Article:

Cade, JE, Taylor, EF, Burley, VJ et al. (1 more author) (2010) Common dietary patterns and risk of breast cancer: analysis from the United Kingdom Women's Cohort Study. Nutrition and Cancer: an international journal, 62 (3). 300 - 306. ISSN 0163-5581

https://doi.org/10.1080/01635580903441246

Common dietary patterns and risk of breast cancer: analysis from the UK Women's Cohort Study

Authors:
Janet E. Cade
E. Faye Taylor
Victoria J. Burley
Darren C. Greenwood

Institution:
Centre for Epidemiology and Biostatistics, 30-32 Hyde Terrace, University of Leeds, Leeds, LS2 9LN.

Corresponding Author and for reprints:
Prof. J.E. Cade
Nutritional Epidemiology Group
Centre for Epidemiology and Biostatistics
Level 8, Worsley Building
University of Leeds
Leeds
LS2 9JT
Tel: 0113 343 6946
Email: j.e.cade@leeds.ac.uk

This analysis was funded by a grant from the World Cancer Research Fund.

Running Title: Dietary patterns and risk of breast cancer

ABSTRACT

The relationship between diet and breast cancer is uncertain. We assessed the relationship of 4 common dietary patterns to the risk of breast cancer using the UK Women's Cohort Study (UKWCS). A total of 35,372 women aged between 35 to 69 yr were recruited from 1995 to 1998. The UKWCS was selected to have a wide range of dietary intakes; 28% were self-reported vegetarian. Diet was assessed at baseline by a 217-item food frequency questionnaire. Four dietary patterns were defined based on a hierarchy of consumption of fish and meat to reflect commonly consumed dietary patterns. Hazards ratios (HRs) were estimated using Cox regression adjusted for known confounders. Subjects were followed up for a mean of 9 yr, and 330 premenopausal and 453 postmenopausal women developed invasive breast cancer. In postmenopausal women, there was a strong inverse association between the fish eating dietary pattern 0.60 (95% CI = 0.38–0.96) but not for a vegetarian pattern 0.85 (95% CI = 0.58–1.25) compared to red meat eaters. There were no statistically significant associations with dietary pattern and risk of premenopausal breast cancer. A fish eating dietary pattern that excludes meat from the diet may confer some benefit with regard to risk of postmenopausal breast cancer.

INTRODUCTION

Diet has been widely studied in relation to breast cancer risk. The traditional approach in nutritional epidemiology has concentrated on the effects of single nutrients or foods. However, nutrients and foods are consumed in combination, so effects on disease risk can only be assessed when the entire eating pattern is considered. Dietary patterns may go further than individual nutrient exposures when explaining disease occurrence (1). Major dietary patterns have been shown to be predictors of plasma biomarkers of cardiovascular disease and obesity risk (2) and colorectal cancer (3), and all-cause mortality in women (4). In terms of breast cancer, relatively few studies have explored dietary patterns with any thoroughness (5). Five cohort studies have explored dietary patterns linked to risk of breast cancer. The two large American Nurses Health cohorts found no association between dietary patterns identified by factor analysis and risk of breast cancer (6,7). A further large American cohort, the Breast Cancer Detection Demonstration Project, did find the traditional southern dietary pattern to be associated with reduced risk of breast cancer in postmenopausal women (8). An Italian cohort, the ORDET study, found that a dietary pattern associated with high intakes of raw vegetables and olive oil was associated with reduced risk of breast cancer (9). The EPIC-Potsdam study used reduced rank regression to describe a food pattern associated with fatty acid intake and found that this food pattern was significantly associated with increased risk of breast cancer (10). These publications have all used statistical approaches to define dietary patterns. We could not identify any publications that used predefined criteria for commonly recognized dietary patterns including vegetarians.

The UK Women's Cohort Study (UKWCS) is a large British cohort and was designed to include a wide range of different dietary intakes, and it forms an ideal database on which to explore the impact of different dietary patterns on risk of breast cancer. Here we examine the association between risk of developing breast cancer and 4 common dietary patterns developed according to a hierarchy of consumption relating to fish and meat intake. These were vegetarian, fish eating, poultry eating, and red meat eating.

SUBJECTS AND METHODS

Study population

Women were recruited into the UKWCS from responders to a direct mail survey of the World Cancer Research Fund (WCRF), with around half a million responders from England, Wales, and Scotland. Permission to undertake the baseline study was obtained from 174 local research ethics committees. Further details of the process have been described previously (11,12). A specific feature of the UKWCS was that it was designed to include large numbers of subjects consuming 3 main dietary patterns: vegetarian, eating fish (not meat), and meat eaters. This approach was adopted to maximize power for comparisons of interest between diet and cancer while minimizing the effect of measurement error (13–15). The WCRF questionnaire included brief dietary details allowing us to select all women who characterized themselves as vegetarian or non-red-meat eaters and a comparison group from the remaining eligible women. The comparison group was chosen by matching by age, within 10 yr of each vegetarian, to the next non-vegetarian responder. A total of 35,372 women aged 35 to 69 yr returned the baseline postal questionnaire. Of these, 15,951 women were classified as being premenopausal and 17,781 postmenopausal at baseline, resulting in 33,725 women available for analysis. Menopausal status was coded using specific criteria related to responses at baseline regarding age and menstrual and obstetric history and age at baseline.

Subjects were flagged with the NHS Central Register for cancer and death notification. Incident cancers and cause of death were coded according to the International Classification of Diseases 9 and 10. The investigation censor date was January 1, 2006, with a mean follow-up of 9 yr. In total, 330 premenopausal and 453 postmenopausal invasive breast cancers were recorded during 309,848 person years of follow-up.

Dietary patterns

The subjects' diet was assessed using a 217-item, self-administered food frequency questionnaire (FFQ). The FFQ is based on that used in the Oxford arm of the European Prospective Investigation into Cancer (EPIC) study and adapted for use with vegetarians. Completion of the questionnaire simply required placing a tick in the box to indicate how frequently each food had been consumed over the last 12 mo. Any single missing items were assumed to have not been consumed. For this analysis, 4 commonly recognized eating patterns were created based on response frequencies of meat and fish items on the FFQ. The hierarchy of the patterns was as follows: vegetarians who consumed red meat, poultry, or fish less than once a week; fish eaters who consumed fish at least once a week but not poultry or red meat; poultry eaters who consumed poultry at least once a week and may eat fish but not red meat; and red meat eaters who were women who consumed meat at least once a week and may or may not consume poultry and fish. Red meat is defined as beef, pork, lamb, offal, and processed meats.

Statistical analysis

The relationship between the dietary patterns and risk of breast cancer was explored using Cox's proportional hazards regression in Stata version 9 (16) weighted by the inverse probability of being sampled to take into account the large proportion of vegetarians in the cohort so that results are representative of the general population. The red meat eating category was used as the reference category. The survival analysis used time (person years) calculated as the time from the date the questionnaire was filled in until either a report of incident breast cancer, death, or the censor date of the analysis, whichever came first. Women with extremely high or low total energy intake (less than 500 kcal or greater than 6,000 kcal) were excluded as were women with prevalent breast cancer and women with missing data on confounders. There were 33,681women available for the minimally adjusted analysis and 27,492women available for the maximally adjusted analysis. A power calculation showed that with about 300 premenopausal breast cancer cases, the study would have 80% power to detect a relative risk of 1.4 comparing two levels of a binary exposure with equal numbers in each group ($P < 0.05$) and with about 400 postmenopausal cases, 90% power to detect a relative risk of 1.4 ($P < 0.05$). Analyzing the exposure as a continuous variable would provide even more power.

Our primary hypothesis was that common dietary patterns would be associated with breast cancer risk. Associations of dietary pattern with risk of breast cancer were estimated for the whole cohort and for premenopausal and postmenopausal women separately, first as a simple model (Model 1) adjusting for age and total energy intake and second as a full model (Model 2) adjusting for further potential confounders. Adjustments in the full model were age, total energy intake, calorie-adjusted fat intake, body mass index, physical activity (hr/day sufficiently vigorous to cause sweating), current or previous oral contraceptive use, current or previous HRT use, smoking habit, parity, age at menarche, alcohol intake (as grams of ethanol/day), length of time breast feeding children, National Statistics Socio-Economic Class (17), and level of education. Information on covariates was obtained from the baseline questionnaire, which also contained the FFQ.

Secondary analysis was undertaken as a result of the findings from the first set of survival analysis. This was carried out to explore aspects of fish eating in more detail including the impact of different types of fish on risk of breast cancer. A logistic regression analysiswas carried out for the fish eaters alone as determined by the previously described definition. The total amount of fish, white fish, and oily fish were analyzed as continuous variables in grams. In addition, a survival analysis for all women with a nonzero fish intake was conducted analyzing type of fish as a continuous variable in grams.

RESULTS

Characteristics according to dietary pattern

Of the 33,725 women in this analysis, 65% (21,951) were classified as red meat eaters, 3% (945) were poultry eaters, 13% (4,338) were fish eaters, and 19% (6,491) were vegetarians. Some lifestyle characteristics at baseline data collection of these groups are summarized in Table 1. The mean age of the red meat eating group was highest at 54 yr, and the vegetarians were the youngest at 49 yr. Body mass index and energy intake were highest in the red meat eaters. Energy intake was lowest in the vegetarians. Physical activity was highest in the fish eaters and lowest in the red meat eaters. A higher percentage of the fish eaters and vegetarians were from a professional and managerial social background compared to the red meat and poultry eating groups.

Dietary patterns and breast cancer

The association between the common dietary patterns and risk of breast cancer are presented in Table 2 for both Model 1 and Model 2 for all women combined and also split according to menopausal status at baseline. Analysis of the total cohort showed a statistically significant difference between the groups for the simple ($P = 0.03$) but not the complex ($P = 0.2$) models. In the fully adjusted model, there were no statistically significant differences between specific dietary patterns; however, fish eaters and vegetarians had borderline statistically non-significantly lower risk of breast cancer than red meat eaters (HR = 0.78, 95% CI = 0.60–1.03; HR = 0.88, 95% CI = 0.69–1.11, respectively). When separate analyses were carried out according to menopausal status at baseline, there were no statistically significant differences between the different dietary patterns and risk of breast cancer in the premenopausal women. However, postmenopausally, risk of breast cancer was statistically significantly lower for both the fish eaters and vegetarians in the minimally adjusted model, and for fish eaters in the fully adjusted model (HR = 0.60, 95% CI = 0.38–0.96), although the result became nonsignificant for the vegetarians in the fully adjusted model (HR = 0.85, 95% CI = 0.58–1.25) compared to red meat eaters.

Fish consumption and breast cancer risk

Since the fish eating group showed reduced risk of breast cancer in the postmenopausal women, we wanted to see whether specific types of fish were involved in this relationship. Exploring the fish eating group showed no statistically significant associations between type of fish consumed and breast cancer incidence, although in general, the HRs are below 1.0. For example, in the fully adjusted model, the hazard ratio for high white fish consumption was 0.45 (95% CI = 0.17–1.18), and for high oily fish consumption it was 0.55 (95% CI=0.21–1.44) compared to non-consumers (data not shown). The survival analysis for all women with a nonzero fish consumption (Table 3) shows no statistically significant associations between type of fish consumed and risk of breast cancer, although HRs are below 1.0 for all types of fish except shellfish, for which the confidence intervals are wide.

DISCUSSION

The UKWCS was designed to have large numbers of women consuming different dietary patterns, maximizing the efficiency of comparison between groups (14). In our analysis, the dietary pattern defined by red meat eating was not statistically significantly associated with higher risks of breast cancer. Our previous analysis found that increasing consumption of total meat was associated with increased risk of breast cancer (12). These findings may appear to be conflicting; however, the red meat eating dietary pattern in our cohort consumed on average relatively low amounts of red meat (mean 74 g/day). In this cohort, a red meat eating pattern may be generally at lower risk than populations with a higher meat consumption; for example, women aged 35 to 59 yr in the National Diet and Nutrition Survey were consuming on average 131 g meat/day (18). Also, our definition of vegetarian was not completely strict, allowing vegetarians to consume meat, poultry, or fish less than once a week.

In our cohort, the red meat eaters were more likely to be older and less well educated (11) with a higher body mass index and lower physical activity and fruit and vegetable intake than the other groups. A similar pattern was seen in subjects who were most likely to eat meat in the East Anglian EPIC cohort (19). Fish eaters in the UKWCS were younger, with a lower energy intake, and were more likely to consume 400 g or more of fruit and vegetables per day. However, characteristics according to dietary pattern can vary by country; for example, in a large Norwegian study, it was the older women who ate most fish (20). A country-specific understanding of dietary patterns is important as is a clear description of the dietary pattern.

The definition of the dietary patterns used in this analysis may have led to the non-significant findings. Use of categories in this way to define dietary patterns does not allow for examination of a possible dose-response effect of key components of the diet. For example, in the categories used in this analysis, the poultry eating dietary pattern was characterized by consumption of similar amounts of fish as was being consumed in the fish eating pattern. Other studies have also found no associations between different dietary patterns and risk of breast cancer. The EPIC cohort explored risk of breast cancer with fruit and vegetable consumption and found no associations (21), in that example however, the whole diet was not considered. This may be important, since another analysis of the EPIC data found that although adherence to the traditional Mediterranean diet was associated with a significant reduction in total mortality, the associations between each individual food group contributing to the Mediterranean-diet score and total mortality were not all individually significant (22). We used a pragmatic definition of dietary pattern based on reported intake. Other approaches have used empirically derived patterns such as principal components analysis and factor analysis. One study using principle components failed to show a relationship between risk of breast cancer and a diet high in vegetables, fish, poultry, and fruit (8). Another study of an Italian cohort showed that a dietary pattern characterized by high intake of salad vegetables was protective against breast cancer (9).

Putative mechanisms that relate dietary patterns to the development of cancer do exist and may include rates of growth and development. For example, a typical high-fat, low-fiber dietary pattern, particularly when associated with inadequate exercise, may be related to breast cancer risk. It may advance the onset of puberty, resulting in earlier menarche, earlier onset of breast development, and an earlier growth spurt. Both earlier menarche and adult tallness are markers of increased risk of breast cancer (23). Adult diets in some (24,25), although not all (26), populations have been correlated with childhood diets, suggesting that diet in adulthood may be a reasonable proxy for diet earlier in life. To date, no studies have been designed with a long enough follow-up throughout the life course to confirm this theory. It may be that by studying adult dietary patterns, we have missed the important time period for dietary exposure.

A randomized controlled trial of postmenopausal women to assess the effects of a low-fat dietary pattern on incidence of breast cancer with a follow-up of 8 yr did not find a statistically significant reduction in risk with a low-fat diet. However, among women who participated actively in the trial, there was a borderline significant reduction in risk in the intervention group (27). In our cohort, women did not have a particularly high-fat intake compared to national levels even for those in the red meat eating pattern, although intakes were not as low as in that trial. In addition, fiber intakes were also high across all the dietary patterns (11).

In the postmenopausal women in the fully adjusted model, the fish eaters had significantly reduced risks of breast cancer compared to the red meat eaters. This trend was not seen in the premenopausal women. A large case-control study exploring dietary patterns and risk of breast cancer in Japan found that women in the highest quartile of the prudent dietary pattern (fruit, vegetables, soya bean curd, fish, and milk) had a 27%

reduction in risk of breast cancer compared to those in the lowest quartile (28), and this finding was even stronger for women aged 50 to 79 yr compared to younger women. Cooked and raw fish were only statistically significantly associated with reduced risk of breast cancer in the postmenopausal women and not the premenopausal women (29), a similar finding to our own. Fish consumption among Japanese people is much higher than in Western countries. In the UKWCS, fish consumers by definition had to eat fish at least once a week; mean intake was 43 g/day. This is similar to the British National Diet and Nutrition Survey that found thatwomen aged 35 to 49 yr who ate fish consumed 41 g/day on average (18). Animal studies have provided evidence of an anticarcinogenic effect of n-3 polyunsaturated fatty acids found in fish onmammary tumors (30). Epidemiological studies have been less conclusive. A Japanese cohort study has shown a protective effect of fish fat and long-chain n-3 fatty acids (31) but not total fat or other components of fat.

We could not find a specific effect of oily or white fish in the UKWCS. This may be due to the fact that we explored type of fish consumed in all women who had eaten any fish rather than just the fish eating group as defined by the common dietary patterns in order to achieve an adequate sample size. However, all fish consumers will have different dietary characteristics – for example, eating more red meat - than the women in our defined fish eating group. We might expect to see a protective effect with oily fish that contains most long chain n-3 fats, which was not apparent in our study. Other cohort studies, including the large EPIC (32) and the Iowa Women’s Study (33) have found no association with fish intake and risk of breast cancer or found an increased risk (34,35). There is the potential for oily fish, in particular, to be contaminated with heavy metals and pesticides that may have estrogenic effects, potentially increasing risk of breast cancer with intake of oily fish. We did not see this association in our cohort.

Although the vegetarian group had a 12% reduction in risk of breast cancer, this was not a statistically significant finding. An analysis of 5 cohort studies did not find any differences in mortality from breast cancer between vegetarians and non-vegetarians (36). In our cohort, the group eating the vegetarian dietary pattern had lower intakes of vitamin C than the poultry eating and fish eating groups. Mean portions of fruit and vegetables consumed per day was similar across the different groups, albeit with the red meat eating group consuming the lowest amounts. It is possible that in our rather health conscious cohort, a dietary pattern described by not eating meat is not necessarily associated with dietary habits and nutrient intakes that are more beneficial than the other dietary pattern groups.

Since this is a prospective study, recall bias is unlikely. However, an ongoing challenge in nutritional epidemiology is accurate measurement of food intake. The FFQ used in this cohort has been validated against biomarkers (37) and follows recommendations for good design (38). The dietary patterns described reflect existing eating patterns in the cohort and may not necessarily be those that are optimal for breast cancer prevention. Our cohort generally had a health conscious outlook as evidenced by relatively low smoking rates and low body mass index (11). The Women's Health Initiative trial showed greater evidence of risk reduction among women in the low-fat diet intervention group who had a higher-fat diet at baseline (27). It is possible that less healthy dietary patterns were underrepresented in our cohort. A further weakness of this study was that we did not have information on hormone receptor status of the tumor. Other studies have shown a possible link between dietary pattern and hormone receptor status, although findings are not consistent. The Nurses' Health Study found that a prudent diet characterized by high fruit and vegetable and low-fat dairy, fish, and poultry consumption was associated with a reduced risk of estrogen receptor negative tumors (39). However, theWomen's Health Initiative found that women who had been randomized to a low-fat dietary pattern had a reduced risk of estrogen receptor positive tumors (27).

In conclusion, among postmenopausal women, a dietary pattern characterized by eating fish but not meat was associated with a reduced risk of developing breast cancer. This finding was not associated with any particular type of fish consumption, suggesting that it may not be the type of fat in the fish that is responsible for this effect. Other aspects of the diet or lifestyle associated with this pattern of eating may be important.

ACKNOWLEDGEMENTS

Thanks to all the women who gave their time to take part in this study. Thanks to Alison Greenhalgh and Clare Calvert for previous cohort management; James Thomas for database management; the UK Women's Cohort Study Steering Group for support and guidance.

The UK Women's Cohort Study was funded by grants from the World Cancer Research Fund.

REFERENCES

1. Hu FB: Dietary pattern analysis: a new direction in nutritional epidemiology. Current Opinion in Lipidology **13**,3-9, 2002.

2. Fung TT, Willett WC, Stampfer MJ, Manson JE, Hu FB: Dietary patterns and the risk of coronary heart disease in women. Arch Intern Med **161**,1857-1862,2001.

3. Fung T, Hu FB, Fuchs C, Giovannucci E, Hunter DJ, et al.: Major dietary patterns and the risk of colorectal cancer in women. Arch Internal Med **163**, 309-314, 2003.

4. Kant AK, Schatzkin A, Graubard BI, Schairer C.: A prospective study of diet quality and mortality in women. J Am Med Assocn **283**, 2109-2115, 2000.

5. World Cancer Research Fund / American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington DC: American Institute for Cancer Research, 2007.

6. Adebamowo CA, Hu FB, Cho E, Spiegelman D, Holmes MD, et al.: Dietary patterns and the risk of breast cancer. Annals of Epidemiology **15**, 789-795, 2005.

7. Fung TT, Schulze M, Manson JE, Willett WC, Hu FB: Dietary patterns, meat intake, and the risk of type 2 diabetes in women. Arch Intern Med **164**, 2235-2240, 2004.

8. Velie EM, Schairer C, Flood A, He JP, Khattree R, et al.: Empirically derived dietary patterns and risk of postmenopausal breast cancer in a large prospective cohort study. Am J Clin Nutr **82**, 1308-1319, 2005.

9. Sieri S, Krogh V, Pala V, Muti P, Micheli A, et al.: Dietary patterns and risk of breast cancer in the ORDET cohort. Cancer Epidemiol.Biomarkers Prev **13**, 567-572, 2004.

10. Schulz M, Hoffmann K, Weikert C, Nothlings U, Schulze MB, et al.: Identification of a dietary pattern characterized by high-fat food choices associated with increased risk of breast cancer: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Br J Nutr **100**, 942-946, 2008.

11. Cade JE, Burley VJ, Greenwood DC. The UK Women's Cohort Study: comparison of vegetarians, fish-eaters and meat-eaters. Public Health Nutr **7**, 871-878, 2004.

12. Taylor EF, Burley VJ, Greenwood DC, Cade JE: Meat consumption and risk of breast cancer in the UK Women's Cohort Study. Br J Cancer **96**, 1139-1146, 2007.

13. Kaaks R, Riboli E: Validation and calibration of dietary intake measurements in the EPIC project: methodological considerations. European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol **26**, Suppl 1, S15-S25, 1997.

14. Schatzkin A, Subar AF, Thompson FE, Harlan LC, Tangrea J, et al.: Design and serendipity in establishing a large cohort with wide dietary intake distributions : the National Institutes of Health-American Association of Retired Persons Diet and Health Study. Am J Epidemiol **154**, 1119-1125, 2001.

15. White E, Kushi LH, Pepe MS: The effect of exposure variance and exposure measurement error on study sample size: implications for the design of epidemiologic studies. J Clin Epidemiol **47,** 873-80, 1994.

16. StataCorp. Stata statistical software: Release 9.1. College Station TX: Stata Corporation, 2005.

17. Bravo Y, Greenwood DC, Cade JE: The impact of social class on a healthy diet: Analysis from the U.K. Women's Cohort Study. Proc Nutr Soc **61**, 142A, 2002.

18. Hoare J, Henderson L, Bates CJ, Prentice A, Birch M, et al.: The National Diet & Nutrition Survey: adults aged 19 to 64 years. London, The Stationery Office 2004.

19. Fraser GE, Welch A, Luben R, Bingham SA, Day NE: The effect of age, sex, and education on food consumption of a middle-aged English cohort-EPIC in East Anglia. Prev Med **30**, 26-34, 2000.

20. Hjartaker A, Lund E: Relationship between dietary habits, age, lifestyle, and socio-economic status among adult Norwegian women. The Norwegian Women and Cancer Study. Eur J Clin Nutr **52**, 565-572, 1998.

21. van Gils CH, Peeters PH, Bueno-De-Mesquita HB, Boshuizen HC, Lahmann PH, et al.: Consumption of vegetables and fruits and risk of breast cancer. J Am Med Assocn **293**, 183-193, 2005.

22. Trichopoulou A, Orfanos P, Norat T, Bueno-de-Mesquita B, Ocke MC, et al.: Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. Br Med J **330**, 991, 2005.

23. Key TJ, Verkasalo PK, Banks E: Epidemiology of breast cancer. Lancet Oncol **2**, 133-140, 2001.

24. Lake AA, Mathers JC, Rugg-Gunn AJ, Adamson AJ: Longitudinal change in food habits between adolescence (11-12 years) and adulthood (32-33 years): the ASH30 study. J Pub Hlth **28**, 10-16, 2006.

25. Mikkila V, Rasanen L, Raitakari OT, Pietinen P, Viikari J: Consistent dietary patterns identified from childhood to adulthood: The cardiovascular risk in young finns study. Br J Nutr **93**, 923-931, 2005.

26. Gallagher AM, Robson PJ, Livingstone MBE, Cran GW, Strain JJ, et al.: Tracking of energy and nutrient intakes from adolescence to young adulthood: the experiences of the Young Hearts Project, Northern Ireland. Pub Hlth Nutr **9**, 1027-1034, 2006.

27. Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, et al.: Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. J Am Med Assocn **295**, 629-642, 2006.

28. Hirose K, Matsuo K, Iwata H, Tajima K: Dietary patterns and the risk of breast cancer in Japanese women. Cancer Sci **98**, 1431-1438, 2007.

29. Hirose K, Takezaki T, Hamajima N, Miura S, Tajima K: Dietary factors protective against breast cancer in Japanese premenopausal and postmenopausal women. Int J Cancer **107**, 276-282, 2003.

30. El Sohemy A, Archer MC: Regulation of mevalonate synthesis in rat mammary glands by dietary n-3 and n-6 polyunsaturated fatty acids. Cancer Res **57**, 3685-3687, 1997.

31. Wakai K, Tamakoshi K, Date C, Fukui M, Suzuki S, et al.: Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan. Cancer Sci **96**, 590-599, 2005.

32. Engeset D, Alsaker E, Lund E, Welch A, Khaw KT, et al.: Fish consumption and breast cancer risk. The European Prospective Investigation into Cancer and Nutrition (EPIC). Int J Cancer **119**, 175-182, 2006.

33. Folsom AR, Demissie Z: Fish intake, marine omega-3 fatty acids, and mortality in a cohort of postmenopausal women. Am J Epidemiol **160**, 1005-1010, 2004.

34. Holmes MD, Hunter DJ, Colditz GA, Stampfer MJ, Hankinson SE, et al.: Association of dietary intake of fat and fatty acids with risk of breast cancer. J Am Med Assocn **281**, 914-920, 1999.

35. Stripp C, Overvad K, Christensen J, Thomsen BL, Olsen A, et al.: Fish intake is positively associated with breast cancer incidence rate. J Nutr **133**, 3664-3669, 2003.

36. Key TJ, Fraser GE, Thorogood M et al. Mortality in vegetarians and nonvegetarians: detailed findings from a collaborative analysis of 5 prospective studies. Am J Clin Nutr 1999;70:516S-24S.

37. Spence M, Cade JE, Burley VJ, Greenwood DC: Ability of the UK Women's Cohort Food Frequency Questionnaire to rank dietary intakes: a preliminary validation study. Proc Nutr Soc **61**, 117A, 2002.

38. Cade J, Thompson R, Burley V, Warm D: Development, validation and utilisation of food-frequency questionnaires - a review. Pub Hlth Nutr **5**, 567-87, 2002.

39. Fung TT, Hu FB, Holmes MD, Rosner BA, Hunter DJ, et al.: Dietary patterns and the risk of postmenopausal breast cancer. Int J Cancer **116**, 116-121, 2005.

Table 1. Characteristics of Subjects from the UK Women's Cohort Study at baseline (1995-1998) according to different dietary patterns

	Red meat-eater n= 21951	Poultry-eater n= 945	Fish-eater n= 4338	Vegetarian n= 6491
Age(years), mean (SD)	54(9)	53(9)	51(9)	49(8)
BMI (kgm^{-2}), mean (SD)	25.1(4.5)	23.6(3.8)	23.3(3.9)	23.4(3.9)
Vigorous physical activity (minutes/day), mean (SD)	13 (28)	16 (30)	17 (31)	16 (28)
Current smoker (%)	11	9	10	10
HRT use (%)	22	22	17	13
OCP use (%)	4	3	4	5
Nulliparous (%)	17	22	26	28
Professional and managerial (%)	60	62	71	70
Breast cancer cases (at census date)	547	19	87	130
Energy intake (MJ), mean (SD)	9.86(2.94)	9.66(3.04)	9.83(3.02)	9.49(3.02)
Fat intake (grams/day), mean (SD)	86 (32)	78 (31)	84 (33)	82 (33)
Ethanol (grams/day), mean (SD)	9 (11)	7 (9)	9 (10)	7 (10)
Vitamin C (milligrams/day), mean (SD)	166 (81)	188 (102)	184 (93)	177 (93)
Mean portions of fruit and vegetables (number/day), mean (SD)	2.7 (1.5)	2.9 (1.7)	3.1 (1.7)	3.1 (1.7)
Meat Consumption (grams/day), mean (SD)	74(46)	3(4)	1(2)	0(1)
Poultry Consumption (grams/day), mean (SD)	24(20)	40(27)	2(4)	0(2)
Fish consumption (grams/day), mean (SD)	32(23)	46(33)	43(31)	2(3)

Table 2. Survival analysis showing risk of breast cancer for common dietary patterns compared to red meat eating pattern as the reference category, from the UK Women's Cohort Study

	Person years	Cases/non cases	Model 1[1]		Model 2[2]	
	Mean (SD)		HR[3]	95% CI[3]	HR	95% CI
Combined analysis:						
Red meat eater	8.7 (1.4)	547/21951	1.00	(Reference)	1.00	(Reference)
Poultry eater	9.5 (1.3)	19/945	0.73	0.46 , 1.16	0.74	0.44 , 1.24
Fish eater	9.4 (1.2)	87/4338	0.76	0.60 , 0.97	0.78	0.60 , 1.03
Vegetarian	9.5 (1.1)	130/6491	0.82	0.67 , 1.01	0.88	0.69 , 1.11
Test for difference between groups			P=0.03		P=0.2	
Test for effect modification by menopausal status			P=0.2		P= 0.5	
Premenopausal:						
Red meat eater	9.0 (1.2)	186/9055	1.00	(Reference)	1.00	(Reference)
Poultry eater	9.6 (1.1)	8/427	0.86	0.42 , 1.74	0.73	0.32 , 1.67
Fish eater	9.5 (1.0)	53/2346	1.00	0.73 , 1.37	0.97	0.69 , 1.37
Vegetarian	9.6 (0.9)	83/4119	0.97	0.74 , 1.27	0.92	0.67 , 1.24
Test for difference between groups			P=0.97		P= 0.8	
Postmenopausal:						
Red meat eater	8.5 (1.5)	361/12896	1.00	(Reference)	1.00	(Reference)
Poultry eater	9.4 (1.5)	11/518	0.66	0.36 , 1.21	0.73	0.37 , 1.44
Fish eater	9.4 (1.4)	34/1992	0.59	0.40 , 0.87	0.60	0.38 , 0.96
Vegetarian	9.4 (1.4)	47/2372	0.70	0.49 , 0.98	0.85	0.58 , 1.25
Test for difference between groups			P=0.008		P=0.1	

[1] adjusting for age, energy intake and menopausal status (combined analysis).
[2] adjusting for age, energy intake, menopausal status (combined analysis), calorie adjusted fat, BMI, physical activity, OCP use, HRT use, smoking status, parity, age at menarche, ethanol, total days breast feeding, socio economic class, level of education.
[3] CI= confidence interval; HR=hazard ratio.

Table 3. Survival analysis showing risk of breast cancer in all women with non-zero fish consumption according to type of fish consumed

	Model 1[1] HR per 50g increment in fish intake	95% CI	P values	Model 2[2] HR per 50g increment in fish intake	95% CI	P values
Combined:						
total fish	0.91	0.78 , 1.07	0.3	0.90	0.75 , 1.09	0.3
• oily fish	0.88	0.64 , 1.22	0.5	0.94	0.66 , 1.34	0.7
• shellfish	2.20	0.89 , 5.47	0.09	1.65	0.59 , 4.61	0.3
• white fish	0.79	0.58 , 1.06	0.1	0.77	0.55 , 1.08	0.1
Premenopausal:						
total fish	0.80	0.61 , 1.06	0.1	0.76	0.56 , 1.04	0.09
• oily fish	0.68	0.38 , 1.21	0.2	0.57	0.29 , 1.13	0.1
• shellfish	1.36	0.25 , 7.42	0.7	0.59	0.11 , 3.11	0.5
• white fish	0.60	0.36 , 1.02	0.06	0.67	0.38 , 1.17	0.2
Postmenopausal:						
total fish	0.96	0.79 , 1.16	0.7	0.99	0.78 , 1.25	0.9
• oily fish	0.99	0.69 , 1.44	0.98	1.18	0.86 , 1.60	0.3
• shellfish	2.79	0.97 , 8.02	0.06	2.87	0.89 , 9.28	0.08
• white fish	0.86	0.61 , 1.22	0.4	0.84	0.56 , 1.27	0.4

[1] adjusting for age, energy intake and menopausal status.
[2] adjusting for age, energy intake, menopausal status, calorie adjusted fat, BMI, physical activity, OCP use, HRT use, smoking status, parity, age at menarche, ethanol, total days breast feeding, socio economic class, level of education.