Cancer Epidemiology 49 (2017) 156–160

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

Tumor characteristics and family history in relation to mammographic density and breast cancer: The French E3N cohort

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ARTICLE INFO

Article history:
Received 15 February 2017
Received in revised form 28 June 2017
Accepted 4 July 2017
Available online 8 July 2017

Keywords:
Breast cancer
Mammographic density
Risk
Prospective study
Family history

ABSTRACT

Background: Mammographic density is a known heritable risk factor for breast cancer, but reports how tumor characteristics and family history may modify this association are inconsistent.
Methods: Dense and total breast areas were assessed using Cumulus™ from pre-diagnostic mammograms for 820 invasive breast cancer cases and 820 matched controls nested within the French E3N cohort study. To allow comparisons across models, percent mammographic density (PMD) was standardized to the distribution of the controls. Odds ratios (OR) and 95% confidence intervals (CI) of breast cancer risk for mammographic density were estimated by conditional logistic regression while adjusting for age and body mass index. Heterogeneity according to tumor characteristic and family history was assessed using stratified analyses.
Results: Overall, the OR per 1 SD for PMD was 1.50 (95% CI, 1.33–1.69). No evidence for significant heterogeneity by tumor size, lymph node status, grade, and hormone receptor status (estrogen, progesterone, and HER2) was detected. However, the association of PMD was stronger for women reporting a family history of breast cancer (OR_{1SD} = 2.25; 95% CI, 1.67–3.04) than in women reporting none (OR_{1SD} = 1.41; 95% CI, 1.24–1.60; $p_{heterogeneity}$ = 0.002). Similarly, effect modification by FHBC was observed using categories of PMD ($p_{heterogeneity}$ = 0.02) with respective ORs of 15.16 (95% CI, 4.23–54.28) vs. 3.14 (95% CI, 1.89–5.22) for ≥50% vs. <10% PMD.
Conclusions: The stronger association between mammographic density and breast cancer risk with a family history supports the hypothesis of shared genetic factors responsible for familial aggregation of breast cancer and the heritable component of mammographic density.

1. Introduction

Mammographic density, measured as absolute dense area (DA) or percent mammographic density (PMD), is a well-established breast cancer risk factor [1,2]. As age and body mass index (BMI) act as negative confounders, PMD always needs to be adjusted for both factors. The role of non-dense breast area (NDA) is less clear; it was inversely associated with breast cancer risk under the assumption that fatty breast tissue influences breast cancer risk, but not related under the assumption that fat in the breast is a surrogate marker of adiposity [3]. A recent meta-analysis reported no difference by HER2 status [4] and the findings for estrogen receptor (ER) status are inconsistent [4–7]. In a pooled analysis, PMD was more strongly associated with the risk of large vs. small and lymph node positive vs. negative tumors [8].

The presence of a family history of breast cancer (FHBC) in first-degree relatives (FDR) consistently shows an approximately 2-fold higher breast cancer risk [9–11]. Of familial risk of breast cancer, around 28% is due to low penetrance common variants and another 20% due to higher penetrance loci [12], but a large proportion still needs to be explained. Twin studies have shown that mammographic density has a strong heritable component [13]; it has been estimated that 50–60% of the variance of mammographic density that predicts breast cancer risk is due to undiscovered genetic factors [14]. Given that shared genetic factors may be related to

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http://dx.doi.org/10.1016/j.canep.2017.07.003
1877-7821/

mammographic density and hereditary breast cancer risk, it has been proposed that mammographic density may mediate the effect of FHBC on breast cancer risk [10]. In fact, recent reports have identified several such genes [15,16]. Findings for a possible effect modification by FHBC are inconsistent; some studies were supportive [11,17,18] and others indicated independent associations of FHBC and mammographic density on breast cancer risk without a significant interaction [10,19,20]. The current analysis builds on a case-control study nested within the E3N French cohort to estimate the associations between mammographic density and breast cancer by tumor characteristics, *i.e.*, tumor size, lymph node status, grade, hormone receptor status, as well as FHBC.

2. Methods

2.1. Study design

The French E3N cohort study is a prospective cohort study of 98,995 women aged 40–65 years at baseline who were recruited between 1990 and 1994 [21]. The French Commission for Data Protection and Privacy approved the study. At baseline, participants completed questionnaires asking about demographic characteristics, anthropometric measures, lifestyle factors, FHBD in FDR, and diet. Follow-up questionnaires updated lifestyle factors and medical events every 2–3 years with stable response rates at 80%. Incident cases of invasive adenocarcinoma of the breast (International Classification of Diseases for Oncology codes C50.0-C50.9) identified through the follow-up questionnaires were verified by pathology reports.

Based on more than 5000 cases diagnosed between baseline and 2008 [22], a nested case-control study was designed using incidence density sampling. For 920 invasive breast cancer cases with known laterality and at least one mammogram taken between baseline and age at diagnosis, one control was randomly selected from women who had not been diagnosed with breast cancer at the age when the matched case was diagnosed (reference age). Matching factors included year of birth (±3 years) and menopausal status at baseline; it was not available for the time at mammogram. For 920 cases and 920 matching controls, we identified the craniocaudal images of the breast ipsilateral to the tumor that was closest and prior to the reference age. After excluding case-controls pairs with a difference in age at mammogram of more than 5 years (97 pairs) and women with missing BMI at mammogram (N = 3), 820 cases and 820 controls were available for the analysis.

2.2. Mammographic density assessment

The mammographic films were digitized with an Array 2905 high-density film digitizer (Array Corporation Europe, Roden, The Netherlands) with a resolution of 300 PPI and were resized for density reading with a proportional maximal size of 800 × 400 pixels.

A single reader (GM) who was blinded to case-control status assessed total breast area and DA in batches of 200 mammograms using a computer-assisted technique (Cumulus, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada) [23]. PMD was computed as the ratio of DA by the total breast area and NDA as the difference between total breast area and DA. For quality control, a random sample of 120 images was read in duplicate with resulting correlations of 0.98 for total breast area, 0.95 for DA, and 0.96 for PMD.

2.3. Statistical analysis

PMD was divided into the categories of less than 10%, 10–19%, 20–49% and ≥50%. To allow comparisons across models, the continuous PMD variable was standardized to the mean and standard deviation of the controls. FHBC was categorized as no FDR vs. at least one affected FDR. Tumor characteristics included pathological tumor size (<2 vs. ≥2 cm), nodal status (negative vs. positive), tumor histological grade (1, 2, or 3), ER status (negative vs. positive), progesterone (PR) status (negative vs. positive), and HER2 status (negative vs. positive), but for all variables a substantial proportion of women had missing values (Table 1).

We estimated the risk of breast cancer fitting conditional logistic regression models under four "causal models" with BMI and age at the time of mammogram as described previously [3]:

$$\text{Logit}\ (P) \sim \text{AGE} + \text{BMI} + \text{DA} + \text{NDA} \quad (1)$$

$$\text{Logit}\ (P) \sim \text{AGE} + \text{BMI} + \text{PMD} \quad (2)$$

$$\text{Logit}\ (P) \sim \text{AGE} + \text{BMI} + \text{DA} \quad (3)$$

$$\text{Logit}\ (P) \sim \text{AGE} + \text{DA} + \text{NDA} \quad (4)$$

Interactions of BMI, DA, NDA and PMD with the reference age were evaluated using the likelihood ratio test; the four causal models were compared using the Akaike's information criterion (AIC). Possible effect modification of mammographic density by FHBC within each causal model was examined by comparing the models with and without the interaction of the mammographic density variable with the FHBC variable using the likelihood ratio test. The heterogeneity of risk estimates for PMD by tumor characteristics was estimated using the duplication method [24].

The risk per adjusted standard deviation of PMD was estimated by entering the residuals of the linear regression of PMD on age, BMI and menopausal status at baseline as predictors into the conditional logistic regression models as described previously [25]. Adjustment for additional breast cancer risk factors including age at menarche (<12, 12, and >12 years), oral contraceptive use (ever vs. never), parity and age at first birth (nulliparous, <25, and ≥25 years), lactation (yes vs. no), use of hormone therapy (never, past, current), consumption of alcohol (abstainers and quartiles among consumers), fruit and vegetable intake (quartiles), and total energy intake (quartiles) did not substantially modify the findings and were not retained. As sensitivity analysis, cases diagnosed within 2 years of mammography as well as ever users of hormone therapy because of their influence on breast density and their matched controls were excluded.

All analyses were conducted using SAS software, version 9.2 (SAS Institute Inc., Cary, North Carolina, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria).

Table 1
Characteristics of the Study Participants.

Characteristic	Controls	Cases
	Mean (SD)	Mean (SD)
Number	820	820
Age at baseline	48.9 (5.3)	49.0 (5.4)
Reference age[a], years	59.2 (6.3)	59.2 (6.3)
Age at mammogram, years	58.3 (6.3)	58.3 (6.3)
Time between mammogram and diagnosis, years	–	1.0 (0–7.2)
Postmenopausal status at mammogram	726 (88.5)	712 (86.8)
Number of children at mammogram	1.9 (1.1)	1.9 (1.1)
BMI at mammogram, kg/m^2	22.9 (3.2)	23.3 (3.4)
Dense area, cm^2	34.6 (20.7)	40.7 (22.1)
Non-dense area, cm^2	71.8 (42.1)	67.8 (42.8)
Percent mammographic density, %	35.5 (19.3)	40.4 (19.2)

[a] Age at diagnosis for cases and reference age for controls.