# Dietary Fish Intake and Risk of Leukaemia, Multiple Myeloma, and Non-Hodgkin Lymphoma

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## Abstract

**This study aimed to determine whether fish intake was protective against leukemia, multiple myeloma, and non-Hodgkin lymphoma (NHL), and if our previous finding of a protective effect of fish-related occupations on the risk of these diseases was due to dietary intake of fish. We used data from a population-based case-control study undertaken in Canada in 1994–1998. Dietary information was available for 919 leukemia cases, 287 myeloma cases, 1418 NHL cases, and 4202 controls. The risk of each of the three cancers was determined using multiple logistic regression analysis according to quartiles of weekly fresh fish intake, percentage of total energy intake from fresh fish, and percentage of total fat intake from fresh fish. After adjusting for age, sex, smoking, BMI, and proxy status, people who consumed greater proportions of their total energy intake from fresh fish had a significantly lower risk of each of the three types of cancer, and there was a significant dose-response for risk of leukemia and NHL. Those in the highest quartile for percentage of fat intake from fish were at lowest risk: leukemia odds ratio (OR) 0.72, 95% confidence interval (CI) 0.58–0.89; multiple myeloma OR 0.64, 95% CI 0.45–0.90; NHL OR 0.71, 95% CI 0.60–0.85; and all LH cancers combined OR 0.70, 95% CI 0.61–0.81. The protective effect previously observed for working with fish on the risk of leukemia and lymphoma was independent of fish intake. These findings suggest that a diet high in fish may be protective against lymphohematopoietic cancers and confirm the reduced risk among fish workers.** (Cancer Epidemiol Biomarkers Prev 2004;13(4):532–537)

## Introduction

The question of whether dietary intake of fish is related to lymphohematopoietic (LH) cancer risk remains unresolved with some studies showing a protective association (1–4) while others show an increase in risk (5) or no association (6).

We recently completed an analysis of Canadian National Enhanced Cancer Surveillance System (NECSS) data which examined the risk of leukemia, multiple myeloma, and non-Hodgkin lymphoma (NHL) in animal-related occupations (7). An unexpected finding of that analysis was a substantial reduction in the risk for leukemia and NHL among those in fishing occupations [leukemia odds ratio (OR) = 0.4; NHL OR = 0.6]. The effect seemed stronger among fishers rather than fish processors and increased with time exposed. We hypothesized that this association may have been due to increased dietary fish intake in people who work in fish-related occupations.

There are no current effective preventive messages for leukemia and NHL and more evidence is needed on the existence and extent of any protective effect of fish intake.

Therefore, this study was undertaken to determine whether fish intake was protective against leukemia, lymphoma, and myeloma and whether the finding of a protective effect of fish-related occupations on the risk of these diseases was due to dietary intake of fish.

## Materials and Methods

This study used data collected as part of the NECSS which was a collaboration between the federal health department (Health Canada) and 8 of the 10 provincial cancer registries. The study collected detailed risk factor information from a large population-based sample of over 20,000 recently diagnosed cancer patients (19 types of cancer) and a comparison sample of population controls. We used data from controls ($n$ = 4202) and from subjects with leukemia ($n$ = 919), multiple myeloma ($n$ = 287), or NHL ($n$ = 1418). Response fractions for questionnaires sent were 70.4%, 73.5%, and 75.1% for leukemia, myeloma, and NHL, respectively. For the

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92.5% of controls with a valid current address, 64.6% of men and 70.2% of women responded. Cases generally completed the questionnaire between 3 and 5 months from diagnosis. Proxy respondents were interviewed in Ontario only, for the 92 subjects who were deceased or too ill to complete the interview.

A self-completed 60-item food frequency questionnaire (FFQ) was included in the NECSS questionnaire. The FFQ was modeled on two extensively validated FFQs (8, 9) from the United States and was altered very slightly to reflect Canadian national food disappearance patterns. A Canadian nutrient database was used to calculate nutrient values (10). To minimize the impact of seasonality, cases were collected over a continuous 2- to 4-year period: for NHL, three randomly selected cases out of every five cases over 2 years; for leukemia, every eligible case over 2 years; and for multiple myeloma, every case over 4 years. Controls were collected evenly over a 1-year period in the mid-year of the study.

The information collected on dietary fish intake related to diet 2 years (and 20 years) before ascertainment (diagnosis date for cases and date of contact for controls). It included: number of servings per month of fresh, frozen or canned fish and smoked, salted or dried fish; total energy (kilojoules) intake; and total fat intake. Using total energy intake and total fat intake estimated by the FFQ, we calculated the proportion of total fat (% fat) and proportion of total energy (% energy) obtained from fresh fish, smoked fish, and all fish.

Subjects were also asked how their current diet compared to their intake 20 years ago. The relevant question for this study was: ''Compared to 2 years ago, 20 years ago I used to consume *X* chicken or fish'' where *X* = much less, somewhat less, about the same, somewhat more, much more. Because chicken and fish were combined in this question, we could not use it directly, but repeated the analyses above using only those subjects who stated that they ate about the same chicken and fish now that they did 20 years ago.

Subjects also completed an occupational history comprising all jobs held for 12 months or more (job title, industry, major tasks performed, and start and end date). Jobs were coded manually according to whether exposure to fish was likely, whether fish exposure was as packaging or fishing, and the duration of fish exposure (7). The coder was blind to case or control status. Fish exposure was aggregated for each subject by combining multiple jobs with fish exposure into total duration exposed.

The three case groups and the controls were compared using means and cross tabulations with regard to: intake of fresh and smoked fish, energy, and fat; age; sex; body mass index (BMI); smoking status (current/ex/never); and whether the interview was conducted with the subject or a proxy.

Multiple logistic regression was used to compare controls with cases of all three cancers combined (referred to as all LH cancers) and then each cancer separately according to quartiles of servings of fresh fish and smoked fish eaten per week, percentage of total fat intake from fresh and smoked fish, and percentage of total energy intake from fresh and smoked fish. Models were adjusted for age, sex, smoking, BMI, and proxy status. Trend tests were used in conjunction with the categorical analysis to examine dose-response relationships. Because of the small numbers of subjects who ate smoked fish, cancer risk was also examined according to whether subjects ever ate smoked fish. All analyses were repeated stratifying for sex.

To determine whether the protective effect of a fish-related occupation was due to diet, multiple logistic regressions were completed for fish work alone, for fish work adjusting for the above co-variates, and for fish work and dietary fish intake adjusting for co-variates.

## Results

We included all of those subjects who were in our initial study of animal occupations (7) and who had information available on energy, total fat, and fish intake. Of the 7612 subjects in the original study, 786 (10.3%) were missing data on fresh fish ($n$ = 149), and/or smoked fish ($n$ = 385), and/or had one or more food frequency items missing which meant total fat and total kilojoules could not be completed ($n$ = 719). We also omitted implausible daily energy intakes of less than 3,000 kJ ($n$ = 42) or more than 21,000 kJ ($n$ = 34). Missing status was not significantly associated with cancer status or with occupational fish exposure (data not shown). The final numbers of subjects included were 4175 controls, 914 leukemia cases, 287 myeloma cases, and 1408 NHL cases.

Compared to the subjects with cancer, controls were more likely to be a current smoker, had a lower BMI, and were less likely to have had proxy respondents answering the questionnaire (Table 1). Leukaemia cases were more likely than the other groups to be male and have a proxy respondent. Myeloma cases were older and less likely to have ever smoked. There was no association between level of education and cancer status. Controls were more likely to have been in a fish-related occupation.

Cases and controls tended to eat a similar number of servings of fish a week, but controls ate less fat, had lower energy consumption, and had greater proportions of their fat and kilojoule intakes coming from fish than cases (Table 2).

After adjusting for age, sex, smoking, BMI, and proxy status (Table 3), increased weekly servings of fresh fish had a protective effect on all LH cancers combined ($P$ value for trend 0.004) and leukemia ($P$ = 0.008). Increasing fat and energy consumption marginally increased the risk of all cancers. Subjects who consumed greater proportions of their total energy or fat from fresh fish had a significantly lower risk of each of the three types of cancer ($P$ for trend <0.01 for all analyses). Few subjects ate smoked fish, and although there was some suggestion that it had a protective effect, this effect was only statistically significant for all LH and for NHL.

Analyses were repeated separately for males ($n$ = 3614) and females ($n$ = 3170). The ORs in males for the percentage of fat and energy coming from fresh fish were generally lower (more protective) than in females (Table 4). For males, the protective effect of fresh fish was particularly strong for leukemia ($P$ for trend <0.001). The protective effect was less marked for males when servings of fresh or smoked fish or percentage of fat and energy from smoked fish was examined (data not

**Table 1. Demographic characteristics of the cases and controls**

| | Controls (*N* = 4175) | Leukaemia (*N* = 914) | Myeloma (*N* = 287) | NHL (*N* = 1408) |
|---|---|---|---|---|
| Age (mean) | 56.0 | 56.2 | 62.8 | 56.7 |
| Male (%) | 51.7 | 61.2 | 48.1 | 54.0 |
| Current smoker (%) | 19.5 | 13.0 | 7.0 | 14.3 |
| Ex smoker (%) | 43.4 | 52.1 | 50.2 | 47.7 |
| Never smoker (%) | 37.2 | 34.8 | 42.9 | 38.1 |
| BMI (mean) | 25.7 | 26.5 | 26.7 | 26.2 |
| Years of education (mean) | 12.4 | 12.2 | 11.8 | 12.3 |
| Proxy respondent (%) | 0.1 | 7.1 | 1.7 | 1.3 |
| Fish-related occupation (%) | 2.5 | 1.0 | 1.0 | 1.4 |

shown). However, statistically significant protective effects were found for percentage of fat and energy from smoked fish for all cancers and for NHL. In females, the effect of fresh or smoked fish intake (as servings or as proportion of energy or fat) was weaker with few results significantly different from unity. However, a statistically significant effect of higher proportions of fat from fresh fish still existed for NHL (*P* for trend 0.01).

When the analyses were restricted to those subjects who stated that their chicken and fish consumption was the same now as it was 20 years ago ($n$ = 3157), the results were essentially the same, although the confidence intervals (CIs) were wider (data not shown).

The three eastern provinces (Nova Scotia, Prince Edward Island and Newfoundland; $n$ = 1044) had slightly different sampling schemes to the rest of the country. Nova Scotia collected additional controls to complement an extended lung cancer data collection. Newfoundland recruited many of their cases while they attended the cancer clinic, and Prince Edward Island took all cases for all three cancers over 3 years because it has a population of only 100,000. Restricting the analysis to subjects from these provinces resulted in similar results for fresh fish and all fish, although none were statistically significant (data not shown). Results for smoked fish were close to unity and were not statistically significant.

To determine if the protective effect of working with fish was due to the fish workers eating more fish in their diet, the regression analyses were repeated including a variable for whether a subject had ever worked with fish. These analyses showed that the effect of working with fish was independent of the effect of fish intake (Table 5).

## Discussion

The major conclusion of this paper is that increasing proportions of total energy and fat obtained from fresh fish seems to protect against the development of leukemia, NHL, and myeloma. For all cancer types, the strongest reduction in risk was associated with increasing proportion of total fat obtained from fresh fish. This supports the hypothesis that dietary fats provided by fish are the key to the protective effect of fish intake against LH and other cancers. The eicosapentaenoic (EPA) and docosahexanoic (DHA) fatty acids are consumed mostly from fatty fish native to cold waters. These long chain polyunsaturated n-3 fatty acids are thought to competitively inhibit the use of arachidonic acid, an n-6 fatty acid, for the production of eicosanoids (*e.g.*, prostaglandins, leukotrienes). Eicosanoids derived from arachidonic acid have been associated with several carcinogenic processes including both tumor promotion and progression (11). A ratio of n-3:n-6 fatty acid intake ≥0.5 may be important in reducing cancer risk; however, Western diets tend to result in a much lower ratio (11).

Estimated energy intakes were low in this study (8405 kj/day for controls) which is probably due to the FFQ design. Assuming underestimation of energy intake was consistent for all respondents, this does not present a problem for our analyses, as to overcome differences in total food intake we examined fish intake relative to total

**Table 2. Number of servings of fish a week, mean total dietary fat and energy intake, and percentage of fat and energy from fish in cases and controls**

| | Controls (*N* = 4202) | Leukaemia (*N* = 919) | Myeloma (*N* = 287) | NHL (*N* = 1418) | *P* value |
|---|---|---|---|---|---|
| Fresh fish servings/wk | | | | | 0.06 |
| 0 | 14.8% | 16.8% | 15.7% | 14.5% | |
| <0.5 | 33.2% | 37.2% | 34.5% | 34.8% | |
| 0.5 to <4 | 34.3% | 31.9% | 30.7% | 35.1% | |
| 4+ | 17.6% | 14.1% | 19.2% | 15.7% | |
| Smoked fish servings/wk | | | | | 0.16 |
| 0 | 77.7% | 80.7% | 79.8% | 81.2% | |
| <0.5 | 14.6% | 12.6% | 12.5% | 11.5% | |
| 0.5 to <4 | 5.4% | 5.2% | 5.6% | 5.2% | |
| 4+ | 2.2% | 1.4% | 2.1% | 2.0% | |
| Total fat g/day—mean | 50.6 | 54.6 | 52.7 | 54.6 | <0.001 |
| Total kj/day—mean | 8405 | 8796 | 8818 | 8833 | <0.001 |
| % fat from fresh fish—mean | 1.92 | 1.50 | 1.64 | 1.67 | <0.001 |
| % fat smoked fish—mean | 0.13 | 0.09 | 0.11 | 0.11 | 0.04 |
| % kj from fresh fish—mean | 1.25 | 1.03 | 1.14 | 1.13 | <0.001 |
| % kj smoked fish—mean | 0.28 | 0.22 | 0.26 | 0.25 | 0.2 |

**Table 3. ORs and 95% CI for risk of LH cancers by fish intake[a]**

| Model | All LH | Leukaemia | Myeloma | NHL |
|---|---|---|---|---|
| Fresh fish servings/wk | | | | |
| <0.5 | 1.00 (0.86–1.17) | 0.97 (0.78–1.21) | 0.87 (00.60–1.23) | 1.05 (0.87–1.27) |
| 0.5 to <4 | 0.90 (0.77–1.05) | 0.80 (0.64–1.00) | 0.68 (0.47–1.00) | 1.01 (0.84–1.22) |
| 4+ | 0.81 (0.68–0.97)* | 0.72 (0.55–0.93)* | 0.76 (0.50–1.16) | 0.88 (0.71–1.10) |
| Smoked fish servings/wk | | | | |
| <0.5 | 0.80 (0.69–0.93) | 0.83 (0.67–1.03) | 0.88 (0.61–1.27) | 0.76 (0.63–0.91) |
| 0.5 to <4 | 0.95 (0.76–1.19) | 0.94 (0.68–1.31) | 1.07 (0.63–1.82) | 0.93 (0.71–1.22) |
| 4+ | 0.78 (0.55–1.12)* | 0.64 (0.36–1.16) | 0.88 (0.38–2.05) | 0.85 (0.56–1.31) |
| Total fat g/day—per gram | 1.004 (1.002–1.006) | 1.002 (1.000–1.004) | 1.003 (1.000–1.005) | 1.004 (1.002–1.006) |
| Total kj/day—per 1000 kj | 1.03 (1.02–1.05) | 1.02 (1.00–1.04) | 1.03 (1.00–1.05) | 1.03 (1.01–1.05) |
| % fat from fresh fish | | | | |
| Q2 | 0.84 (0.73–0.97) | 0.89 (0.73–1.09) | 0.87 (0.62–1.22) | 0.80 (0.68–0.95) |
| Q3 | 0.79 (0.69–0.91) | 0.77 (0.63–0.95) | 0.65 (0.46–0.92) | 0.83 (0.70–0.99) |
| Q4 | 0.70 (0.61–0.81)* | 0.72 (0.58–0.89)* | 0.64 (0.45–0.90)* | 0.71 (0.60–0.85)* |
| % fat from smoked fish | | | | |
| any | 0.83 (0.74–0.94) | 0.84 (0.70–1.01) | 0.92 (0.68–1.25) | 0.81 (0.69–0.94) |
| % kj from fresh fish | | | | |
| Q2 | 0.87 (0.76–1.00) | 0.95 (0.78–1.16) | 0.84 (0.60–1.17) | 0.84 (0.70–0.99) |
| Q3 | 0.77 (0.67–0.89) | 0.74 (0.60–0.91) | 0.61 (0.43–0.87) | 0.82 (0.69–0.98) |
| Q4 | 0.75 (0.65–0.87)* | 0.73 (0.59–0.90)* | 0.69 (0.49–0.97)* | 0.78 (0.66–0.93)* |
| % kj from smoked fish any | 0.83 (0.74–0.94) | 0.84 (0.70–1.01) | 0.92 (0.68–1.25) | 0.81 (0.69–0.94) |

[a]Adjusted for age, sex, smoking, BMI, and proxy.
*$P$ value for trend <0.01.

energy intake and relative to total fat intake. One shortcoming of our dietary assessment is that we were not able to separate the consumption of fatty fish, which are richer in EPA and DHA, from lean fish types. However, much of the fish consumed in our Canadian study population is likely to be fatty fish, as these are fished from cold waters.

We found the protective effect of fish to be much stronger in males than females for all three cancers. Case-control studies in Italy reported the risks for myeloma and NHL separately by sex (1). For myeloma, there was a protective effect for both sexes (OR = 0.8 for males and 0.7 for females) although it was not statistically significant. For NHL, there was a protective effect for males (OR = 0.8) but not for females (OR = 1.0) as in our study. However, a case-control study in Japan (12) found a protective effect of eating fish dishes more than three times a week on NHL to be stronger in females.

Leukemia and fish intake was examined in a cohort study in the United States which found no association between fish and seafood intake and later development of all leukemias combined (6). However, when acute myeloid leukemia (AML, $n$ = 48) and chronic lymphocytic leukemia (CLL, $n$ = 58) were examined separately, there was a nonsignificant decrease of AML risk with increasing fish consumption, and a nonsignificant

**Table 4. ORs and 95% CI for risk of LH cancers by proportion of fat and energy coming from fresh fish intake by sex[a]**

| Model | All LH | Leukaemia | Myeloma | NHL |
|---|---|---|---|---|
| Males | | | | |
| % fat from fresh fish | | | | |
| Q2 | 0.79 (0.66–0.95) | 0.77 (0.60–0.99) | 0.82 (0.52–1.31) | 0.79 (0.63–0.99) |
| Q3 | 0.76 (0.63–0.92) | 0.62 (0.47–0.82) | 0.69 (0.43–1.13) | 0.87 (0.69–1.10) |
| Q4 | 0.63 (0.52–0.77)* | 0.56 (0.42–0.74)* | 0.51 (0.30–0.86)* | 0.71 (0.56–0.91) |
| % kj from fresh fish | | | | |
| Q2 | 0.79 (0.66–0.95) | 0.79 (0.61–1.02) | 0.79 (0.50–1.27) | 0.79 (0.63–1.00) |
| Q3 | 0.73 (0.61–0.89) | 0.62 (0.78–0.82) | 0.64 (0.40–1.04) | 0.83 (0.66–1.04) |
| Q4 | 0.66 (0.54–0.80)* | 0.54 (0.40–0.71)* | 0.57 (0.35–0.95) | 0.77 (0.60–0.97) |
| Females | | | | |
| % fat from fresh fish | | | | |
| Q2 | 0.93 (0.75–1.15) | 1.17 (0.83–1.65) | 0.91 (0.55–1.49) | 0.93 (0.64–1.07) |
| Q3 | 0.85 (0.69–1.05) | 1.10 (0.78–1.55) | 0.62 (0.37–1.03) | 0.80 (0.62–1.03) |
| Q4 | 0.81 (0.65–1.00) | 1.05 (0.75–1.48) | 0.78 (0.48–1.27) | 0.72 (0.56–0.93) |
| % kj from fresh fish | | | | |
| Q2 | 1.01 (0.82–1.25) | 1.32 (0.94–1.85) | 0.88 (0.54–1.44) | 0.90 (0.70–1.16) |
| Q3 | 0.84 (0.68–1.04) | 1.01 (0.71–1.44) | 0.58 (0.35–0.98) | 0.82 (0.64–1.06) |
| Q4 | 0.89 (0.73–1.10) | 1.14 (0.81–1.60) | 0.82 (0.551–1.32) | 0.81 (0.63–1.04) |

[a]Adjusted for age, smoking, BMI, and proxy.
*$P$ value for trend <0.01.

**Table 5. ORs and 95% CIs for working with fish, with and without adjusting for fish in diet**

| Model | Model | All LH | Leukaemia | Myeloma | NHL |
|---|---|---|---|---|---|
| 1. Unadjusted | Fish work | 0.50 (0.33–0.74) | 0.40 (0.20–0.78) | 0.42 (0.13–1.32) | 0.56 (0.35–0.91) |
| 2. Adjusted[a] | Fish work | 0.51 (0.35–0.78) | 0.39 (0.20–0.77) | 0.42 (0.13–1.35) | 0.57 (0.35–0.92) |
| 3. Adjusted[a] | % fat from fresh fish | | | | |
| | Q2 | 0.84 (0.73–0.97) | 0.89 (0.73–1.09) | 0.87 (0.62–1.22) | 0.80 (0.68–0.95) |
| | Q3 | 0.79 (0.69–0.91) | 0.77 (0.63–0.95) | 0.65 (0.46–0.92) | 0.83 (0.70–0.99) |
| | Q4 | 0.70 (0.61–0.81) | 0.72 (0.58–0.89) | 0.64 (0.45–0.90) | 0.71 (0.60–0.85) |
| 4. Adjusted[a] | Fish work | 0.51 (0.34–0.76) | 0.41 (0.20–0.81) | 0.43 (0.14–1.38) | 0.58 (0.36–0.94) |
| | % fat from fresh fish | | | | |
| | Q2 | 1.00 (0.86–1.17) | 0.97 (0.78–1.21) | 0.88 (0.60–1.27) | 1.05 (0.87–1.27) |
| | Q3 | 0.91 (0.78–1.06) | 0.80 (0.64–1.01) | 0.69 (0.47–1.00) | 1.02 (0.84–1.23) |
| | Q4 | 0.82 (0.69–0.98) | 0.73 (0.56–0.95) | 0.77 (0.51–1.73) | 0.89 (0.72–1.11) |

[a]Adjusted for age, sex, smoking, BMI, and proxy.

increase of CLL risk. A small case-control study of leukemia in those under 25 years old near a nuclear reprocessing plant found a raised risk with consumption of local fish and seafood but this result was not adjusted for any potential confounders (5).

There have been three case-control studies of myeloma which have reported ORs for fish consumption (1, 2, 4). These have all shown a statistically significant protective effect of fish consumption with the OR for the highest tertile or quartile similar to our finding of about 0.6–0.7. However, a report of a cluster of seven myelomas in a small Japanese village found the only common factor to be that five of the seven cases had been fishermen for long periods (13). The authors suggest that contaminated seafood may have been the causal factor.

Two case-control studies (1, 2) and one cohort study (3) have found nonsignificant decreases in the risk of NHL with the highest group of fish consumption at a similar level to ours. Another case-control study (14) reported that fish consumption was not associated with NHL risk, but did not show the effect estimates. All these studies were much smaller than ours, ranging from 104 to 429 cases. No relation was found between NHL and consumption of fish or of fish n-3 fatty acids in the Nurses' Health Study (15).

Animal studies have found that consumption of fish oils increases survival of animals with cancer (16).

None of the indicators of fish intake examined in this study could explain our finding of a protective effect of working in a fish-related occupation on risk of leukemia, multiple myeloma, and NHL. We had previously hypothesized (7) that the effect we found was due to diet, as it is known that fishers tend to eat more fish than the general population. Those in fish-related occupations in our study did eat more fish than the rest of the subjects, but when we adjusted for the amount of fish in their diet, the effect of occupation did not disappear. There have been four previous cohort studies of fishers in Scandinavian countries (17–20). Generally, the SMRs and SIRs reported in these studies have been between 1.0 and 2.0 for leukemia, around 1.0 for NHL, and between 1.0 and 4.0 for myeloma. All reported results have wide CIs because they are based on small numbers of cases or deaths. The authors of one of the studies have hypothesized that the increase in risk was due to increased intake of persistent organochlorine compounds found in the Baltic Sea (18). A study of commercial fishermen in Atlantic Canada found an increased risk of lymphoma and leukemia when compared to the general population, after adjusting the SMRs so that the all cause SMR was equal to 1 (21). When they examined SMRs by age group, fishers under the age of 45 had a higher risk than older fishers.

One possible explanation of this finding is that people in fish-related occupations may be more likely to eat lobster, crab, mussels, or other shellfish that might provide some protective effect. We were unable to evaluate this component of diet because our FFQ did not capture seafood intake. No previous publications have specifically addressed this issue. Another possible explanation is the discordance in time between the fish-related work and the diet. The fish-related occupation may have been held at any time during the subject's life, while the diet information referred to a time 2 years before the questionnaire was completed. It may well be that the diet questionnaire did not therefore measure the true level of fish intake at the time of the fish-related job.

Apart from these two explanations, it is not clear what other factors may be responsible for our finding among Canadians in fish-related occupations. Fishing is a difficult job which involves heavy physical stress, long working hours including shift work, exposure to noise, extreme weather, vibration, heat, and cold (22). Their working environment has been described as ''A cramped mini-factory which pitches and rolls'' (22). Similarly, fish processing involves hard, repetitive boring tasks. Few studies have been done evaluating whether high levels of physical activity protect against LH cancers, and the ones which have been published have found no association between exercise and NHL (23, 24). It may be that despite the large sample size and the robustness of the finding within our data, that it is a chance finding which is not repeatable within other data sets.

Advantages of this study include the large numbers of cases and controls, the nationwide population-based sample frame, the case-by-case assessment of occupational fish exposure, and the ability to adjust for a range of potential confounding factors. Selection bias was probably minimal because the response rate for cases and controls was respectable, and proxy respondents allowed us to include data from deceased subjects, at least in the largest province. Although about 10% of subjects were missing FFQ data, inclusion was not associated with case status or with fish occupation. Some of the analyses, especially of multiple myeloma, were based on smaller numbers of exposed cases, and should be interpreted with caution.

In summary, in a very large case-control study, we have found a strong protective effect of fresh fish intake for leukemia, myeloma, and NHL which is consistent with previous literature.

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