Does the Mediterranean dietary pattern or the Healthy Diet Index influence the risk of breast cancer in a large British cohort of women?

Running Title: Dietary patterns and risk of breast cancer

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ABSTRACT

Objective: to assess the risk of developing breast cancer associated with consumption of two common dietary patterns: a Mediterranean dietary pattern and a dietary pattern which conforms to the WHO Healthy Diet Index (HDI).

Methods: dietary data from a 217-item food frequency questionnaire was used to generate two dietary patterns according to pre-defined criteria in 33,731 women from the UK Women's Cohort Study (UKWCS). Hazards ratios (HRs) for risk of breast cancer were estimated using Cox regression adjusted for known confounders.

Results: Overall, there were no statistically significant associations between either the Mediterranean dietary pattern of the WHO HDI and risk of breast cancer. In pre-menopausal women, there is a non-significant trend showing that increasing compliance with the Mediterranean diet reduces risk of developing breast cancer. Maximal adherence to the Mediterranean diet is associated with HR=0.65 (95% CI: 0.42 to 1.02, p trend=0.087) compared to minimal adherence. In post-menopausal women there do not appear to be any noticeable trends.

Conclusions: there is no strong association between risk of breast cancer and consumption of either a Mediterranean type diet or one characterized by adherence to the WHO HDI. In pre-menopausal, but not post-menopausal women, there was a non-significant inverse association with increasing adherence to the Mediterranean diet pattern.

INTRODUCTION

Exploration of dietary patterns may be a helpful addition to the traditional approach to studying diet and breast cancer which has focused on single foods and nutrients(Hu 2002). Results linking diet to breast cancer risk have been conflicting(Gandini *et al*. 2000; Smith-Warner *et al*. 2001). This may be because studies of single foods or nutrients cannot account for highly correlated food items or synergistic effects of food combinations; or there may be other non-nutrient phytochemicals involved or other factors affecting nutrient availability such as cooking practices(Velie *et al*. 2005). Major dietary patterns, including a Mediterranean-type diet have been shown to be predictors of other chronic disease such as: acute myocardial infarction(Martinez-Gonzalez *et al*. 2002); colorectal cancer(Fung *et al*. 2003); and all cause mortality in women(Kant *et al*. 2000). In terms of breast cancer risk, dietary patterns have been less well studied. One large American study failed to show an effect on risk of breast cancer with a diet high in vegetables, fish, poultry and fruit(Velie *et al*. 2005). Another study, of an Italian cohort showed that a dietary pattern characterized by high intake of salad vegetables was protective against breast cancer(Sieri *et al*. 2004).

Further research which maximizes the range of dietary patterns and minimizes biases inherent to a case-control design might help to elucidate the relationship between diet and breast cancer. The UK Women's Cohort Study was designed to include a wide range of different dietary intakes and forms an ideal database on which to generate dietary patterns and to explore their impact on risk of breast cancer.

METHODS

Subjects

The UK Women's Cohort Study (UKWCS) recruited 35,372 women aged 35-69 years between 1995 to 1998. Ethical approval was obtained from 174 local research ethics committees. Further details of the process have been described previously(Cade *et al*. 2007; Taylor *et al*. 2007). The cohort was designed to include a wide range of dietary patterns with similar large numbers of women consuming a vegetarian type diet, women who ate fish but not meat and meat eaters. This approach ensures adequate power whilst minimizing the effects of measurement error(Kaaks *et al*. 1997; Schatzkin *et al*. 2001; White *et al*. 1994).

The study was registered with the National Health Service Central Register so that all incident cancer cases and deaths were notified to the study team. Incident cancers and cause of death were coded according to the International Classification of Diseases 9 and 10. The investigation censor date was 1st April 2006, mean follow up of 9 years with 828 incident breast cancers recorded. Of the study participants, 15,952 women were classified as being pre-menopausal and 17,779 post-menopausal at baseline. Menopausal status was coded using specific criteria related to responses at baseline regarding menstrual and obstetric history and age at baseline.

Dietary patterns

Subjects' diet was assessed at recruitment using a 219-item self-administered food frequency questionnaire(FFQ). A description of the two scores generated is presented in table 1. A score indicating compliance with a traditional Mediterranean diet was based on one by Trichopoulou *et al*.(Trichopoulou *et al*. 2003). Out of 10 components selected as being significant indicators of the Mediterranean Diet, each woman from the cohort was assigned a value of 0 or 1 for 9 of these components, using the cohort median as a cutoff. Above average intake of vegetables, legumes, fruit and nuts, cereal, fish and ratio of monounsaturated fatty acids to saturated fatty acids each increased the score by 1. Below average intake of meat, poultry and dairy products also increased the score by 1. For the tenth component, alcohol, women consuming between 5-25g of alcohol per day increased

their score by 1. This generated a score ranging from 0-10. Due to small numbers in the extremities of the scale, women scoring 0, 1 or 2 were combined and women scoring 7 to 10 were combined.

WHO guidelines were used as a basis for developing a healthy diet indicator (WHO Technical Report Series 2003). Use of the entire set of guidelines was not possible since comparable dietary data for some dietary factors listed were not available from our FFQ. Dietary data was available for total fatty acids, saturated fatty acids and polyunsaturated fatty acids but n-6 polyunsaturated fatty acids, n-3 polyunsaturated fatty acids and trans fatty acids could not be derived accurately from the FFQ without further validation. Monounsaturated fatty acids were available, however the corresponding recommendation from the WHO document is a difference between the other fats hence this component was not used as part of the score. Total carbohydrates, Englyst fibre, fruit and vegetables consumption, protein, cholesterol and salt in food were readily available from the FFQ. We were able to generate amounts of non-milk extrinsic sugars (NMES) by subtracting sugar from fruit, vegetables and milk from total sugar. For salt added to food during cooking or at the table, a value was assigned based on a separate question, assuming a standard pinch of salt of 0.25g. Total daily salt intake was obtained by summing total salt in food, salt added during cooking and salt added at the table. The HDI is measured from 0 to 10 by assigning a score of 1 if a woman's diet was within the recommended range for a component and 0 otherwise. Due to small numbers in the extremities of the scale, women scoring 0, 1 or 2 were combined and women scoring 7 to 10 were combined, leaving 6 categories.

Statistical analysis

Cox's proportional hazards regression was used to explore the relationship between the dietary patterns and risk of breast cancer using Stata version 9(StataCorp. 2005). 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 was calculated in person years. Women were excluded if they had extremely high (>6000kcal/day) or low total (<500 kcal/day) energy intake, as were women with prevalent breast cancer and women with missing data on confounders. Associations were estimated for pre- and post-

menopausal women separately, first as a simple model (model 1) adjusting for age and total energy intake by the residuals method(Willett *et al*. 1986) and secondly as a full model (model 2) adjusting for further potential confounders. Adjustments in the full model were age, total energy intake, calorie adjusted fat, body mass index, physical activity(hours/day sufficiently vigorous to cause sweating), oral contraceptive use, HRT use, smoking habit, parity, age at menarche, alcohol intake (as grams of ethanol/day), length of time breast fed children, National Statistics Socio-Economic Class(Bravo Y *et al*. 2002) and level of education.

RESULTS

Characteristics according to dietary pattern

Of the 35,372 women in the cohort for this analysis X women had a prevalent breast cancer, Y women could not be flagged for cancer registration with the Office of National Statistics, Z women had missing data or energy intakes outside the expected levels. Therefore, 33,731 women were included in the analysis. Since only 122 subjects had the highest concordance with the Mediterranean dietary pattern and 42 subjects had the highest concordance with the WHO HDI, for further analyses the top 4 categories in each pattern were grouped to ensure more equal distribution of participants by category.

Lifestyle characteristics of the women at baseline data collection for each dietary pattern are summarized in tables 2 and 3. As concordance with both dietary patterns increased so the age of the women decreased. Women with the highest scores on both patterns had a lower body mass index and were less likely to smoke and took more physical activity.

Mediterranean dietary pattern and breast cancer risk

The association between the Mediterranean dietary patterns and risk of breast cancer is presented in table 4 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 no statistically significant differences between the groups for either the simple or the complex model. When separate analyses were carried

out according to menopausal status at baseline there was no statistically significant association between concordance with Mediterranean dietary pattern and risk of breast cancer in the premenopausal women, although the trend in the premenopausal women approached significance, with women with the highest level of adherence having a HR of 0.65 (95% CI: 0.42, 1.02) (P, trend 0.087). However, postmenopausally, there was no association between adherence to the Mediterranean dietary pattern and risk of breast cancer.

HDI dietary pattern and breast cancer risk

The association between the WHO HDI dietary pattern and risk of breast cancer is presented in table 5 for all women combined and also split according to menopausal status at baseline. There were no statistically significant associations between the HDI and risk of breast cancer in either the simple or fully adjusted model or by menopausal status.

DISCUSSION

The UKWCS was designed to allow comparison between women consuming different dietary patterns(Schatzkin *et al*. 2001). In this cohort, the women who had the highest scores for both the Mediterranean pattern and the WHO HDI had healthier lifestyle characteristics, with lower body mass index; were less likely to smoke and took more exercise compared to women with the lowest scores. Similar results were seen in a cohort from Greece which showed that those with higher Mediterranean diet score had healthier characteristics, being less likely to smoke, more likely to have a higher level of physical activity and a lower body mass index(Trichopoulou *et al*. 2003). A random sample of subjects from Mediterranean southern France found that those with a lower Mediterranean diet score were more likely to be smokers(Scali *et al*. 2001), although in this study they also tended to be younger, unlike those in the UKWCS.

Dietary patterns have the potential to be a useful tool for health promotion activity by reflecting the whole diet as opposed to single nutrients. The two patterns considered in this analysis are generally recognized as healthy. However, the definition of these patterns is

not straightforward with a number of different scores using different components having been developed. For example, there are a number of Mediterranean diet definitions(Knoops *et al*. 2004; Martinez-Gonzalez *et al*. 2002; Scali *et al*. 2001; Trichopoulou *et al*. 2003), each of which have different constructs. Medians(Trichopoulou *et al*. 2003), quintiles(Martinez-Gonzalez *et al*. 2002) or specific cut offs(Scali *et al*. 2001) are used as boundaries. ?HDI diffs??? + how our scores might be different or these affect results? Differences in definitions could lead to differences in associations between the dietary pattern and health outcomes under consideration. Although a recent comparison of dietary patterns generated by three different methods: cluster analysis; factor analysis and index score analysis found similar beneficial health characteristics in those with the highest quintiles of factor and index scores, suggesting some similarities across the approaches(Reedy *et al*. 2009). However, no comparison was made across patterns with health outcomes. Other approaches to describe dietary patterns, such as reduced rank regression, may be helpful in explaining variation in nutrient intakes. This approach has shown that similar patterns can account for relatively large amounts of variation across European countries(Kroger *et al*. 2009).

Healthy dietary patterns, and in particular the Mediterranean diet, has been explored with regard to cardiovascular disease outcomes(Martinez-Gonzalez et al. 2002; Panagiotakos et al. 2006; WHO Technical Report Series 2003; Willett 2006). Less is known about how these patterns relate to risk of cancer(Cottet *et al*. 2009; de Lorgeril *et al*. 1998; Fung *et al*. 2005). In our study we were not able to find any statistically significant associations between either the Mediterranean diet score or the WHO HDI and risk of breast cancer. As far as we are aware, no other cohort studies have published results which assess a Mediterranean *diet score* in association with risk of breast cancer.

Studies which have explored a Mediterranean dietary pattern with breast cancer risk have all used factor analysis to assign the dietary pattern(Cottet *et al*. 2009; Fung *et al*. 2005; Murtaugh *et al*. 2008; Ronco *et al*. 2006; Sieri *et al*. 2004; Velie *et al*. 2005). This approach is very different from using scores since it groups correlated food types into patterns. Patterns identified in one population may well be different from patterns identified in

another, making the potential for health promotion messages as a result less clear. Our results are not conclusive with regard to the patterns described. Other studies have used different dietary patterns to describe diet. The EPIC cohort explored risk of breast cancer with fruit and vegetable consumption and found no associations(van Gils *et al*. 2005), however, the whole dietary pattern was not considered in that analysis. 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(Trichopoulou *et al*. 2005).

A large French cohort with 2,381 postmenopausal invasive breast cancer cases obtained dietary patterns by factor analysis rather than using a score. The 'healthy/Mediterranean' dietary pattern was negatively associated with breast cancer risk, particularly in women who were estrogen-receptor positive and progesterone-receptor negative. The Nurses Health cohort also used factor analysis to identify two main dietary patterns: the prudent diet, similar to a Mediterranean type diet and the Western diet. They did not observe an overall association between either dietary pattern and risk of postmenopausal breast cancer. Unlike the French cohort, amongst the 17% of women who were estrogen receptor negative there was a reduced risk of breast cancer with higher prudent diet score(Fung *et al*. 2005). Hormone receptor status is not currently available for the UKWCS.

Putative mechanisms which relate dietary patterns to the development of cancer do exist and may include rates of growth and development. For example, a high fat, low fibre dietary pattern 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(Key *et al*. 2001). To date, no studies have been designed with a long enough follow up throughout the lifecourse to confirm this theory. A randomized controlled trial of post-menopausal women to assess the effects of a low-fat dietary pattern on incidence of breast cancer with a follow up of 8 years did not find a statistically significant reduction in risk with a low fat diet. However, amongst

women who participated actively in the trial there was a borderline significant reduction in risk in the intervention group(Prentice *et al*. 2006).

Since this is a prospective study recall bias is unlikely. However, accurate measurement of food intake is important for studies of dietary pattern. The FFQ used in this cohort has been validated against biomarkers(Spence *et al*. 2002) and follows recommendations for good design(Cade *et al*. 2002). The dietary patterns described reflect existing predefined scores and may not necessarily be those which are optimal for breast cancer prevention. The UKWCS has a health conscious outlook with relatively low smoking rates and low body mass index(Cade *et al*. 2004). It is possible that less healthy dietary patterns were under-represented in our cohort. A further weakness of this study was that we did not have information on hormone receptor status of the tumour. Other studies have shown a possible link between dietary pattern and hormone receptor status although findings are not consistent(Cottet *et al*. 2009; Fung *et al*. 2005).

In conclusion, no statistically significant associations were seen between two common healthy dietary patterns, the Mediterranean diet and the WHO Healthy Diet Index, assessed by a standard scoring method and risk of development of breast cancer. In pre-menopausal, but not post-menopausal women, there was a non-significant inverse association with increasing adherence to the Mediterranean diet pattern.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Table 1 Derivation of the dietary patterns used: Mediterranean diet score and WHO Healthy Diet Index

	Indicator value		% cohort meeting guideline
	1	0	
Mediterranean diet score			
Vegetables (grams/day)	>=281	<281	
Legumes (grams/day)	>=31	<31	
Fruit and nuts (grams/day)	>=271	<271	
Cereals (grams/day)	>=226	<226	
Fish (grams/day)	>=24	<24	
Polyunsaturated:saturated fatty acid ratio	>=0.96	<0.96	
Meat (grams/day)	<40	>=40	
Poultry (grams/day)	<13	>=13	
Dairy (grams/day)	<97	>=97	
Alcohol (grams/day)	5-25	>5 or >25	
WHO HDI			
Total fat (% total E)	15-30	<15 or >30	29
Saturated fatty acids (% total E)	0-10	>10	34
Polyunsaturated fatty acids (% total E)	6-10	<6 or >10	51
Total carbohydrate (% total E)	55-75	<55 or >75	26
Non-milk extrinsic sugars (% total E)	0-10	>10	27
Non starch polysaccharides (g)	>20	<20	67
Fruit and vegetables (g)	>=400	<400	75
Protein (% total E)	10-15	<10 or >15	39
Cholesterol (g)	<300	>=300	74
Salt (g)	<5	>=5	12

Table 2. Characteristics of subjects according to Mediterranean diet score

Mediterranean Diet Score	**0 to 2**	**3**	**4**	**5**	**6**	**7 to 10**
Age (years), mean(SD)	53.6(9.4)	53.6(9.5)	52.9(9.5)	52.2(9.3)	51.7(9.2)	50.5(8.9)
BMI (kg/m^2), mean(SD)	25.6(5.2)	25(4.4)	24.8(4.4)	24.5(4.3)	24.2(4.4)	23.5(3.7)
Total energy intake including alcohol (MJ), mean(SD)	8.8(2.5)	9.0(2.7)	9.3(2.8)	9.7(3.0)	10.1(3.1)	10.8(3.0)
Physical Activity (minutes), mean(SD)	12(30)	12(24)	12(24)	12(30)	18(30)	18(30)
Current smoker, n(%)	481(13.4)	603(13.8)	663(11.3)	650(10.6)	537(9.6)	692(9.4)
Current HRT use, n(%)	758(21.2)	976(22.3)	1132(19.3)	1269(20.7)	1068(19)	1337(18.1)
Current OCP use, n(%)	136(3.8)	171(3.9)	225(3.8)	256(4.1)	199(3.5)	311(4.2)
Nulliparous, n(%)	620(17.3)	833(19)	1212(20.8)	1242(20.3)	1165(20.8)	1612(22)
Professional and managerial class, n(%)	1971(55.2)	2504(57)	3570(60.9)	3868(63.1)	3733(66.1)	5236(70.7)
No education >14yr, n(%)	740(22.5)	922(22.8)	1025(18.8)	966(16.9)	759(14.3)	782(11.1)
Menarche <12yr, n(%)	771(21.5)	955(21.8)	1247(21.3)	1356(22.1)	1292(22.9)	1690(22.7)
Postmenopause, n(%)	2183(59.5)	2631(58.7)	3347(55.7)	3318(52.9)	2915(50.7)	3385(44.9)
Premenopause, n(%)	1485(40.5)	1855(41.4)	2661(44.3)	2954(47.1)	2840(49.4)	4157(55.1)
Incident breast cancer, n(%)	94(2.56)	123(2.74)	140(2.33)	165(2.63)	124(2.15)	182(2.41)
Vegetables (g/day), mean(SD)	189.7(89.6)	222.5(112.2)	260.4(138.8)	310.9(160.1)	362.6(179.3)	441.4(203.5)
Legumes (g/day), mean(SD)	21(20.2)	26(24.1)	31.3(29.3)	40.1(35.6)	50.1(42.1)	66.2(50.4)
Fruit and nuts (g/day), mean(SD)	190.4(129.8)	232.4(177.1)	272.5(195.2)	320.6(224.3)	364.9(239.5)	441.9(268)
Cereal (g/day), mean(SD)	165.7(82)	189.3(98.7)	215.3(109.8)	240.8(118.5)	277(136.3)	321.6(140.1)
Fish and fish products (g/day), mean(SD)	19.7(14.1)	23.6(17.8)	26.7(21.5)	29.4(26.5)	30.3(29.1)	32.9(33.2)
Monounsaturated/saturated fat ratio, mean(SD)	0.8(0.1)	0.9(0.1)	0.9(0.2)	1(0.2)	1(0.2)	1.1(0.3)
Poultry and poultry products (g/day), mean(SD)	23.7(18.2)	21.3(18.4)	19.9(20)	18.1(20.3)	15.3(20.7)	9.1(18.3)
Dairy (g/day), mean(SD)	122.5(81.6)	112.2(79.6)	114.8(83.3)	117.3(90.8)	118.3(91.2)	107.5(90.5)
Meat and meat products (g/day), mean(SD)	75.7(41.7)	67.1(45.7)	60.2(51.2)	50.4(54.3)	38.6(51)	19.1(37.7)
Ethanol (g/day), mean(SD)	6.5(11.1)	8(11.2)	8.7(10.8)	9(10.7)	9.1(10)	9.7(8.7)
Fruit and vegetable (portions/day), mean(SD)	5.1(2.3)	6.1(3)	7.1(3.5)	8.5(4.1)	9.8(4.5)	12(5.3)
Fat intake (g/day), mean(SD)	80.8(28.7)	80.6(30.5)	81.3(31.3)	83.8(33.3)	85.9(33.7)	89.5(32.7)
Vitamin C (mg/day), mean(SD)	118.4(55.1)	133(62)	149.6(70.8)	169.5(79)	187.9(84.3)	219.1(97)

Table 3 Characteristics of subjects according to WHO Healthy Diet Index

WHO HDI	**0 to 2**	**3**	**4**	**5**	**6**	**7 to 10**
Age (years), mean(SD)	53.85(9.65)	52.64(9.48)	51.92(9.26)	51.36(9.19)	51.99(9.12)	51.15(8.86)
BMI (kgm-2), mean(SD)	25.29(4.65)	24.7(4.33)	24.45(4.14)	24.09(4.39)	24.28(4.44)	23.78(4.08)
Total energy intake including alcohol (MJ), mean(SD)	9.6(2.7)	10.1(3.2)	10(3.2)	9.8(2.8)	9.5(2.7)	9.4(2.9)
Physical Activity (minutes), mean(SD)	12.1(28.3)	13.8(27.3)	14.7(29.7)	16.2(30.8)	16.7(27.7)	18.8(29.9)
Current smoker, n(%)	923(15.7)	734(12.3)	733(11.7)	571(9.8)	324(7.4)	341(7.5)
Current HRT use, n(%)	1248(21.2)	1219(20.4)	1237(19.7)	1087(18.6)	882(19.9)	867(18.9)
Current OCP use, n(%)	237(4)	217(3.6)	265(4.2)	233(4)	162(3.6)	184(4)
Nulliparous, n(%)	1081(18.3)	1113(18.6)	1230(19.7)	1176(20.3)	973(22.1)	1111(24.5)
Professional and managerial class, n(%)	3371(57.3)	3689(61.5)	4021(64)	3884(66.5)	2859(64.5)	3058(66.9)
No education >14yr, n(%)	1129(20.9)	944(16.9)	943(16)	789(14.4)	721(17.3)	668(15.4)
Menarche <12yr, n(%)	1213(20.6)	1231(20.5)	1334(21.3)	1361(23.3)	1069(24.1)	1103(24)
Postmenopause, n(%)	3597(59.6)	3362(54.8)	3280(51.2)	2850(47.8)	2388(52.8)	2302(49.2)
Premenopause, n(%)	2435(40.4)	2776(45.2)	3127(48.8)	3107(52.2)	2131(47.2)	2376(50.8)
Incident breast cancer, n(%)	151(2.5)	155(2.53)	163(2.54)	139(2.33)	109(2.41)	111(2.37)
Total fat (% total E)	36.2(4.2)	35.7(4.3)	34.9(5)	33.2(5.6)	29.1(5.5)	26.9(4)
Saturated fatty acids (% total E)	14.2(2.8)	13.1(2.6)	12.2(2.5)	11(2.6)	9(2.1)	7.7(1.6)
Polyunsaturated fatty acids (% total E)	5.6(1.3)	6.3(1.6)	6.7(1.7)	6.9(1.9)	6.3(1.9)	6.3(1.5)
Cholesterol (mg)	327.3(126.1)	299(132.2)	260.2(121.1)	209.6(86.2)	177.5(77.4)	135.5(68.8)
Total carbohydrate (% total E)	47.2(4.4)	48.2(4.4)	49.4(4.8)	51.6(4.9)	55.4(4.8)	58.6(4.1)
Non-milk extrinsic sugars (% total E)	14.1(4.2)	13.3(4.4)	12.8(4.6)	12.6(4.5)	12.5(4.7)	11.6(4.6)
Protein (% total E)	16.9(2.5)	16.4(2.7)	15.9(2.8)	15.4(2.8)	15.7(2.7)	14.6(2.4)
Dietary fibre (englyst) (g)	18.5(6.8)	22.6(8.5)	24.7(9.2)	26.8(9.3)	29.2(10.1)	32.1(11.7)
Fruit and vegetables (g)	404.4(203.6)	536.8(270.9)	606.2(295.5)	668.1(304.8)	759.2(362.3)	886.2(428.9)
Salt (g)	7.8(2.3)	8.2(2.9)	8.1(2.9)	7.9(2.6)	7.7(2.6)	7.3(2.7)
Fruit and veg (portions/day), mean(SD)	5.5(2.7)	7.3(3.7)	8.3(4.1)	9.2(4.3)	10.3(4.9)	11.9(5.8)
Fat intake (g/day), mean(SD)	89.9(28.4)	93.7(34.4)	91(35.2)	85.2(31.1)	72(27.1)	66(23.4)
Ethanol (g/day), mean(SD)	8.9(10.7)	9.4(10.5)	9.5(10.7)	8.9(10.2)	7.8(9.5)	7.3(10)
Vitamin C (mg/day), mean(SD)	127.5(61.4)	155.2(75.6)	166.2(79.2)	176.7(77.6)	195.1(91.2)	215(105)

Table 4 Mediterranean diet score and risk of breast cancer

	Person years	Cases/non-cases	Model 1[a] HR	95% CI	Model 2[b] HR	95% CI
Combined Analysis						
0-2 (ref)	8.83(1.5)	94/3574	1.00	-	1.00	-
3	8.96(1.5)	123/4363	1.08	(0.82 , 1.41)	1.06	(0.77 , 1.46)
4	9.07(1.44)	140/5868	0.91	(0.7 , 1.18)	0.98	(0.72 , 1.33)
5	9.21(1.38)	165/6107	1.04	(0.8 , 1.35)	0.99	(0.73 , 1.35)
6	9.36(1.35)	124/5631	0.86	(0.65 , 1.14)	0.84	(0.6 , 1.17)
7-10	9.55(1.24)	182/7360	0.97	(0.74 , 1.26)	0.96	(0.7 , 1.32)
			P(trend)=0.424		P(trend)=0.365	
Premenopausal						
0-2 (ref)	9.12(1.34)	36/1449	1.00	-	1.00	-
3	9.28(1.22)	40/1815	0.89	(0.56 , 1.4)	0.71	(0.43 , 1.16)
4	9.33(1.21)	58/2603	0.89	(0.58 , 1.36)	0.88	(0.56 , 1.36)
5	9.47(1.14)	63/2891	0.81	(0.53 , 1.24)	0.72	(0.46 , 1.13)
6	9.56(1.11)	57/2783	0.76	(0.48 , 1.18)	0.69	(0.43 , 1.1)
7-10	9.66(1.04)	96/4061	0.86	(0.57 , 1.3)	0.65	(0.42 , 1.02)
			P(trend)=0.356		P(trend)=0.087	
Postmenopausal						
0-2 (ref)	8.64(1.58)	58/2125	1.00	-	1.00	-
3	8.74(1.63)	83/2548	1.20	(0.85 , 1.68)	1.46	(0.95 , 2.23)
4	8.86(1.57)	82/3265	0.92	(0.65 , 1.29)	1.10	(0.71 , 1.69)
5	8.97(1.53)	102/3216	1.19	(0.86 , 1.66)	1.26	(0.83 , 1.94)
6	9.17(1.53)	67/2848	0.92	(0.64 , 1.33)	0.98	(0.61 , 1.58)
7-10	9.42(1.43)	86/3299	1.03	(0.73 , 1.46)	1.30	(0.83 , 2.05)
			P(trend)=0.73		P(trend)=0.92	

CI= confidence interval; HR=hazard ratio.
[a] adjusting for age, energy intake and menopausal status (combined analysis).
[b] 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.

Table 5 WHO Healthy Diet Index and risk of breast cancer

			Model 1[a]		Model 2[b]	
	Person years	Cases/non-cases	HR	95% CI	HR	95% CI
Combined Analysis						
0-2 (ref)	8.84(1.53)	151/5881	1.00	-	1.00	-
3	9.06(1.39)	155/5983	1.04	(0.83 , 1.31)	0.95	(0.72 , 1.24)
4	9.19(1.38)	163/6244	1.05	(0.84 , 1.32)	1.08	(0.83 , 1.41)
5	9.37(1.34)	139/5818	0.87	(0.68 , 1.12)	0.94	(0.7 , 1.24)
6	9.4(1.34)	109/4410	0.99	(0.76 , 1.28)	0.95	(0.68 , 1.34)
7-10	9.53(1.31)	111/4567	0.95	(0.73 , 1.24)	0.94	(0.67 , 1.32)
			P(trend)=0.422		P(trend)=0.765	
Premenopausal						
0-2 (ref)	9.18(1.31)	55/2380	1.00	-	1.00	-
3	9.33(1.16)	61/2715	0.98	(0.67 , 1.43)	0.97	(0.64 , 1.48)
4	9.41(1.19)	69/3058	0.97	(0.67 , 1.4)	1.11	(0.74 , 1.66)
5	9.56(1.1)	69/3038	0.88	(0.6 , 1.3)	1.02	(0.67 , 1.54)
6	9.61(1.08)	43/2088	0.90	(0.58 , 1.38)	0.89	(0.53 , 1.49)
7-10	9.67(1.04)	53/2323	0.84	(0.56 , 1.27)	0.83	(0.5 , 1.39)
			P(trend)=0.338		P(trend)=0.608	
Postmenopausal						
0-2 (ref)	8.61(1.63)	96/3501	1.00	-	1.00	-
3	8.84(1.52)	94/3268	1.07	(0.8 , 1.42)	0.92	(0.64 , 1.31)
4	8.99(1.5)	94/3186	1.10	(0.82 , 1.46)	1.05	(0.74 , 1.49)
5	9.15(1.53)	70/2780	0.85	(0.62 , 1.17)	0.85	(0.57 , 1.27)
6	9.22(1.51)	66/2322	1.03	(0.74 , 1.43)	0.96	(0.61 , 1.5)
7-10	9.39(1.53)	58/2244	1.00	(0.71 , 1.41)	0.99	(0.63 , 1.55)
			P(trend)=0.706		P(trend)=0.859	

CI= confidence interval; HR=hazard ratio.
[a] adjusting for age, energy intake and menopausal status (combined analysis).
[b] 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.

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