Short Communication

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

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Epidemiological studies conducted thus far have mainly used a single-nutrient approach which may not be sufficient in detecting diet–cancer relationships. The aim of the study was to examine the association of a food pattern based on explained variations in fatty acid intake by means of reduced rank regression with breast cancer risk. Study participants were female subjects (*n* 15 351) of the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study free of cancer at baseline and with complete dietary and outcome information followed for an average of 6·0 years. Among those, 137 incident cases of invasive breast cancer were identified. We identified a food pattern characterized by low consumption of bread, and fruit juices, and high consumption of processed meat, fish, butter and other animal fats, and margarine explaining > 42 % of total variation in fatty acid intake (SFA, MUFA, *n*-3 PUFA, *n*-6 PUFA). Intake of all four fatty acid fractions was positively associated with the pattern score. Adherence to this food pattern adjusted for covariates was associated with a two-fold risk (hazard ratio 2·00; 95 % CI 1·30, 3·09) of breast cancer comparing extreme tertiles of the pattern score. There was no evidence of effect modification by menopausal status, overweight status and use of hormone replacement therapy, respectively. In conclusion, a food pattern characterized by high-fat food choices was significantly associated with increased risk of breast cancer. Given that the food pattern was high in all fatty acid fractions, we found evidence for total dietary fat rather than for specific fatty acids to be associated with breast cancer risk.

Breast cancer: Fat intake: Food pattern: EPIC-Potsdam Study

High fat intake[1−3], and possibly high intake of specific fatty acids[4,5], has been shown to be an important modulator of breast cancer risk in animal studies[6−8]. These hypotheses were supported by case–control studies conducted in the 1970s and 1980s[3]. However, cohort studies thus far have been rather inconsistent, with the majority showing no association for total fat intake, reviewed in Hunter *et al.* [9] and Smith-Warner *et al.* [10], and some showing direct associations for saturated and *n*-6 fatty acids[11,12]. Recent results of the Women's Health Initiative dietary modification trial suggest a weak, if any, inverse association between a low-fat diet and risk of breast cancer[13].

The aim of the present study was to identify a food pattern which explains variation in fatty acid intake (SFA, MUFA, *n*-3 PUFA, *n*-6 PUFA), and to relate this pattern to breast cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort[14].

Methods

The study population for the present study stems from the female population of the EPIC-Potsdam cohort[15], a German population sample of 27 548 participants (10 904 males and 16 644 females) mostly aged 35–65 years, contributing to the large multi-centre EPIC cohort study[16]. The baseline examination of the study participants took place between August 1994 and September 1998.

We included 15 861 women free of any cancer at baseline recruitment and excluded women with missing information on diet and lifestyle factors, who reported an extreme energy intake (ratio between energy intake and estimated energy expenditure above ninety-ninth or below first percentile) or who had missing follow-up times, leaving 15 351 women for the statistical analysis.

Habitual dietary behaviour of the past 12 months before baseline was assessed with a validated 148-item semi-quantitative FFQ[17]. Food items were collapsed into thirty-nine food groups based on origin, culinary usage or nutrient profiles, and absolute intakes in gram per day were computed.

Cases of incident invasive breast cancer were identified via a combination of follow-up methods including active follow-up through study participants and their next-of-kin, health

insurance, cancer and mortality registries[18]. To classify mammary tumours, International Classification of Diseases ICD-10 (code C50) and ICD-O-2 were used. All new diagnoses were physician-verified.

Recently, our group has introduced reduced rank regression into nutritional epidemiology as a new tool for dietary pattern analysis[19]. Reduced rank regression identifies linear functions of predictors (e.g. food group intake) that explain as much variation as possible in a set of so-called response variables, e.g. nutrients[19] or biomarkers[20], that are presumed to affect disease risk. The principle of the reduced rank regression method has been described in full elsewhere[19]. Briefly, maximum variation in response variables (nutrient densities of fatty acid fractions, i.e. SFA, MUFA, n-3 PUFA, n-6 PUFA, expressed as g/1000 kJ) is explained by linear functions of predictors (thirty-nine food groups). Four factors were generated with the first factor explaining 42·8 % of total response variation (SFA, 26·4 %; MUFA, 58·3 %; n-3 PUFA, 49·1 %; n-6 PUFA, 37·5 %) and the remaining factors explaining 27·8, 7·3 and 2·2 % respectively. Only the first

factor showed significant associations in the diet–disease model and was further investigated. To derive a simplified food intake pattern, food groups explaining most of the inter-individual variation in the response score were identified via stepwise linear regression. The score for the simplified food pattern was calculated by summing standardized intakes of the food groups taking into account their positive or inverse association with the original pattern score[21]. The simplified pattern explained 41·3 % of variation in response variables.

In Cox's Proportional Hazards models relative risk for the association between tertiles of the simplified pattern score and breast cancer incidence was estimated with age as the primary time variable in the counting process formulation with entry time defined as the subject's age at recruitment and exit time defined as the subject's age at breast cancer diagnosis or censoring date (death, emigration, last complete follow-up). Three sets of models were conducted, one model which was only controlled for age in the strata statement of the PHREG procedure in SAS, one model, additionally controlling for known breast cancer risk factors including BMI,

Table 1. Sample characteristics across tertiles of the simplified pattern score, European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study*

(Mean values and standard deviations)

| | Tertiles of the food pattern score (limits) | | | | | | |
| | T1 (< -0.86) | | T2 (-0.86 to 0.69) | | T3 (>0.69) | | |
	Mean†	SD	Mean†	SD	Mean†	SD	P value‡
n	5116		5118		5117		
General characteristics							
Age (years)	49·5	9·4	49·2	9·4	48·4	9·2	<0·0001
BMI (kg/m^2)	25·5	4·4	25·8	4·6	26·1	4·9	<0·0001
% Nullipara	10·6		9·6		9·4		0·09
% Early menarche§	10·5		10·1		11·2		0·46
% Postmenopausal	40·5		38·6		33·9		<0·0001
% HRT users‖	42·9		40·9		42·9		0·36
% Smokers	13·8		15·8		18·9		<0·0001
% University degree	30·1		29·4		26·9		0·0006
Dietary characteristics							
Response variables							
SFA (g/MJ)	3·41	0·63	3·84	0·62	4·26	0·73	<0·0001
MUFA (g/MJ)	2·80	0·43	3·20	0·39	3·59	0·46	<0·0001
n-3 PUFA (g/MJ)	0·19	0·03	0·21	0·03	0·24	0·05	<0·0001
n-6 PUFA (g/MJ)	1·29	0·35	1·45	0·40	1·61	0·50	<0·0001
Food intake pattern							
Bread (g/d)	174·5	65·7	146·1	57·2	142·0	58·4	<0·0001
Fruit juices (g/d)	308·2	288·2	157·4	150·2	131·4	134·6	<0·0001
Processed meat (g/d)	40·1	23·5	52·6	26·6	76·6	44·1	<0·0001
Fish (g/d)	13·8	11·3	18·2	13·0	31·0	30·0	<0·0001
Butter/other animal fats (g/d)	5·9	7·5	7·5	8·9	11·7	14·2	<0·0001
Margarine (g/d)	11·3	9·8	14·1	11·2	20·2	16·8	<0·0001
Other dietary factors							
Total energy (kJ/d)	7742	2111	7559	2008	8472	2233	<0·0001
Total fat (g/MJ)	8·28	1·13	9·36	1·04	10·42	1·22	<0·0001
Fibre (g/MJ)	3·00	0·70	2·78	0·59	2·48	0·52	<0·0001
Alcohol (g/d)	7·52	9·73	8·61	10·7	9·43	11·3	<0·0001
β-Carotene (mg/MJ)	0·37	0·21	0·36	0·19	0·33	0·16	<0·0001
Vitamin C (mg/MJ)	19·1	8·1	16·2	6·1	14·3	5·4	<0·0001
Vitamin E (mg/MJ)	1·39	0·29	1·41	0·30	1·43	0·32	<0·0001
Fruits and vegetables (g/d)	312	145	302	131	306	139	0·03

HRT, hormone replacement therapy.

* Sum of standardized intakes of bread, fruit juices, processed meat, fish, butter and other animal fats, margarine.
† Percentage value where indicated.
‡ P value for linear trend (continuous variables); P value of χ^2 test for categorical variables.
§ Age at menarche ≤11 years.
‖ Postmenopausal women only (n 5784).

menopausal status, hormone replacement therapy, educational attainment, parity, alcohol consumption, smoking and age at menarche, and one model that additionally adjusted for other dietary factors (total energy intake, dietary fibre, vitamin C, vitamin E and β-carotene) that may confound the diet–disease association.

All statistical analyses were performed with SAS for Windows, version 9.1 (SAS Institute, Cary, NC, USA).

Results

After an average follow-up of 6·0 years, 137 verified incident cases of invasive breast cancer were identified. Baseline characteristics across tertiles of the simplified pattern score are presented in Table 1. Notably, concerning the distribution of fatty acid fractions used as response variables in the applied pattern technique, it became apparent that intakes of all fatty acid fractions (SFA, MUFA, *n*-3 PUFA and *n*-6 PUFA) were significantly positively associated with the score, i.e. intakes increased with increasing pattern score. The same direct association was found for total dietary fat. With regard to other dietary characteristics, we observed a decrease in fibre, β-carotene and vitamin C intake, and an increase in alcohol and vitamin E intake. Focusing on foods characterizing the simplified pattern, we found that the consumption of bread and of fruit juices was lower and that the consumption of processed meat, fish, butter and other animal fats, and margarine was higher with higher pattern score.

Table 2 shows risk estimates for the association between the simplified pattern score and breast cancer. Both the crude (Model 1) and the adjusted (Model 2) model yielded a significant direct association between the food pattern and risk of breast cancer. Women in the third tertile of the pattern score were at a two-fold increased risk to develop breast cancer compared to women in the first tertile (hazard ratio 2·00; 95 % CI 1·30, 3·09). Further adjustment for other dietary factors strengthened the association in that women in the third tertile displayed a 2·3-fold increase in risk, indicating that these dietary factors were not responsible for the observed association. There was no evidence of effect modification by menopausal status, overweight status and use of hormone replacement therapy when we stratified our analysis according to these factors (data not shown).

Discussion

The dietary pattern, extracted to explain variation in nutrient densities of fatty acid intake, significantly predicted breast cancer risk in a cohort of >15 000 German middle-aged women. The dietary pattern was positively associated with all fatty acid fractions used to derive the pattern. Thus, the observed association between the food pattern and risk of breast cancer may not be explained by differential effects of specific fatty acid fractions, even though some of them are thought to be protective of breast cancer, but rather by total fat intake related to the pattern. This might have occurred due to correlations between intakes of fatty acids, taking into consideration that with increasing total fat intake, intakes of fatty acids increase correspondingly. Indeed, in the present study, we observed strong positive correlations between total fat and the examined fatty acid fractions. The association of the food pattern with vitamin E can be explained in the same way. Although there is some evidence that vitamin E may protect from cancer, in the present study its intake was highly correlated with overall fat intake and intake of fatty acids.

Given the weak evidence from recent results of the Women's Health Initiative dietary modification in relation to breast cancer risk[13] and the inconclusive results of studies using the single-nutrient approach[9,10], studying dietary patterns in relation to breast cancer risk is of outstanding relevance. The common strategy of considering only individual dietary factors or only a limited number of them may not be sufficient in detecting diet–disease relationships, because it is not capable of modelling and estimating the overall effect of diet on cancer risk. Principal component analysis and the closely related factor analysis were the methods most often used to identify comprehensive food factors (dietary pat-

Table 2. Crude and adjusted hazard ratios (HR) and 95 % CI for the association between the simplified food pattern score* and risk of breast cancer, European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study (*n* 15 351)

Models†	Simplified pattern score			P for trend
	Tertile 1	Tertile 2	Tertile 3	
Cases	32	44	61	
Person-years	30 131	30 798	31 714	
Model 1				
HR	1·00	1·39	1·94	0·0021
95 % CI		0·88, 2·19	1·26, 2·98	
Model 2				
HR	1·00	1·42	2·00	0·0014
95 % CI		0·90, 2·25	1·30, 3·09	
Model 3				
HR	1·00	1·52	2·34	0·0004
95 % CI		0·95, 2·44	1·45, 3·79	

* Sum of standardized intakes of bread, fruit juices, processed meat, fish, butter and other animal fats, margarine.
† Model 1, stratified for age; Model 2, additionally adjusted for BMI, education, alcohol intake, smoking, parity, menopausal status, hormone replacement therapy, age at menarche; Model 3, Model 2 additionally adjusted for other dietary factors (total energy, fibre, β-carotene, vitamin C, vitamin E).

terns) consisting of highly correlated foods[22,23]. However, if an underlying hypothesis about the diet–disease pathway exists, the application of these pattern techniques in nutritional epidemiology might be limited, as both methods focus on the variation of food intake only, disregarding the possibly more important variation of nutrients and other food constituents. Since nutrients and other food constituents are considered as the actual biologically active compounds of foods, this disregard might lead to overlooking variation of specific dietary factors which is important for the development or prevention of cancer. Indeed, epidemiologic studies to examine dietary patterns in relation to breast cancer risk have yielded mainly null results[24–26]. Application of the reduced rank regression method overcomes this flaw, since it combines the two sources of information: a priori knowledge about possible pathways in disease aetiology and the dietary data at hand.

The present study has limitations that are worth mentioning. First, the relatively short follow-up period (6 years) yielded only a limited number of breast cancer cases. Therefore, risk estimates in sub-samples of the study population may be rather unstable and need to be repeated after a longer follow-up. Second, like in many other cohort studies, in the present study dietary intake was measured only once (at baseline recruitment) and not again during the course of follow-up in order to catch dietary changes. For the examination of diet–disease relations this implies the assumption of stable dietary behaviour of the study participants, which may not always be the case.

In conclusion, we found a dietary pattern characterized by a high consumption of processed meat, fish, butter and other animal fats, and margarine, and a low consumption of bread and fruit juices, and associated with dietary fat intake to be a significant risk factor for breast cancer. The present study findings give also new opportunities for a better understanding of the relationships between a high-fat diet and breast cancer risk from a population perspective. The identification of a food pattern generally high in fat being predictive of breast cancer nourishes the current debate about the role of fat intake in breast cancer development.

Acknowledgements

References

1. Ziegler RG, Hoover RN, Pike MC, et al. (1993) Migration patterns and breast cancer risk in Asian-American women. J Natl Cancer Inst 85, 1819–1827.
2. Bartsch H, Nair J & Owen RW (1999) Dietary polyunsaturated fatty acids and cancers of the breast and colorectum: emerging evidence for their role as risk modifiers. Carcinogenesis 20, 2209–2218.
3. Howe GR, Hirohata T, Hislop TG, et al. (1990) Dietary factors and risk of breast cancer: combined analysis of 12 case–control studies. J Natl Cancer Inst 82, 561–569.
4. Freedman LS, Potischman N, Kipnis V, et al. (2006) A comparison of two dietary instruments for evaluating the fat–breast cancer relationship. Int J Epidemiol 35, 1011–1021.
5. Bingham SA, Luben R, Welch A, Wareham N, Khaw KT & Day N (2003) Are imprecise methods obscuring a relation between fat and breast cancer? Lancet 362, 212–214.
6. Carroll KK & Khor HT (1975) Dietary fat in relation to tumorigenesis. Prog Biochem Pharmacol 10, 308–353.
7. Connolly JM, Gilhooly EM & Rose DP (1999) Effects of reduced dietary linoleic acid intake, alone or combined with an algal source of docosahexaenoic acid, on MDA-MB-231 breast cancer cell growth and apoptosis in nude mice. Nutr Cancer 35, 44–49.
8. Fay MP, Freedman LS, Clifford CK & Midthune DN (1997) Effect of different types and amounts of fat on the development of mammary tumors in rodents: a review. Cancer Res 57, 3979–3988.
9. Hunter DJ, Spiegelman D, Adami HO, et al. (1996) Cohort studies of fat intake and the risk of breast cancer – a pooled analysis. N Engl J Med 334, 356–361.
10. Smith-Warner SA, Spiegelman D, Adami HO, et al. (2001) Types of dietary fat and breast cancer: a pooled analysis of cohort studies. Int J Cancer 92, 767–774.
11. Wirfalt E, Mattisson I, Gullberg B, Johansson U, Olsson H & Berglund G (2002) Postmenopausal breast cancer is associated with high intakes of omega 6 fatty acids (Sweden). Cancer Causes Control 13, 883–893.
12. Boyd NF, Stone J, Vogt KN, Connelly BS, Martin LJ & Minkin S (2003) Dietary fat and breast cancer risk revisited: a meta-analysis of the published literature. Br J Cancer 89, 1672–1685.
13. Prentice RL, Caan B, Chlebowski RT, et al. (2006) Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 295, 629–642.
14. Boeing H, Wahrendorf J & Becker N (1999) EPIC-Germany – a source for studies into diet and risk of chronic diseases. European Investigation into Cancer and Nutrition. Ann Nutr Metab 43, 195–204.
15. Boeing H, Korfmann A & Bergmann MM (1999) Recruitment procedures of EPIC-Germany. European Investigation into Cancer and Nutrition. Ann Nutr Metab 43, 205–215.
16. Riboli E, Hunt KJ, Slimani N, et al. (2002) European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr 5(6B), 1113–1124.
17. Kroke A, Klipstein-Grobusch K, Voss S, et al. (1999) Validation of a self-administered food-frequency questionnaire administered in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study: comparison of energy, protein, and macronutrient intakes estimated with the doubly labeled water, urinary nitrogen, and repeated 24-h dietary recall methods. Am J Clin Nutr 70, 439–447.
18. Bergmann MM, Bussas U & Boeing H (1999) Follow-up procedures in EPIC-Germany – data quality aspects. European Prospective Investigation into Cancer and Nutrition. Ann Nutr Metab 43, 225–234.
19. Hoffmann K, Schulze MB, Schienkiewitz A, Nothlings U & Boeing H (2004) Application of a new statistical method to derive dietary patterns in nutritional epidemiology. Am J Epidemiol 159, 935–944.
20. Hoffmann K, Zyriax BC, Boeing H & Windler E (2004) A dietary pattern derived to explain biomarker variation is strongly associated with the risk of coronary artery disease. Am J Clin Nutr 80, 633–640.

21. Schulze MB, Hoffmann K, Kroke A & Boeing H (2003) An approach to construct simplified measures of dietary patterns from exploratory factor analysis. *Br J Nutr* **89**, 409–419.
22. Schulze MB & Hu FB (2002) Dietary patterns and risk of hypertension, type 2 diabetes mellitus, and coronary heart disease. *Curr Atheroscler Rep* **4**, 462–467.
23. Schulze MB, Hoffmann K, Kroke A & Boeing H (2001) Dietary patterns and their association with food and nutrient intake in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Br J Nutr* **85**, 363–373.
24. Adebamowo CA, Hu FB, Cho E, Spiegelman D, Holmes MD & Willett WC (2005) Dietary patterns and the risk of breast cancer. *Ann Epidemiol* **15**, 789–795.
25. Fung TT, Hu FB, Holmes MD, *et al.* (2005) Dietary patterns and the risk of postmenopausal breast cancer. *Int J Cancer* **116**, 116–121.
26. Velie EM, Schairer C, Flood A, He J-P, Khattree R & Schatzkin A (2005) Empirically derived dietary patterns and risk of postmenopausal breast cancer in a large prospective cohort study. *Am J Clin Nutr* **82**, 1308–1319.