: a case–reference study in Japan. *Eur J Cancer Prev* **12**, 109–115.
30. Sanzo JM, Dorronsoro M, Amiano P, Ammurio A, Aquinagalde FX, Azpiri MA, *et al.* (2001) Estimation and validation of mercury intake associated with fish consumption in an EPIC cohort of Spain. *Public Health Nutr* **4**, 981–988.
31. Sjodin A, Hagmar L, Klasson-Wehler E, Bjorg J & Berman A (2000) Influence of the consumption of fatty Baltic Sea fish on plasma levels of halogenated environmental contaminants in Latvian and Swedish men. *Environ Health Perspect* **108**, 1035–1041.
32. Hu FB, Bronner L, Willett WC, Stampfer MJ, Rexrode KM, Albert CM, *et al.* (2002) Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *J Am Med Assoc* **28**, 1815–1821.
33. Oomen CM, Feskens EJ, Rasanen L, Fidanza F, Nissinen AM, Menotti A, *et al.* (2000) Fish consumption and coronary heart disease mortality in Finland, Italy, and The Netherlands. *Am J Epidemiol* **151**, 999–1006.
34. Welch AA, Lund E, Amiano P, Brustad M, Kumle M, Rodriguez M, *et al.* (2002) Variability of fish consumption within the 10 European countries participating in the European Investigation into Cancer and Nutrition (EPIC) study. *Public Health Nutr* **5**, 1273–1285.
35. Sosial og helsedirektoratet (2005) *Utviklingen i norsk kosthold 2005*.