

## A prospective evaluation of plasma phospholipid fatty acids and breast cancer risk in the

### EPIC study

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## Abstract

**Background:** Intakes of specific fatty acids have been postulated to impact breast cancer risk but epidemiological data based on dietary questionnaires remain conflicting.

**Material and methods:** We assessed the association between plasma phospholipid fatty acids and breast cancer risk in a case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Sixty fatty acids were measured by gas chromatography in pre-diagnostic plasma phospholipids from 2,982 incident breast cancer cases matched to 2,982 controls. Conditional logistic regression models were used to estimate relative risk of breast cancer by fatty acid level. The false discovery rate (q-values) was computed to control for multiple comparisons. Subgroup analyses were performed by estrogen receptor (ER) and progesterone receptor (PR) expression in the tumours.

**Results:** A high level of palmitoleic acid (odds ratio, OR for the highest quartile compared with the lowest OR[Q4-Q1]=1.37; 95%CI=1.14-1.64;  $p$  for trend=0.0001, q-value=0.004) as well as a high desaturation index (DI<sub>16</sub>) (16:1n-7/16:0) (OR[Q4-Q1]=1.28; 95%CI=1.07-1.54;  $p$  for trend=0.002, q-value=0.037), as biomarkers of *de novo* lipogenesis, were significantly associated with increased risk of breast cancer. Levels of industrial trans-fatty acids were positively associated with ER-negative tumors (OR for the highest tertile compared with the lowest [T3-T1]=2.01; 95% CI=1.03-3.90;  $p$  for trend=0.047), while no association was found for ER-positive tumors ( $P$ -heterogeneity =0.01). No significant association was found between n-3 polyunsaturated fatty acids and breast cancer risk, overall or by hormonal receptor.

**Conclusion:** These findings suggest that increased *de novo* lipogenesis, acting through increased synthesis of palmitoleic acid, could be a relevant metabolic pathway for breast tumorigenesis. Dietary trans fatty acids derived from industrial processes may specifically increase ER-negative breast cancer risk.

**Key words:** fatty acids, biomarkers, breast cancer, epidemiology, EPIC

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**Key message:** Early increased endogenous synthesis of monounsaturated fatty acid palmitoleic acid may increase breast cancer risk, and industrial trans fat may increase ER-negative breast cancer

## Introduction

Breast cancer is the most frequently diagnosed cancer among women worldwide with an estimated 1.8 million new cancer cases diagnosed in 2013 (25% of all cancers) [1]. While multiple risk factors for breast cancer such as family history, obesity, alcohol, breastfeeding, and reproductive history, are well established, very few additional modifiable risk factors have been identified.

A potential link between dietary fat and breast cancer has been a focus of intense research; however, overall findings to date are conflicting [2]. Epidemiological studies indicate that, rather than total fat intake, subtypes of fatty acids could diversely affect breast cancer risk [3,4]. However, data are still discrepant.

Epidemiological data on biomarkers of exposure to fatty acids and breast cancer risk are limited. Meta-analyses of epidemiological studies have suggested a protective effect of n-3 polyunsaturated fatty acids (PUFA) on breast cancer risk [5], while some saturated (SFA), monounsaturated (MUFA), and industrial *trans* fatty acids (ITFA) have been associated with an increased risk [6]. However, data are discrepant [7]. Additional studies that integrate biomarkers of exposure to fatty acids are needed.

## **Materials and Methods**

### **The EPIC STUDY**

The EPIC study includes 519,978 participants in 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. Participants completed questionnaires on diet, lifestyle, and medical history [8]. Following a standardized protocol, blood samples were collected at baseline (1993-2002), aliquoted into plasma, serum, white blood cells and erythrocytes, and stored in liquid nitrogen [8].

### **Outcome assessment**

Incident breast cancer cases were identified through population cancer registries or by active follow up using health insurance records, cancer and pathology registries, and contacts with participant.

### **Nested case-control study**

The present analysis excluded women with prevalent cancers at any site (n=19,853), missing diagnosis or censoring date (n=2,892), missing dietary or lifestyle information (n=3,339), in the top or bottom 1% of the ratio of energy intake to energy requirement (n=6,753), and non-first breast cancer cases (n=217), which left 202,553 women with blood samples. Within this subgroup, 3,858 women with invasive breast cancer were identified after a median follow-up of 11.5 years. Samples from Denmark were not included in this analysis, leading to 2,982 cases. For each case, one matched control was chosen randomly among the cohort women without breast cancer. Controls were matched to cases by center, age at blood donation ( $\pm 3$  months), menopausal status (pre; surgical post; natural post), time of the day at blood collection ( $\pm 1$  hour), fasting status (< 3hrs; 3-6 hrs.; >6 hrs.) and phase of the menstrual cycle (early follicular; late follicular; peri-ovulatory; midluteal; other luteal).

The EPIC study was approved by the Ethical Committee of the International Agency for Research on Cancer and individual EPIC centers.

### **Fatty acid analyses**

As previously described [6], total lipids were extracted from plasma samples, phospholipids were purified by adsorption chromatography, and fatty acid methyl esters were formed by transmethylation. Analyses were carried out on 7890A gas chromatographs (Agilent Technologies). Samples from cases and controls were processed in the same batch, and laboratory staff was blinded to any participant characteristics. The relative concentration of each fatty acid, expressed as percent of total fatty acids, was quantified by integrating the area under the peak and dividing the result by the total area.

Coefficients of variation for fatty acids ranged from 1.81% for large peaks to 9.75% for the smallest peaks.

We calculated the percentage of the following groups: SFA, cis- MUFA, ruminant trans fatty acids, ITFA, cis-n-6 PUFA, long-chain n-6 PUFA, n-3 PUFA, long-chain n-3 PUFA , and ratio of n-6/ n-3 PUFA. We also determined the desaturation indexes (DI) as the ratio of product to substrate, either oleic acid to stearic acid ( $DI_{18}$ ) or the ratio of palmitoleic acid to palmitic acid ( $DI_{16}$ ), as biomarkers of endogenous lipogenesis [9].

#### **Hormonal receptor status**

Information on estrogen receptor (ER) expression was available for 2,047 cases (1,649 ER-positive, 398 ER-negative), and on progesterone receptor (PR) expression for 1,729 cases (1,150 PR-positive, 579 PR-negative). Immunohistochemical measurement of ER and PR expression was performed in each EPIC centre. The following criteria were applied for a positive receptor status:  $\geq 10\%$  cells stained, any 'plus system' description,  $\geq 20$ fmol/mg, an Allred score of  $\geq 3$ , an IRS  $\geq 2$ , or an H-score  $\geq 10$ . Subjects with ambiguous positive hormone receptor scores were excluded from analyses involving tumor receptor status (10% cells stained,  $\approx 20$ fmol/mg, Allred score=3, IRS "1-2" or 2, H-score=10).

#### **Statistical analyses**

Baseline characteristics of cases and controls were compared using paired t-tests for continuous variables. For categorical variables, the statistical significance of case – control differences was tested using a chi-square test. All missing values were excluded from calculations.

In order to evaluate the association between fatty acids and breast cancer risk, odds ratios (OR) and their 95% confidence intervals (CI) were estimated using conditional logistic regression models. Plasma fatty acids were categorized into quartiles or tertiles (analyses by hormonal receptor subtypes) based on the distribution of plasma levels in controls.

Multivariable models included potential confounding factors related to fatty acids and breast cancer risk: date of blood collection, body mass index (BMI, kg/m<sup>2</sup>) (as a continuous variable), years of education (low; medium; high), height (as a continuous variable), menopausal hormone use at baseline (ever; never), alcohol intake at recruitment (as a continuous variable), age at first birth and parity combined (nulliparous; first birth before age 30y, 1-2 children; first birth before age 30y, ≥3 children; first birth after age 30y), energy intake (as a continuous variable), and family history of breast cancer (yes; no). Further adjustment for possible dietary sources of fatty acids (meat, dairy products, fish, nuts and seeds, vegetable oil, olive oil, margarine; continuous) did not change the risk estimates (data not shown) and were not included in the final model. Tests for trend were computed using the quartile-or tertile-specific means of each fatty acid.

Sub-analyses were conducted according to hormonal receptor status (ER-positive, ER-negative, PR-positive, PR-negative), as well as lag-time (≤2 years; >2 years) and menopausal status at the time of blood collection (pre; post), and tests of heterogeneity of associations were performed. Formal tests of heterogeneity were based on chi-square statistics, calculated as the deviations of logistic beta-coefficients observed in each of the subgroups relative to the overall beta-coefficient.

The false discovery rate (FDR, q-values) was computed for results from the multivariable models from the main analysis using the Benjamini-Hochberg correction to control for multiple comparisons [10].



Statistical tests were 2-sided, and  $P < 0.05$  was considered significant. All analyses were performed with the SAS 9.2 software (SAS Institute Inc., Cary N. Base SAS® 9.3 Procedures Guide. 2011).

## Results

Cases had a significantly higher BMI, adult height, a lower number of full term pregnancies and an older age at first full term pregnancy (Table 1).

Individual and total SFA were not statistically significantly associated with breast cancer risk (Table 2). Higher levels of cis-MUFA were associated with increased risk of breast cancer (OR for the highest quartile compared with the lowest [Q4-Q1]=1.17; 95%CI=0.98-1.39; *p* for trend=0.042, *q*-value=0.259). Only palmitoleic acid remained statistically significantly related to breast cancer risk after FDR correction (OR [Q4-Q1]=1.37; 95%CI=1.14-1.64; *p* for trend=0.0001, *q*-value=0.004).

No significant association was found between breast cancer and levels of trans-MUFA or trans PUFA from natural ruminant sources or industrial sources (Table 2).

Levels of individual cis n-6 or n-3 PUFA were not significantly associated with breast cancer incidence (Table 2). However, levels of total cis n-6 PUFA were inversely associated with breast cancer risk (OR [Q4-Q1]=0.81; 95%CI=0.69-0.96; *p* for trend=0.035), while no further association was detected with total cis n-3 PUFA. However, the association with n-6 PUFA did not withstand correction for multiple testing (*q*-value=0.259). Further, the ratio of n-6 to n-3 PUFA was not associated with breast cancer development (Table 2).

Increased risk of breast cancer was associated with a high  $DI_{16}$ , even after controlling for multiple testing (OR [Q4-Q1]=1.28; 95%CI=1.07-1.54; *p* for trend=0.002, *q*-value=0.037).

Although not statistically significant, the positive association between breast cancer risk and  $DI_{16}$  remained irrespective of hormonal receptor status (Table 3). Increased risk of ER-negative breast cancer was specifically associated with high levels of ITFA (OR for the highest tertile compared with the lowest [T3-T1]=2.01; 95%CI=1.03-3.90; *p* for trend=0.047), while no significant association was found with ER-positive breast cancer (*p* for heterogeneity=0.015).

Stratification by menopausal status or by time between blood collection and diagnosis revealed no substantial difference in the association between individual fatty acids, fatty acid groupings, desaturation indexes and breast cancer risk (data not shown).

## Discussion

In this large prospective study, we found evidence that higher levels of plasma phospholipid palmitoleic acid as well as higher  $DI_{16}$ , as biomarkers of *de novo* lipogenesis, were associated with increased risk of breast cancer. In addition, higher levels of ITFA were specifically associated with ER-negative breast cancer.

The association between dietary fatty acids estimated through questionnaires and breast cancer has been a focus of intense research but overall findings to date are conflicting [2]. However, there is a strong biological plausibility underlying the association of fatty acids to breast cancer development [11]. Changes in fatty acids can affect numerous cellular processes, including cell growth, proliferation, differentiation and motility.

The measurement of plasma phospholipid fatty acids is a complementary tool to information based on dietary assessment methods. Measurement of plasma phospholipid fatty acid offer the potential to capture specific biomarkers of past dietary intakes of fatty acids that cannot be endogenously synthesized, such as PUFA and trans fatty acids, irrespective of the source and quality of food [12,13]. However, weak associations were found between dietary intakes and SFA and MUFA, likely because of endogenous synthesis and complex fatty acid metabolism [13]. Thus, SFA and MUFA levels in blood among free-living individuals are probably markers of not only dietary intake but also *de novo* lipogenesis and of the relative activity of the different enzymes involved in this metabolic process [14].

Our data suggest that *de novo* lipogenesis, acting through increased synthesis of palmitoleic acid, could be a determinant metabolic pathway involved in breast carcinogenesis. Indeed, fatty acid synthase (*FASN*) is overexpressed in breast tumours independently of the level of circulating lipids [15]. The product of this pathway is palmitic acid, which can be further desaturated into palmitoleic acid. Stearoyl-CoA desaturase-1 (*SCD-1*) is the key enzyme in the synthesis of palmitoleic acid, potentially implicating *SCD-1* activity in the biological alterations of breast cancer [9,15]. Similarly,

different types of cancer displayed abundant amounts of MUFA relative to PUFA in the cancer microenvironment compared with the adjacent normal tissue, leading to decreased in membrane fluidity, which, in turns, influences many crucial membrane-associated functions [16]. On the other hand, data available from epidemiological studies have generally shown a negative association between dietary intake of MUFA and breast cancer risk [17], suggesting the role of endogenously synthesized MUFA in breast cancer development, rather than exogenous dietary MUFA. Further studies are needed to confirm this finding that suggests that *de novo* lipogenesis might represent a specific target for breast cancer prevention.

We found no significant association between breast cancer risk overall or by hormonal receptor status and levels of n-3 PUFA from marine sources. In contrast, prospective studies conducted in some Asian populations consistently reported an inverse association [3], specifically with ER+PR+ breast cancer [18]. Because of the competition between n-3 PUFA and n-6 PUFA for eicosanoids production as an underlying mechanism, ratio of n-3/n-6 PUFA has been suggested to play a determinant role in breast cancer risk, rather than individual n-3 and n-6 PUFA [19]. However, in agreement with our finding, no significant association remained among European populations, suggesting that n-3 PUFA intake might be too low, or the ratio of n-6 to n-3 PUFA too high, in the European population to reveal a possible protective effect on breast cancer [20].

ITFA are formed when fats and oils are partially hydrogenated during industrial processing techniques, and these fatty acids are found in fast foods, industrially-produced products, snack, deep-fried foods, and baked goods. The average intake of ITFA in many European countries is now relatively low; however, as the majority of the European countries still do not limit the content of ITFA in food, a large number of products containing high levels of ITFA are still available in Europe [21].

In the current study, we confirm and expand upon our previous data on breast cancer [6] by reporting a positive association between ITFA isomers and ER-negative breast cancer. Few mechanistic data on the effect of ITFA on cancer development are available. One study showed that

elaidic acid, the main ITFA, specifically induces hepatic *de novo* fatty acid synthesis through upregulating the SREBP-1 pathway [22]. Further epidemiological studies are needed to replicate this finding.

This study had several strengths including its prospective design, based on a very large number of incident breast cancer cases with detailed clinical and epidemiologic data. Additionally, we were able to separate trans fatty acid isomers from natural and industrial processes. The major limitation of the study is the single collection of blood samples at baseline. Another limitation is that residual unmeasured confounding factors associated with blood fatty acid levels might be responsible for the observed associations.

In conclusion, these findings suggest that increased *de novo* lipogenesis, acting through increased synthesis of palmitoleic acid, could be a relevant metabolic pathway for breast tumorigenesis. The identification of dietary/lifestyle factors as potential regulators of endogenous MUFA synthesis could provide new strategies for breast cancer prevention. ITFA may also specifically increase ER-negative breast cancer risk. The poor prognosis and high burden of ER-negative breast cancer mortality make this subtype a priority for prevention. Eliminating ITFA in industrial processes and in foods could potentially offer a relatively straightforward public health action for reducing non-communicable disease risk.

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## **Disclosure**

The authors have declared no conflicts of interest.

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