Author’s response to reviews

Title: Fatty fish and fish omega-3 fatty acid intakes decrease the breast cancer risk: a case-control study

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Version: 2 Date: 25 March 2009

Author’s response to reviews: see over
Dear Editor-in-Chief:

Thank you very much for your letter dated Feb 27th, 2009 inviting us to submit a revised manuscript, referred to above, to your journal. The authors greatly appreciate the detailed and invaluable comments from the editor and referees to improve this manuscript. We have made modifications to the manuscript according to the referees’ suggestions. Changes are highlighted in the revised manuscript. Detailed information regarding the revision is provided in the attached document “Authors’ Responses”.

We hope that we have adequately addressed the referees’ concerns and that the revised manuscript is now acceptable for publication in the *BMC Cancer*. We are looking forward to hearing from you regarding the journal’s decision.

Sincerely,

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Response to the Associate Editor:

1) Editor: As one of the referees also comments on there seems to be a mismatch between the last paragraph of the result section (regarding table 4) and table 4. This needs to be sorted out. Please also check with the statements and figures given in the result section of the abstract.
Authors: The previous version of Table 4 did not reflect the final results. We have corrected Table 4 and the text with the final results.

2) Editor: Using the paper by Hirose et al 2007 (reference 31) as a reference, the authors state that the fish consumption in Japan and Korea is much higher than in Western countries. Still, the fish intake reported in the present study is low. The surprisingly low fish intake should be commented on.
Authors: The mean daily consumption of 24.1 g of total fish identified by this study, consists of 2.3 % of total daily energy intake, but the US population consumed only 0.74% of their total energy from fish. The proportion was 6.21% in the Japanese population. The sentence has been added to page 12, lines 19-22.

Response to the Referee #1:

1. Major Compulsory revisions
Referee: A number of risk factors for breast cancer have been established, most of which relate to reproductive events. Risk is increased by an early onset of menarche, nulliparity, late age at first birth and late natural menopause. The authors failed to observe these definite associations among the present study population. It may be indeed impossible for the reader to critically evaluate to which extent the controls reflect the exposure prevalence in the study base which gave rise to the cases. The authors should provide a bit more discussion on this point.
Authors: We agree with the referee’s concern and have inserted a discussion on the possibility of selection bias of the control group as one of the limitations of the current study (page 14, lines 16-23).

Referee: I would like to know the meat, fruit and vegetables intake among subjects who have higher intake of fish. Please provide the information of nutrient intake according to ω-3 fatty acids intake level. The intake frequency of fish may tend to be negatively associated with the intake of meat, or to be positively associated with the intake of fruit and vegetables. This effect observed in the present study may be related, in part, to lower intake of meat, higher intake of dietary fiber and antioxidant vitamins.
Authors: As indicated in Supplementary Tables 1 and 2 provided to the referee, the intakes of meat, vegetables, fruits, dietary fiber, and antioxidant vitamins were all positively correlated with the intake amounts of total fish, fatty or lean fishes, and ω-3 fatty acids. Therefore, adjusting for total energy intake accounts for most of the effects of other food intake.
Referee: The results form validation study concerning estimation of fish ω-3 fatty acids or fish intake should be helpful.

Authors: The validity of the FFQ used in the current study has been tested using 3-day dietary records as a gold standard in a total of 202 persons. The de-attenuation correlation coefficients, percent agreements of the same plus adjacent quartile categories, and percent gross misclassification for total ω-3 fatty acids were 0.491, 75.2%, and 8.3%, respectively, 0.482, 70.6%, and 10.1% for EPA, respectively, and 0.549, 74.3%, and 5.5% for DHA, respectively (page 7, lines 19-25).

2. Minor Essential Revisions

Referee: <Background> (first paragraph) fish old --> fish oil ?

Authors: The correction was made as the referee indicated (page 4, line 8).

Referee: <Method> I would like to know how many food items were included in fatty and lean fish group. Please list up the kind of fish of each fish group.

Authors: Eight fish items, covering 6 fatty fishes and 17 lean fishes, were included in the FFQ. The eight items were raw fish, blue (fatty) fish, hair tail, eel, yellow croaker/sea bream/flat fish, Alaskan pollack/Alaskan pollack (frozen)/Alaskan Pollack (dried), anchovy/anchovy (marinated) and tuna (canned) (page 7, lines 13-16). The list of fatty fishes covered by the eight fish items are as follows: 1) tuna, bluefin yellow-fin tuna, canned; 2) mackerel, raw; 3) anchovy, raw; 4) Spanish mackerel, raw; 5) Pacific saury, raw; 6) tuna, bluefin yellow-fin tuna, raw.

The list of lean fishes covered by the eight FFQ items are as follows: 1) Alaskan pollack, dried, immature; 2) bastard halibut, raw; 3) eel, conger eel, raw; 4) Alaskan pollack, semi-dried; 5) Alaskan pollack, dried; 6) Alaskan pollack, raw; 7) eel, raw; 8) Alaskan pollack, dried strip; 9) flat fish, raw, flounder; 10) yellow croaker, salt-cured, dried; 11) eel, hagfish; 12) sea bream, blanquillo; 13) yellow croaker, raw; 14) Alaskan pollack, frozen; 15) fine-spotted, flounder; 16) common sea bass, raw; 17) hair tail, raw.

Referee: The author should state briefly the energy-adjusted method in text.

Authors: Total energy intake (continuous variable) was adjusted in the multivariate logistic model as one of the independent variables (page 8, lines 16-17).

Referee: <Results> Is the statement of Table 4 is right? Please make sure the values of ORs.

Authors: The previous Table 4 did not reflect the final results, and both Table 4 and the text have been corrected with the final results.

Response to the Referee #2:

Referee: In general, I found the language a bit difficult. Having English as a second language myself, I know how difficult it is to write good and proper English. My advice to the authors is to have someone with good English skills (preferably a native English spoken
person) to check the language.

Authors: The revised manuscript has been edited by qualified, native English-speaking editors.

(Minor Essential Revisions)

Referee: Background: In the first paragraph, line 7, you write “…. and fish old or a diet containing…” What do you mean by “fish old”?
Authors: The typo has been corrected to “fish oil” (page 4, line 8).

(Discretionary Revisions)

Referee: Further, you mention a Swedish study and a Danish study have examined the association between lean and fatty fish consumption and breast cancer risk. This is correct, but it is also worth mentioning that the large multi-centre EPIC study examined this association as well. In this study they saw a positive association with high consumption of fatty fish and risk of breast cancer.
Authors: The results of the EPIC study have been mentioned in the revised manuscript (page 4, lines 18-23).

(Minor Essential Revisions)

Referee: Methods: Subjects: I am a bit uncertain about the control group. Could you explain what kind of patients they are? The “Centre for Early Detection and Prevention” sound like a place where people go for screening, mammography etc, am I right? Then this will be healthy women who as been checked and found nothing wrong with, as I understand it. Please clarify.
Authors: Visitors to the Center for Early Detection and Prevention received health check-ups, including screening for five major cancers (stomach, colorectal, liver, breast, and uterine cervix) based on their eligibility for National Cancer Screening Program (page 6, lines 7-12).

Referee: Data collection: You state that a trained dietician collected information on different lifestyle factors, and diet using a structured questionnaire. Later, you write that a FFQ was developed to determine regular dietary intake. What kind of dietary data did you use in this study: data collected of the dietician by a structured questionnaire or data from the FFQ? Or did the dietician use the FFQ when he/she collected the data; hence the structured questionnaire and the FFQ is the same thing? Please clarify.
Authors: A structured questionnaire was designed to collect information on demographic and lifestyle factors (excluding dietary intakes) and the FFQ was used to collect information for dietary intakes. To avoid confusion, the sentence was revised as followed: “A trained dietitian collected information on participant demographics and lifestyle factors (e.g., smoking habits, alcohol intake, and physical activity), using a structured questionnaire.”

Referee: Type of menopause – is this the menopausal status (pre-menopausal/post-menopausal)? Clarify.
Authors: “Type of menopause” was corrected to “menopausal status” (page 7, line 2; page 8,
Referee: Why do you look at α-linolenic acid? As far as I know, this do not belong to the fish omega-3 fatty acids, but is a omega-3 fatty acid found in plants. Thus, it should not be a part of this study.

Authors: The intake amount of α-linolenic acid presented in the previous version of the manuscript only included α-linolenic acid derived from fish. However, as per the referee’s concern, the main sources of α-linolenic acid are generally plants. Including α-linolenic acid may confuse the readers. We therefore decided to remove all of the results for α-linolenic acid from the revised manuscript.

Referee: Statistical analysis: The categorizing of alcohol consumption into never/ever is a bit vague. Alcohol is an important risk factor for breast cancer, and you can not really adjust for it by using the never/ever category.

Authors: As shown in the revised Table 1, the intake of alcoholic drinks was not associated with breast cancer risk in the current study population. This was mainly due to the small number of heavy drinkers in this population. Therefore, we think the never/ever category for alcohol consumption is appropriate for adjustment.

Referee: Use “occupation” instead of “job”.

Authors: We made corrections throughout the manuscript according to the referee’s recommendation (page 8, line 14; page 9, line 5; Table 1; Table 3; Table 4).

Referee: Discussion: First paragraph, line 11: “…. was detected in Norway [10, 20]…”. Reference 10 is for the EPIC study (not a Norwegian study), (Discretionary Revisions) which I think is worth mentioning in the discussion since it is one of the largest cohort studies that have investigated the relationship between fish and breast cancer.

Authors: The correction was made according to the referee’s recommendation (page 11, lines 11-13).

Referee: Fourth paragraph: “In comparison with the consistent protective effect of long-chain omega-3 fatty acids in some of the studies populations was too low to produce a protective effect.”

I do not understand this sentence. Please re-write it for clarification.

Authors: The sentence has been deleted.

Referee: Last paragraph: You state that your hospital-based control group may over-represent those with healthier habits. According to table 1, the control group has higher education and more persons working in profession/office, and less unemployed etc than the cases. These are factors that seem to be determinants for healthier lifestyle and could be used
to support your statement. More labourer/unemployed and ex-smokers among cases, higher age at menarche (a bit strange; thought low age at menarche was considered a risk factor), and fewer users of hormones, HRT (use of HRT are also considered a risk factor for breast cancer).

Authors: We added a discussion of the possibility of a selection bias in the control group (page 14, lines 16-23).

(Minor Essential Revisions)

Referee: “Notably, the specifics regarding the fish and preparation were not included in this study, such the type of fish (fatty or lean), species …” You did categorize fish into fatty and lean in your study, so this statement is wrong.

Authors: “The type of fish” has been deleted from the sentence.

Referee: Table 1: BMI – there are very few persons in the first category (<18.5), consider joining categories. Why did you not use the commonly used categories (underweight <18.5, normal weight 18.5 – 25, overweight >25)?


Referee: Referee: Table 2: Is it g/day? Table 3: Is it g/day?

Authors: g/day is the unit for Table 2, 3, and 4. Unit has been added in the tables.

Referee: At all the different fish levels, there are exactly 90 controls – is this correct? Please check. Please check for table 4 as well.

Authors: As the quartile categorizations of fish and fatty acids intake were based on the quartile distribution of the control group, exactly one quarter of the controls were distributed to each of the categories.