Dietary patterns derived with multiple methods from food diaries and breast cancer risk in the UK Dietary Cohort Consortium

Running title: dietary patterns and breast cancer

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Abstract

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Background/ Objectives: In spite of several studies relating dietary patterns to breast cancer risk, evidence so far remains inconsistent. This study aimed to investigate associations of dietary patterns derived with three different methods with breast cancer risk.

Subjects/ Methods: The Mediterranean Diet Score (MDS), principal components analyses (PCA) and reduced rank regression (RRR) were used to derive dietary patterns in a case-control study of 610 breast cancer cases and 1891 matched controls within 4 UK cohort studies. Dietary intakes were collected prospectively using 4-to 7-day food diaries and resulting food consumption data were grouped into 42 food groups. Conditional logistic regression models were used to estimate odds ratios (ORs) for associations between pattern scores and breast cancer risk adjusting for relevant covariates. A separate model was fitted for post-menopausal women only.

Results: The MDS was not associated with breast cancer risk (OR comparing 1st tertile with 3rd 1.20 (95% CI 0.92; 1.56)), nor the first PCA-derived dietary pattern, explaining 2.7% of variation of diet and characterized by cheese, crisps and savoury snacks, legumes, nuts and seeds (OR 1.18 (95% CI 0.91; 1.53)). The first RRR-derived pattern, a 'high-alcohol' pattern, was associated with a higher risk of breast cancer (OR 1.27; 95% CI 1.00; 1.62), which was most pronounced in post-menopausal women (OR 1.46 (95% CI 1.08; 1.98).

Conclusions: A 'high-alcohol' dietary pattern derived with RRR was associated with an increased breast cancer risk; no evidence of associations of other dietary patterns with breast cancer risk was observed in this study.

Introduction

Diet could play a role in the on-going rise of breast cancer incidence (1, 2) but to what extent is still unclear. Individual dietary risk factors have been studied in relation to breast cancer but often the approach of focussing on single foods or nutrients when investigating diet breast cancer associations has resulted in null findings or inconclusive results (2-5). An alternative approach is to study dietary patterns. This has been done in a number of studies, but again findings are inconsistent (6, 7). The majority of studies have used *posteriori* dietary patterns, mainly using principal components analysis (PCA) or using predefined diet quality scores, like the Mediterranean Diet score (MDS) (8, 9). A few studies have used the reduced rank regression (RRR) method (10-14), which combines *a priori* knowledge with *posteriori* analyses and therefore benefits from using information on potential diet-disease associations (15). A combination of multiple methods to study dietary patterns in relation to breast cancer risk could give a more complete picture but this approach has rarely been used (16). Most studies of dietary patterns have used food frequency questionnaires (FFQs) as the method of dietary assessment. To assess dietary intake, food diaries are generally thought to result in more accurate and varied dietary data than FFQs (6). In our analyses, we aimed to explore multiple methods to derive dietary patterns using detailed dietary information from food diaries and relate this to breast cancer risk; we also explored these associations in post-menopausal women separately as dietary risk factors could be different for this subgroup (2).

Subjects and Methods

Subjects

The UK Dietary Cohort Consortium was set up to investigate associations between dietary intake, assessed using prospective food diaries, and cancer risk (5). The participating cohorts in these analyses were EPIC-Norfolk (17), EPIC-Oxford (18), the UK Women's Cohort Study (UKWCS) (19), and Whitehall II study (20). Participants gave informed consent and each study was approved by the respective ethics committees. The designs, selection of controls, methods of pooling and standardization of dietary data have been described in detail elsewhere (4, 5).

Briefly, cases were women who developed breast cancer, defined as codes CD 174 or C50 of the 9^{th} and 10^{th} Revision of the International Statistical Classification of Diseases, Injuries, and Causes of Death. Cases were free of cancer (except for non-melanoma skin cancer) at the time of dietary assessment and developed breast cancer ≥12m later (6m in EPIC-Oxford). In total, there were 610 cases, of which 409 were post-menopausal (**Table 1**). Each case was matched to four control subjects within each cohort who were free of cancer (except for non-melanoma skin cancer) at the date of dietary assessment and free of breast cancer at the end of follow-up within the appropriate stratum of matching criteria. Matching criteria included cohort, age at enrolment (±3y), and date of diet diary completion (±3m). In total, 1891 controls were matched to the cases. There is some minor variation in the matching design since these independent studies approached matching differently before the UK Dietary Cohort Consortium was set up (5).

Information on demographic and socio-economic variables, including social class and education, were obtained through standard questionnaires, either self-administered or administered by trained researchers, at or close to time of dietary assessment.

Dietary assessment

All participating cohorts collected dietary information in the form of estimated food diaries over 4-7 days, the period depending on the cohort (from 1991 to 2002; Table 1)

(17-20). Participants were asked to record all foods and drinks consumed and to describe portions using household measures or by reference to photographs that showed various serving sizes of representative food items. Food records were coded using the data entry and processing programs Data Into Nutrients for Epidemiological Research (DINER) and DINERMO (21) and for UKWCS using the Diet and Nutrition Tool for Evaluation (DANTE) (22). Data output included nutrients and food groups, the latter being aggregated into 42 predefined food groups according to usage or differences in energy density and total fat content.

Dietary patterns

To explore the association of dietary patterns and breast cancer risk, dietary patterns were investigated using three methods. The first method used was a predefined diet quality score, the MDS based on Trichopoulou et al (23) using foods (vegetables, legumes, fruits and nuts, cereals, fish and seafood, dairy, meat and meat products) and a number of nutrients (ratio MUFA/SFA, alcohol) which were scored based on the median intake or for alcohol using 5-25g/d as an acceptable range. As alcohol on its own is an established risk factor for breast cancer (2, 3, 24) the MDS was also calculated excluding alcohol from the score and adjusting the analyses for alcohol intake. The maximum score attainable was 9 when including alcohol and 8 when excluding alcohol. Second, PCA was used; the 42 predefined food groups were entered into the model and based on evaluation of eigen values and scree plots, patterns were derived and rotated using VARIMAX. Only factor loadings >0.25 were presented for ease of interpretation.

Thirdly, RRR (13) was used on the 42 food groups; alcohol, total fat (as % energy) and fibre were chosen as response variables as they have been suggested as dietary factors that are associated with breast cancer risk (2, 5, 25-29). The number of response variables dictates the maximum number of dietary patterns, which were three in these analyses. Both PCA and RRR analyses were checked by repeating the analyses on a 50% random split sample.

Statistical methods

Tertiles of dietary patterns scores were entered into conditional logistic regression models that calculated odds ratios (ORs) and 95% confidence intervals (CI); these models automatically adjust for the matching variables. However, since the age matching of cases and controls was up to 3y, analyses were also adjusted for age as a continuous variable. Multivariable analyses were also adjusted for parity (0,1,2,3,4+ children), use of hormone replacement therapy (HRT) (yes or no), weight (<60, 60-65, 66-71, ≥72 kg), height (<158, 158-162, 163-167, ≥168 cm), physical activity (low, low-medium, medium-high, or high), menopausal status (pre-, peri-, and post-menopausal) and energy intake (continuous). We refer to this as model 1.

A number of risk factors with weaker associations with breast cancer risk were included in a second extended model, resulting in more missing data. Model 2 included variables in model 1 and additionally family history of breast cancer (yes/no; missing for EPIC-Oxford and Whitehall), breastfeeding (yes/no; missing for Whitehall), and education level (low to high). A total of 696 individuals had at least one of these variables missing. To see whether any differences between model 1 and 2 were due to the additional adjustments or due to the population being reduced due to missing data, model 1 was fitted again restricting to those subjects contributing to model 2 (we refer to this as model 1 adjusted). Other potential covariates, such as smoking, age at first birth, were not adjusted for due to the amount of missing data. Further sensitivity analyses included subgroup analyses for post-menopausal women only and for cases with a breast cancer diagnosis ≥2y after completion of the food diary to reduce the possible effect of reverse causality. To test for linear trends across tertiles, median scores of the respective tertile were assigned. Finally, the assumption of no heterogeneity across the different cohorts was tested by including an exposure by centre interaction term in the models. Analyses were carried out using SAS statistical software (SAS version 9.3) and p values of <0.05 were considered statistically significant.

Results

Breast cancer cases were significantly younger, older at first live birth, taller, had fewer children (parity), and more often had family history of breast cancer than their matched controls (**Table 2**). Differences in menopausal status were observed, with more controls being post-menopausal. In terms of dietary intake, breast cancer cases had higher intakes of energy, dietary fibre, legumes, and alcohol and ratio of MUFA/SFA than controls.

MDS

The MDS was not significantly associated with breast cancer risk in this study (model 1 OR 1.20 (95% CI 0.92; 1.56) comparing 1st tertile with 3rd) nor was it after further adjustment (model 2 OR 1.05 (95% CI 0.77; 1.43)), among only post-menopausal women (OR 1.10 (95% CI 0.80; 1.51)), nor for those diagnosed ≥2 year after completing the food diary (OR 1.22 (95% CI 0.92; 1.62)) (**Table 3**). Leaving out alcohol from the MDS score and adjusting the models for alcohol intake led to similar non-significant findings (OR 1.15 (95% CI 0.83; 1.60)).

No evidence of heterogeneity across the different cohorts for these analyses was observed (p interaction 0.16) and MDS results were comparable between the different cohorts (data not shown).

PCA

Three dietary patterns were identified, which explained 6.2% of the variation in the 42 food groups. The first pattern explained 2.7% of the total variation and was positively loaded by cheese, crisps and savoury snacks, fresh fruit, legumes, low fat milk, nuts and seeds, other fruit, rice/pasta/other grains, sauces, vegetable mixed dishes and negatively loaded by potatoes, poultry, and red meat (Supplementary Table 1). The first dietary pattern score was not associated with breast cancer risk (model 1, OR 1.18 (95% CI 0.91; 1.53)), nor after further adjusting the model (model 2, OR 1.02 (95% CI 0.75;

1.39)) nor in post-menopausal women only (OR 1.27 (95% CI 0.93; 1.73)) nor for the two subgroups analysed (**Table 4**).

As the second and third pattern explained even less of the variation (1.9% and 1.6% respectively), these patterns were not investigated further. No evidence of heterogeneity across the different cohorts for these analyses was observed (p interaction 0.66).

PCA results on a random 50% split sample showed that the first pattern showed similarities for the highest loading food groups but factor loadings were minor contributors to the pattern (Supplementary Table 1).

RRR

Using RRR with the response variables alcohol, total fat and fibre, three factors were generated and these explained 76.6% of the total variation in food intake, of which 33.5% was explained by the first factor. A high response score for factor 1 reflected a diet high in alcohol hence the naming of the dietary pattern as 'high-alcohol'; this pattern was mainly driven by consumption of wines, spirits, and beers and ciders (Supplementary Table 2). For this first dietary pattern a positive association with breast cancer risk was found: OR 1.27 (95% CI 1.00; 1.62; p for trend 0.04) comparing the third tertile of factor loading score with the first (**Table 5**); for post-menopausal women the association appeared stronger, with OR 1.46 (95% CI 1.08; 1.98; p for trend 0.01). For those diagnosed ≥2 years after completing the food diary results were also stronger than compared to the model including all subjects, OR 1.32 (95% CI 1.01; 1.71; p for trend 0.03).

The second pattern reflected a diet high in fibre and low in alcohol and total fat and was mainly driven by fresh fruit, raw and boiled vegetables, high fibre bread, and high fibre breakfast cereals. This second pattern was not associated with breast cancer risk (OR 1.08 (95% CI 0.84; 1.38); p for trend 0.55) nor for post-menopausal women (OR 1.23 (95% 0.91; 1.66); p for trend 0.18) nor those diagnosed ≥2 years after completing the food diary (OR 1.10 (95% CI 0.84; 1.43; p for trend 0.48). No evidence of heterogeneity across the different cohorts for these analyses was observed (p interaction 0.83).

The third pattern explained 14.4% of the variation in food intake but as this pattern showed overlap in foods driving this pattern with the second pattern it was not taken further.

The factor loadings of the first derived RRR patterns of a random 50% split sample showed similar factor loadings as in the total sample, especially for the highest loading food groups (Supplementary Table 2).

Discussion

The results of this exploratory study on dietary patterns and breast cancer do not indicate that the MDS or dietary patterns derived with PCA were associated with breast cancer risk. The first dietary pattern derived with RRR, the 'high-alcohol' pattern, was associated with an increased risk of breast cancer, and this was most pronounced in post-menopausal women. The second RRR-derived dietary pattern, the 'high-fibre' pattern, was not associated with breast cancer risk.

By using three different methods to derive dietary patterns, each with their own strengths and limitations (6, 30), this study aimed to provide a better overview of how dietary patterns are associated with breast cancer risk. The MDS is an hypothesis-driven approach describing a dietary pattern including consumption of vegetables, legumes, fruit and nuts, cereals, fish and seafood, dairy, meat, ratio MUFA/SFA and alcohol, which was not associated with breast cancer risk in this study. This was in line with previous studies also showing no association of the MDS with breast cancer risk (8, 31, 32), though another study did find a marginally inverse association amongst postmenopausal women only (23). As the MDS does not describe the overall diet pattern, other methods to derive dietary patterns were included in this study. The data-driven approach PCA did not result in meaningful dietary patterns in this study and only explained 6.2% of the variation in foods consumed. Examples of dietary patterns that were found to be associated with breast cancer risk from previous studies include a 'Western' dietary pattern, including higher consumption of red and processed meat, refined grains, sweets and desserts and high-fat dairy products (33, 34) and a Mediterranean dietary pattern characterized by fruit, raw and cooked vegetables, fish and crustaceans and olive oil, which was found to be inversely associated with breast cancer risk (8, 35, 36). RRR, a hybrid approach combining elements of both a hypothesis and data driven approach, did result in a dietary pattern that was found to be associated with breast cancer risk in this study, which mainly described a dietary pattern related to alcoholic drinks. Thus by including these three different methods to derive dietary patterns, the overall picture seems to suggest that it was mainly a dietary pattern describing alcoholic drinks that emerges from the three methods studied to be associated with breast cancer risk in this study. These findings are in line with the results of the latest report of the continuous update programme (CUP) of the World Cancer Research Fund in 2010 which reported that of the dietary factors commonly investigated to date, the most convincing evidence is for alcohol intake (3); this is also supported by two recent systematic reviews by Albuquerque et al (34) and by Brennan et al (7) both also identifying a 'dietary drinker pattern' to be positively associated with breast cancer risk.

One could argue that studying a dietary pattern representing mostly alcohol intake (RRR pattern 1) is not useful; however, by considering alcohol within a dietary pattern we aimed to consider the contexts of its consumption, i.e. consider the role of foods often consumed alongside alcohol. This could eliminate the need for complex adjustment modelling and minimizes residual confounding. Alcoholic drinks were split into three groups, wines, spirits, and beers and ciders, to aid interpretation of the derived dietary pattern. Previously, we showed that for every 10g of alcohol consumption per day breast cancer risk increases with 10%, but this was only shown for measurements that combined the 7d food diary with long-term measurements from a FFQ(24). This highlights the importance of reducing alcohol intake for breast cancer prevention independent of consumption of other foods.

In spite of pooling a moderately large number of cases from four established cohorts for these analyses, the analyses presented in this paper were limited by inadequate power for subgroup analyses (2, 3), especially for menopausal status, which is an important aspect of breast cancer risk (3). It would also have been of interest to explore the dietary patterns of pre-menopausal women only. A limitation of bringing together the data of four different cohorts is that this could have led to additional variation despite standardizing the research methods in the analysis phase; this could have reduced the power to detect any dietary patterns, especially for the data-driven approaches like PCA and RRR. For PCA and RRR, analyses were repeated in a random 50% split sample showing similar results, though factor loadings were somewhat different. MDS results were comparable between the different cohorts (data not shown). Moreover, no evidence of heterogeneity across the different cohorts in any analysis was observed.

The proportion of missing data for the covariates limited the study, especially in the second extended model; however, the analyses of model 2 did not lead to different conclusions. When using RRR to derive dietary patterns different choices of response variables can be made. To date, studies using RRR to derive dietary patterns have used both biomarkers (e.g. C-reactive protein (12)) or nutrients (e.g. dietary fatty acids (10)) as response variables; both approaches suffer from measurement error. The variation explained by biomarker responses may be influenced by measurement, medical, genetic and environmental factors while the larger variation often explained by nutrient responses may, in part, be due to the correlated measurement errors of predictors and responses. Nutrient responses have been chosen in this study due to our interest in the food-nutrient-cancer pathways, and also partly due to the lack and uniformity of other measures, like biomarkers, in these UK cohorts.

A key strength of this study is that food diaries were used for dietary assessment, rather than FFQs. Food diaries have taken over from the now rarely performed weighed assessments as the gold standard for dietary assessment (37). The prospective assessment of dietary intake in our study reduces information bias from selected recall. Moreover, a sensitivity analyses was conducted to take into account the potential for reverse causality and these showed that the associations were largely similar in those who completed the diary ≥2 years before diagnosis. Additionally, this study benefits from including MDS, PCA and RRR methods to study dietary patterns in relation to breast cancer and by using these different methods in one study a broader overview of dietary patterns in relation to breast cancer in this cohort is given. A previous study, including more than one method to study dietary patterns, showed that using different methods may lead to different and sometimes complementary findings (16). The results of this study support previous evidence that alcohol is the most important dietary risk factor for breast cancer risk and that other dietary patterns were not associated with breast cancer risk.

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The authors’ responsibilities were as follows—AMS, CCD, TJK, BJC, VJB, JEC, DCG, RHK, AB, AMcT, MAHL, GM, EJB and KTK: acquired data; GP performed statistical analyses and wrote the manuscript; and all authors: interpreted data, contributed to and reviewed the manuscript, and read and approved the final manuscript.

Conflict of Interest

DCG has received grant funding from Danone and WCRF. The other authors had no personal or financial conflict of interest.

TABLE 1 number of controls and cases per cohort of the UK dietary consortium

TABLE 2 Characteristics of controls (n=1891) and cases of breast cancer (n=610) of the UK Dietary consortium#

TABLE 3 Odds ratios for breast cancer risk according to tertiles of Mediterranean Diet Score (MDS), with and without including alcohol in MDS score

TABLE 4 Odds ratios for breast cancer according to tertiles of the first factor score of dietary patterns derived with principal components analyses (PCA) using 42 predefined food groups.

TABLE 5 Odds ratios for breast cancer according to tertiles of RRR-derived dietary patterns using 42 predefined food groups using alcohol, total fat and fibre as response variables. Results are presented for tertiles of the factor loading score for the first dietary pattern.

Supplementary information is available at EJCN's website

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