

Anthropometric factors, adult weight gain, and mammographic features

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Abstract

Purpose To evaluate the association between anthropometric factors, weight gain during adulthood, and mammographic features among 1,435 women recruited at screening mammography.

Methods Spearman's partial coefficients were used to evaluate the correlation of anthropometric factors with mammographic features (percent density, absolute dense area, and non-dense area). Multivariate generalized linear models were used to evaluate the associations between weight change categories and mammographic features.

Results Body mass index was inversely correlated with percent density ($r = -0.49$, $p < 0.0001$) or absolute dense area ($r = -0.21$, $p < 0.0001$) and positively correlated with absolute non-dense area ($r = 0.69$, $p < 0.0001$). However, body mass index was positively correlated with absolute dense area when adjusting for absolute non-dense area ($r = 0.16$, $p < 0.0001$). Similar results were observed for weight, waist circumference, and waist-to-hip ratio with mammographic features. Within increasing categories of

weight change, percent density ($p_{\text{trend}} < 0.0001$) and absolute dense area ($p_{\text{trend}} = 0.025$) increased, while absolute non-dense area decreased ($p_{\text{trend}} < 0.0001$). After stratification by the median of non-dense area, the positive association between weight gain and absolute dense area remained only among women with higher non-dense area. **Conclusions** Adiposity seems positively associated with both dense and non-dense areas following adjustment for each other. Our findings suggest a higher breast dense area among women who gained weight and that a minimum of breast fat may be needed to promote the proliferation of this fibroglandular tissue.

Keywords Mammographic breast density · Breast cancer · Anthropometry · Weight gain · Adiposity · Body mass index

Introduction

Breast density is a well-recognized breast cancer risk factor [1]. It reflects breast tissue composition as it appears on a mammogram: The area occupied by fibroglandular tissue appears white and is therefore named “dense area,” and the adipose tissue area appears black and is therefore named “non-dense area.” Percent density is the proportion of fibroglandular tissue in the breast and is calculated by dividing the absolute dense area by the total breast area. Women having $\geq 75\%$ of their breast occupied by dense tissue compared with those having $< 5\%$ density have a more than fourfold relative risk of developing breast cancer [2]. Because cells at risk of cancer development are mainly located in fibroglandular tissue, the absolute amount of this tissue can also be considered as a risk factor [3], and it can be evaluated through absolute dense area. Furthermore,

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breast adipose tissue, which can be evaluated through absolute non-dense area, is considered a microenvironment potentially influencing carcinogenesis [4]. For these reasons, scientists are interested in the specific association of the absolute measures of dense and non-dense areas with breast cancer risk. Like percent density, absolute dense area has consistently shown a positive association with breast cancer risk [5–9]. As yet, results are less clear for the non-dense area. In a recent meta-analysis, Pettersson et al. [7] found a strong inverse association between absolute non-dense area and breast cancer risk, independent of dense area. This observation is supported by other studies [10, 11], although not all [12, 13].

At a body level, adiposity can be characterized with several factors that reflect different aspects of adiposity: total body fatness, body fat distribution, or dynamic evaluation of adiposity through a defined period of time. In epidemiological studies, the most widely used index to evaluate body fatness is body mass index (BMI), which is weight (kg) divided by squared height (m^2) [14]. Abdominal body fat distribution is easily evaluated with the measurements of waist circumference and waist-to-hip ratio (WHR), and weight gain during adulthood is used as a dynamic measure of adiposity. Total and abdominal body fatness and weight gain during adulthood are recognized risk factors for postmenopausal breast cancer development [15], but it is still unclear for premenopausal women [16–20].

BMI, waist circumference, or WHR has been shown to be negatively associated with percent density [21–30] or absolute dense area [24–26, 29, 30], although not consistently for the latter [21, 27, 28], while positively associated with absolute non-dense area [21, 24–30]. Meanwhile, the association between weight gain during adulthood and breast density was seldom studied and led to inconsistent results [21–23]. The apparent paradox is that absolute non-dense area seems negatively associated with breast cancer risk but is positively associated with factors reflecting total or abdominal body fatness that are risk factors for breast cancer. Further studies to understand the associations between anthropometric factors or adult weight gain and mammographic features could help to better understand the pathophysiological mechanisms linking obesity to breast cancer risk. Therefore, we aimed to evaluate these associations among Caucasian women recruited at screening mammography.

Materials and methods

Study design and methods were described elsewhere [31]. Briefly, 1,574 Caucasian women (783 premenopausal, 791 postmenopausal) were recruited in two

private radiology clinics as part of the Quebec screening mammography program in 2001–2002. Eligibility criteria were to be premenopausal or postmenopausal (Nurses' Health Study criteria [32]), not pregnant, to have no personal history of any cancer or breast surgery and no endocrine or hepatic disease, never used tamoxifen or raloxifene, and not used hormone medication in the past 3 months. Of the 1,574 women recruited, 114 were excluded because of missing values for weight at the age of 18. Among the remaining 1,460 women, 25 were excluded because of missing ($n = 23$) or aberrant ($n = 2$) values in at least one of the variables used for adjustments. Missing values for height at 18 years were imputed by the height at the time of mammography ($n = 22$) since correlation between height at 18 years and at mammography was high ($r = 0.92$, $p < 0.0001$). The 139 excluded women were older than our study population [mean (\pm SD) age of 58.3 ± 9.4 vs 53.7 ± 9.3 years], with higher proportion of postmenopausal women (66 vs 51 %). As expected with the older age, these women had, for instance, a lower mean percent density, a lower mean absolute dense area, and a higher mean absolute non-dense area. All study participants gave a written informed consent. The study protocol was approved by the Research Ethics Review Board of Hôpital Saint-Sacrement at the CHU de Québec.

Data collection

Known or suspected breast cancer risk factors were collected within the month following mammography, during an in-depth structured telephone interview: reproductive and menstrual history, family history of breast cancer, personal history of breast biopsies, past use of oral contraceptives and hormone replacement therapy, smoking status, alcohol intake, education and last year physical activity [Nurses' Health Study (NHS) II Activity and Inactivity Questionnaire [33]], and dietary intake [semi-quantitative food frequency questionnaire (97GP copyrighted at Harvard University [34])].

Anthropometric measurements were obtained by a trained research nurse at the time of mammography. Current weight (kg) and height (cm) were measured, while women were wearing light clothing without shoes. Waist circumference (cm) was measured using a soft tape midway between the lowest rib margin and the iliac crest in a standing position, while hip circumference (cm) was measured over the widest of the gluteal region. Next, BMI (kg/m^2) and WHR at the time of mammography were calculated. Weight and height at the age of 18 were self-reported. Weight change was calculated as the body weight at mammography minus self-reported weight at the age of 18.

Mammographic features were blindly assessed on batches of 100 digitalized mammograms (Kodak Lumiscan85 digitizer), randomly selected from the left or right cranio-caudal view, by one trained reader (CD) using a computer-assisted thresholding program (Cumulus) [35]. The number of pixels in the identified dense area and total breast area was translated in cm^2 . Absolute non-dense area was calculated as total breast area minus absolute dense area, and percent density was calculated as dense area divided by total breast area. Reproducibility of assessment of mammographic features was very high, as shown by the within-batch intraclass correlation coefficient of 0.98, 0.98, and 0.99 and the between-batch coefficient of variation of 4, 5, and 1 %, for percent density, absolute dense area, and non-dense area, respectively.

Statistical analysis

Spearman correlation coefficients were used to evaluate the association between anthropometric factors (weight and BMI at age 18, current weight, BMI, height, waist circumference, and WHR) and the three mammographic features (percent density, absolute dense area, and absolute non-dense area). Correlations were adjusted for the following potential confounders: age at mammography (years), menopausal status (premenopause/postmenopause), alcohol consumption (drinks/week), last year mean daily caloric intake (kcal/day), last year level of physical activity (METs-h/week), parity (yes/no), smoking status (non/former/current smoker), age at menarche (years), number of full-term pregnancies, age at first full-term pregnancy (years), total duration of lactation (months), family history of breast cancer in a female first-degree relative (yes/no), number of previous breast biopsies, highest completed education level (primary/secondary/college/university degree), duration of past oral contraceptives (years), and hormonal replacement therapy uses (years).

Multivariate generalized linear models were used to evaluate the associations between weight change and the three mammographic features. Percent density and absolute areas were square-root-transformed to obtain a normal distribution, and the means were translated back to allow an easier interpretation of the results. Analysis of covariance was used to provide adjusted estimates of the means of each mammographic feature according to categories of weight change. Weight change was grouped into six categories: one weight loss category (≥ 5 kg), one stable weight category (loss of < 5 kg to gain of ≤ 5 kg), and four weight gain categories (> 5 to ≤ 15 ; > 15 to ≤ 25 ; > 25 to ≤ 35 ; > 35 kg). Tests for trends (p_{trend}) were based on the F-test of the linear contrast of mammographic features across categories of weight change. All models were adjusted for

BMI (kg/m^2), WHR, and height (cm) in addition to all potential confounders as in the correlations. Further adjustments were done with absolute dense or non-dense area where appropriate. As separate analyses for premenopausal and postmenopausal women gave similar results, we present the results for the whole population. All statistical analyses were performed using the SAS software package (version 9.4; SAS institute Inc.). All tests were two-sided, and a p value < 0.05 was considered statistically significant.

Results

Study population

Details of the population characteristics were previously presented [31]. As mentioned, women included in the present analyses were slightly younger than the excluded women. However, upon stratification by menopausal status, characteristics of included women did not differ from the original population (data not shown). Briefly, 51 % of the included women were premenopausal ($n = 737$) with a mean age (\pm SD) of 53.7 (± 9.3) years. Mean body weight at mammography was 66 (± 12) kg and mean BMI 26.1 (± 4.7) kg/m^2 . Mean self-reported weight at the age of 18 was 52 (± 7) kg with a mean BMI of 20.1 (± 2.6) kg/m^2 . Almost 80 % of the women gained > 5 kg during their adulthood, while 41 % gained > 15 kg and 15 % > 25 kg. Mean weight change during adulthood was 13.9 (± 11.3) kg corresponding to a mean BMI variation of 6.0 (± 4.6) kg/m^2 .

Mammographic features

Mean percent density was 30.7 (± 24.0) %, mean absolute dense area 35.2 (± 27.6) cm^2 , and mean non-dense area 100.8 (± 64.7) cm^2 . Absolute dense area was positively correlated with percent density (Spearman $r = 0.90$, $p < 0.0001$) and negatively correlated with absolute non-dense area (Spearman $r = -0.58$, $p < 0.0001$). Conversely, absolute non-dense area was inversely correlated with percent density (Spearman $r = -0.85$, $p < 0.0001$).

Association between anthropometric factors and mammographic features

Spearman correlations between anthropometric factors and mammographic features are presented in Table 1. As expected, weight, BMI, waist circumference, and WHR were inversely correlated with percent density or absolute dense area and positively correlated with absolute non-dense area (all $p < 0.0001$). However, these anthropometric factors

Table 1 Correlations of anthropometric factors and mammographic features

	Percent density		Absolute dense area				Absolute non-dense area			
	Fully adjusted ^a		Fully adjusted ^a		Fully adjusted ^a + absolute non-dense area		Fully adjusted ^a		Fully adjusted ^a + absolute dense area	
	<i>r</i> ^b	<i>p</i> value	<i>r</i> ^b	<i>p</i> value	<i>r</i> ^b	<i>p</i> value	<i>r</i> ^b	<i>p</i> value	<i>r</i> ^b	<i>p</i> value
Weight (kg)	−0.44	<0.0001	−0.17	<0.0001	0.17	<0.0001	0.63	<0.0001	0.63	<0.0001
Weight (kg) at 18 years	−0.17	<0.0001	−0.08	0.0018	0.02	0.40	0.22	<0.0001	0.21	<0.0001
Height (cm)	0.03	0.28	0.04	0.17	0.03	0.28	−0.02	0.37	−0.01	0.76
Body mass index (BMI, kg/m ²)	−0.49	<0.0001	−0.21	<0.0001	0.16	<0.0001	0.69	<0.0001	0.68	<0.0001
BMI (kg/m ²) at 18 years	−0.18	<0.0001	−0.09	0.0007	0.02	0.39	0.24	<0.0001	0.22	<0.0001
Waist circumference (cm)	−0.49	<0.0001	−0.23	<0.0001	0.12	<0.0001	0.67	<0.0001	0.65	<0.0001
Waist-to-hip ratio	−0.36	<0.0001	−0.17	<0.0001	0.06	0.024	0.47	<0.0001	0.45	<0.0001

^a Spearman correlations adjusted for age at mammography, menopausal status, alcohol intake, caloric intake, physical activity, parity, smoking status, age at menarche, full-term pregnancies, age at first full-term pregnancy, lactation, family history of breast cancer, breast biopsies, education, oral contraceptives, and hormonal replacement therapy uses

^b *r*: Spearman partial correlation coefficient

were positively correlated with absolute dense area following adjustment for absolute non-dense area but remained positively correlated with non-dense area after adjustment for absolute dense area.

Weight change and mammographic features

Results of the multivariate linear models testing the relation of weight change with mammographic features are presented in Fig. 1a–c. For increasing categories of weight change, adjusted mean percent density increased linearly from 21 % (loss of ≥ 5.0 kg) to 42 % (gain of >35.0 kg) ($p_{\text{trend}} < 0.0001$, Fig. 1a). Dense area also increased linearly from 28 to 39 cm² ($p_{\text{trend}} = 0.025$, Fig. 1b), while non-dense area decreased from 115 to 63 cm² ($p_{\text{trend}} < 0.0001$, Fig. 1c). In these latter analyses, further adjustments for non-dense or dense area, respectively, abolished the positive association between weight gain and absolute dense area ($p_{\text{trend}} = 0.93$) but not the association between weight gain and absolute non-dense area ($p_{\text{trend}} < 0.0001$). Similar results were observed for increasing categories of BMI variation with mammographic features (data not shown).

To gain knowledge on these associations, we stratified the population by the median of absolute non-dense (89.3 cm²; Fig. 2a, b) or dense areas (30.3 cm²; Fig. 2c, d). Among women with an absolute non-dense area equal or above the median, a higher weight gain was associated with a greater dense area ($p_{\text{trend}} = 0.01$, Fig. 2b). However, this association was not present among women with an absolute non-dense area below the median ($p_{\text{trend}} = 0.43$, Fig. 2a). In contrast, the negative association between weight change and the absolute non-dense area remained for both strata of

absolute dense area $<$ median and \geq median ($p_{\text{trend}} = 0.0001$, Fig. 2c and $p_{\text{trend}} = 0.007$, Fig. 2d, respectively). Similar results were observed for BMI variation (data not shown).

Discussion

In our study population, anthropometric factors reflecting body fatness or abdominal fat distribution were negatively associated with percent density and dense area and positively associated with non-dense area. However, the negative association we found for dense area became positive when adjusting for non-dense area. In contrast, the magnitude of weight gain during adulthood was associated with higher percent density as well as higher dense area particularly among women having higher non-dense area and negatively associated with absolute non-dense area.

The negative association we observed between anthropometric factors and percent density or dense area is consistent with the literature [21–30], although more conflicting results are reported for dense area [21, 24–30], possibly due to important variation in the adjustments performed in the analyses. Interestingly, this inconsistency is also illustrated in our results by the inversion of the correlations between adiposity and dense area after adjustment for non-dense area. This means that when the part of the correlation attributable to breast fat is withdrawn, i.e., when controlling for non-dense area, adiposity is positively associated with dense area. What we observe with this adjustment is consistent with what is known about breast cancer risk. Since both adiposity and dense area are risk factors for breast cancer and as adiposity influences breast density, they are expected to be positively correlated.

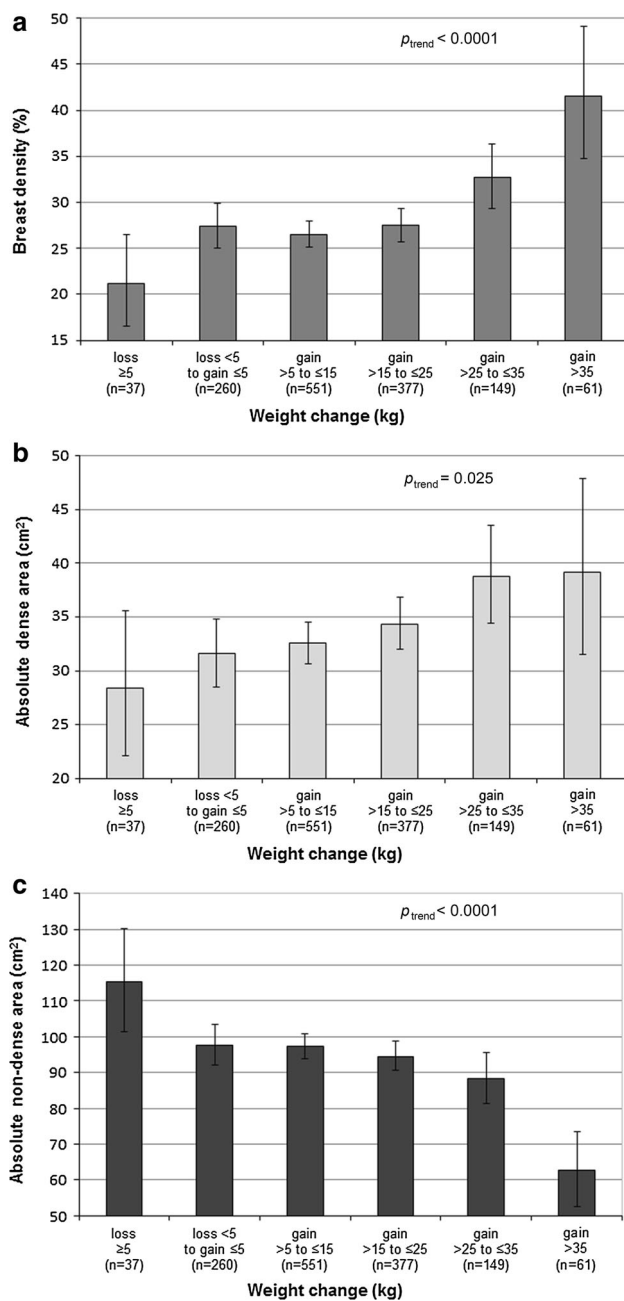


Fig. 1 Associations between weight change (a–c) and mammographic features. Adjusted means and 95% confidence intervals of percent density (a), absolute dense area (b), and absolute non-dense area (c). Multivariate generalized linear models adjusted for: age at mammography, menopausal status, body mass index, waist-to-hip ratio, height, alcohol intake, caloric intake, physical activity, parity, smoking status, age at menarche, number of full-term pregnancies, age at first full-term pregnancy, lactation, family history of breast cancer, breast biopsies, education, oral contraceptives, and hormonal replacement therapy uses

The positive association between weight gain and percent density or dense area that we observed is also consistent with the current understanding of the association between weight gain and breast cancer risk. Indeed, higher

breast density is associated with higher breast cancer risk, and there is some evidence that higher weight gain is also. However, we observed a positive association between weight gain and dense area only among women having a high amount of fat in their breast (non-dense area \geq median). This suggests that a sufficient amount of breast fat is needed to allow the proliferation of the fibroglandular tissue. In the same idea, some scientists have explored the association between breast density and breast cancer risk according to body fatness, and some showed a higher association among obese or overweight women [36, 37], however not all [38]. To date, few studies have examined the relation between adult weight gain and percent density [21–23] or dense area [21]. In line with our results, Pollan et al. [22] reported a positive association between adult weight gain and percent density, while Tseng and Byrne [21] found no association, when factors reflecting current adiposity were included in the model. In the latter study, a positive association was observed between adult weight gain and dense area, particularly among women with low BMI [21]. Conversely, Samimi et al. [23] found a negative association between adult weight gain and percent density, but their association was not adjusted for current adiposity. In a 2-year low-fat diet intervention study, Boyd et al. [39] showed that the intervention and weight loss were independently associated with a decrease in dense area but not in percent density. Their result for dense area is in line with ours: Weight loss had the opposite effect as weight gain on dense area.

The strong positive correlations of anthropometric factors reflecting adiposity with non-dense area that we found are in line with the current scientific knowledge [21, 24–30]. However, these results seem in contradiction with what is known about breast cancer risk. As adiposity is a risk factor for breast cancer, a higher non-dense area is expected to be associated with a higher breast cancer risk. However, this remains a matter of debate as some studies have suggested a protective effect. In their meta-analysis, Pettersson et al. [7] found a strong inverse association between non-dense area and breast cancer risk, independent of dense area. The same authors had already found a similar inverse association in a nested case–control study [10]. Moreover, Torres-Meija et al. [11] found that women with the highest non-dense area had lower, but statistically not significant, hazard ratio for breast cancer. Stone et al. [12] also found an inverse association which was lost after adjustment for dense area. On the other hand, Lokate et al. [13] found a positive association between non-dense area and breast cancer risk. These discrepant results have been thought to be due to the difference in the mammogram view used for the evaluation of non-dense area. Indeed, authors who used mediolateral views were more likely to find a positive association between non-dense area and

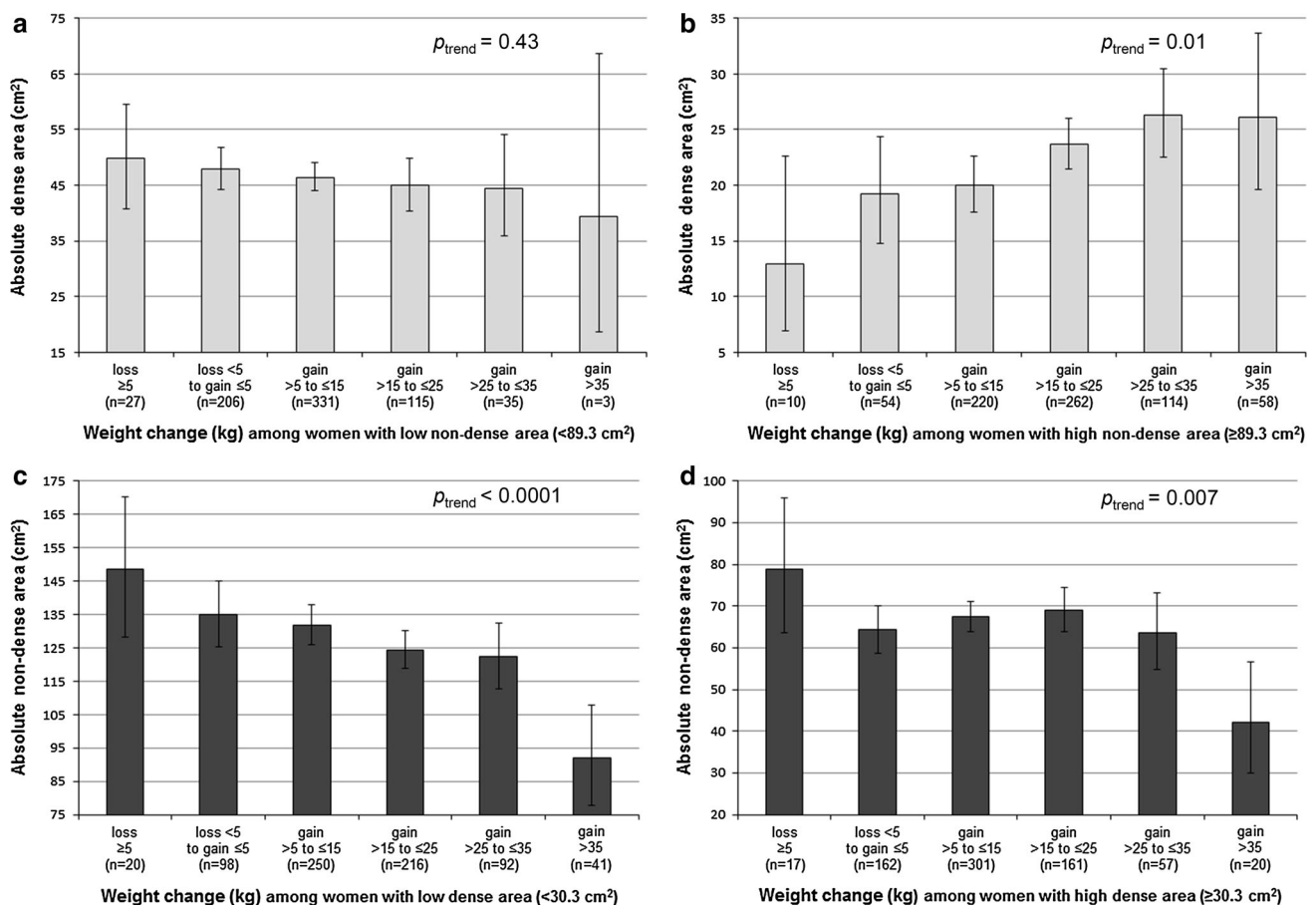


Fig. 2 Associations between weight change and mammographic features, stratified by the median of absolute non-dense (a, b) or absolute dense area (c, d). Adjusted means and 95% confidence intervals of absolute dense area (a, b) and absolute non-dense area (c, d). Multivariate generalized linear models adjusted for: age at mammography, menopausal status, body mass index, waist-to-hip

ratio, height, alcohol intake, caloric intake, physical activity, parity, smoking status, age at menarche, number of full-term pregnancies, age at first full-term pregnancy, lactation, family history of breast cancer, breast biopsies, education, oral contraceptives, and hormonal replacement therapy uses

breast cancer risk because the mediolateral projection tends to overestimate non-dense area due to the inclusion of some subcutaneous fat to the breast fat. Therefore, the increased risk observed when using mediolateral views could be due to total body fatness instead of breast non-dense area [40]. Interestingly, we found that weight gain during adulthood was negatively associated with absolute non-dense area, and this is in line with current knowledge on breast cancer risk. This could possibly mean that adult weight gain better reflects what happens in terms of risk, catching the impact of the exposure time to a risk factor. To our knowledge, Tseng and Byrne [21] are the only authors to have assessed the association between adult weight gain and non-dense area and found no association when variables reflecting current adiposity were included in the model.

Our results also draw attention on a paradox surrounding the association between weight gain, breast fat

tissue, and breast cancer risk as we observed that weight gain was positively associated with dense area, only among women with high-fat breasts, whereas adipose tissue in the breast is thought to have a protective effect. It seems that it is a matter of equilibrium between fibroglandular and adipose tissues. The mechanism by which non-dense area could be protective has not yet been elucidated. One possible explanation is that fat tissue is capable of storing vitamin D, known for its protective effect against breast cancer development [41]. On the other hand, breast adipose tissue has also been shown to contribute to the development and progression of mammary tumors in co-culture experiments and animal models [42], and its dysfunction is believed to cause chronic low-grade inflammation, sex hormones alterations, and insulin resistance [43, 44]. For instance, the breast adipose tissue has been described as a surrounding environment favoring breast tumor development due to its role in the local

production of estrogens by aromatase, a key enzyme in this hormone synthesis pathway. Vachon et al. [45] measured the aromatase immunoreactivity in biopsies performed in dense and non-dense areas of the breast and showed that the highest overall aromatase immunoreactivity was found in dense area where stromal cells showed very high levels. However, immunoreactivity was also present in non-dense area. More specifically, adipocytes had higher immunoreactivity for aromatase as compared to at-risk epithelial cells. These findings illustrate that aromatase activity in the breast, causing a potentially carcinogenic environment, is not limited to the dense area. So we can hypothesize that when breast fat becomes important, the concentration of aromatase within this tissue rises enough to create a particular microenvironment that acts on the fibroglandular tissue proliferation.

The strengths of our study are the relatively large sample size and the important number of potential confounders available in the database, allowing highly adjusted analyses. Furthermore, the assessment of the mammographic features was rigorously done and presented high validity and reliability. Our study has also several limitations. First, the cross-sectional design does not allow causal inference. Missing values of weight at the age of 18 necessitate the exclusion of 114 women (7 %), slightly older than the whole cohort. However, we think that this should not have significantly influenced our findings as premenopausal and postmenopausal women included in the present study had similar characteristics than premenopausal and postmenopausal women of the initial study population. Finally, one important limitation was self-reported weight at the age of 18. As it is subjected to be underestimated, and probably particularly among obese women, or overestimated by persons who took the greatest weight [46], this could have led to increase or decrease the association in these two subgroups, respectively.

In conclusion, we found that a positive correlation between adiposity and dense area, in line with breast cancer risk, emerges only after adjustment for breast fat. Furthermore, with the magnitude of weight gain, non-dense area decreases linearly in all women, but dense area increases only among women with highly fatty breasts, possibly revealing a paradoxical effect of fat tissue in the breast. Indeed, as adipocytes are not the type of cells at risk of carcinogenesis, fat tissue appears to play a protective role to a certain extent but, also, to be a risk factor for breast cancer, acting as a microenvironment favoring proliferation of the cells at risk of carcinogenesis in the fibroglandular tissue. Longitudinal studies evaluating the impact of weight gain on mammographic features and further breast cancer risk are needed to better understand the causal links.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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