Adiposity, breast density, and breast cancer risk: epidemiological and biological considerations

Ludivine Soguel[a,c,g], Francine Durocher[b,e], André Tchernof[e,f] and Caroline Diorio[a,c,d]

Excess total body fat and abdominal adipose tissue are recognized risk factors for metabolic diseases but also for some types of cancers, including breast cancer. Several biological mechanisms in connection with local and systemic effects of adiposity are believed to be implicated in breast cancer development, and may involve breast fat. Breast adipose tissue can be studied through mammography by looking at breast density features such as the nondense area mainly composed of fat, or the percent breast density, which is the proportion of fibroglandular tissue in relation to fat. The relation between adiposity, breast density features, and breast cancer is complex. Studies suggest a paradoxical association as adiposity and absolute nondense area correlate positively with each other, but in contrast to adiposity, absolute nondense area seems to be associated negatively with breast cancer risk. As breast density is one of the strongest risk factors for breast cancer, it is therefore critical to understand how these factors interrelate. In this review, we discuss these relations by first presenting how adiposity measurements and breast density features are linked to breast cancer risk. Then, we used a systematic approach to capture the literature to review the relation between adiposity and breast density features. Finally, the role of adipose tissue in carcinogenesis is discussed briefly from a biological perspective. ***European Journal of Cancer Prevention*** **26:511–520 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Departments of [a]Social and Preventive Medicine, [b]Molecular Medicine, Cancer Research Center, Laval University, 2325 rue de l'Université, [c]CHU de Québec Research Center, [d]Deschênes-Fabia Center for Breast Diseases, Saint-Sacrement Hospital, 1050 Chemin Ste-Foy, [e]CHU de Québec Research Center, CHUL, 2724 Laurier Boulevard, [f]Department of Nutrition, Laval University, 2425 rue de l'Agriculture, Quebec City, Quebec, Canada and [g]Department of Nutrition and Dietetics, University of Applied Sciences Western Switzerland (HES-SO) Geneva, 25 rue des Caroubiers, Carouge, Switzerland

Correspondence to Caroline Diorio, PhD, Oncology axis, CHU de Québec Research Center, Laval University, Saint-Sacrement Hospital, 1050 Chemin Ste-Foy, Quebec City, QC, Canada G1S 4L8
Tel: +1 418 525 4444 x84726; fax: +1 418 682 7949;
e-mail: caroline.diorio@crchudequebec.ulaval.ca

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Introduction

Breast cancer is the most common cancer in women worldwide, accounting for 25% of the total new cases in 2012 and affecting 1.67 million women (Ferlay *et al.*, 2014). With 522 000 estimated deaths in 2012, it is one of the leading causes of mortality due to cancer in women worldwide (Ferlay *et al.*, 2014).

Excess adiposity is an established risk factor for breast cancer among postmenopausal women and both total body fatness and abdominal body fat distribution seem to play a role (World Cancer Research Fund, American Institute for Cancer Research, 2010). The association is less consistent in premenopausal women, for whom the underlying biological mechanisms remain undetermined (Anderson and Neuhouser, 2012; Cecchini *et al.*, 2012; Cheraghi *et al.*, 2012; Amadou *et al.*, 2013; Pierobon and Frankenfeld, 2013; Emaus *et al.*, 2014). Furthermore, the role of breast fat in breast cancer development is not well understood as yet. Actually, fat tissue has been described as a microenvironment promoting carcinogenesis through different mechanisms, in particular, chronic inflammation (Park *et al.*, 2014; Perez-Hernandez *et al.*, 2014), but it also has a potentially protective role, especially as a source of vitamin D (Narvaez *et al.*, 2014).

The relation between fat tissue located in the breast and breast cancer risk can be studied through mammographic density features. Indeed, the absolute nondense area reflects breast fat tissue and, inversely, percent density represents the proportion of nonfat tissue in the breast. Percent density is one of the strongest identified risk factors for breast cancer and is used frequently as a surrogate for breast cancer risk in epidemiological studies (Boyd *et al.*, 2007). The apparent paradox in the relation between adiposity, breast density, and breast cancer risk is that adiposity and absolute nondense area are correlated positively but, even though adiposity is a recognized risk

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factor for breast cancer, there is some indication that absolute nondense area is associated negatively with breast cancer risk (Pettersson *et al.*, 2014).

Adiposity can be assessed or estimated using various techniques, and can thus be described with a number of different markers. In addition, breast density can also be defined with many variables such as percent density, absolute dense, and nondense areas or volumes. The relation between adiposity, breast density features, and breast cancer risk can therefore be evaluated using many different approaches. In this article, we aim to discuss these relations from an epidemiological and biological point of view. We will first present currently used techniques of measurement and markers of adiposity and describe their association with breast cancer risk. Similarly, for breast density features, we will describe these measurements and their associations with breast cancer risk. We will then review the link between adiposity and breast density features. Finally, we will briefly address the potential role of adipose tissue in carcinogenesis.

Adiposity

Adiposity can be described with several markers to reflect body fatness or body fat distribution.

Body fatness

Body fatness can be assessed or estimated using many different techniques (Gibson, 2005a, 2005b; Willett, 2013). The most valid methods are dual-energy X-ray absorptiometry and densitometry, although they are rarely used in epidemiology. Dual-energy X-ray absorptiometry enables the measurement of total body fat, which can also be expressed in percent body fat, by excluding bone mineral mass and fat-free mass. Densitometry enables the calculation of percent body fat from the weight of a patient in the air and under water, or with the easier air displacement plethysmography technique (Siri, 1961). Percent body fat can also be estimated by bioelectrical impedance, an inexpensive and noninvasive technique based on the difference in conductance and resistance of fat and lean tissue (Lukaski *et al.*, 1986), or extrapolated from an evaluation of subcutaneous fat performed by the measurement of skinfold (s) thickness with a simple caliper (Durnin and Womersley, 1974).

Several obesity indices have also been developed to characterize body fatness. The one that is universally used, both in epidemiology and in the clinical setting, is BMI, which is weight (kg) divided by squared height (m^2) (Quetelet, 1869). This index has the advantage of being poorly correlated with height and rather highly correlated with total body fat (Willett, 2013). However, it remains an indirect measure of body fatness that could be influenced by various factors such as age or body proportions in addition to body composition (Heymsfield *et al.*, 2004). The use of BMI as an estimation of body fatness has been debated widely among scientists. However, from a public health perspective, even if the correlation between BMI and total body fat is not ideal [the correlation coefficient is about 0.75 (Willett, 2013)], WHO recommends this easy-to-use marker to characterize individuals presenting with a similar level of health risk. According to WHO, overweight and obesity are defined as a BMI between greater than or equal to 25 and less than 30 kg/m^2 and a BMI greater than or equal to 30 kg/m^2, respectively (WHO Expert Committee on Physical Status, 1995; WHO Consultation on Obesity, 2000; WHO Expert Consultation, 2004). Somatotypes, which are, images representing silhouettes of different BMI ranging from very thin to obese, such as those developed first by Stunkard *et al.* (1983), have also been used in epidemiological studies for self-reported body shape perception. The validity of such tools varies mainly according to sex, age, or ethnicity. The correlations between self-perceived body shape and a measure of body fatness, such as BMI for example, range from 0.56 to 0.99 in the adult general population (Gardner and Brown, 2010). Of importance is that many tools are not validated for use with obese individuals. As in this specific population perceived body shape can be subjected to distortion, special attention should be paid to the choice of a measurement instrument (Pull and Aguayo, 2011).

The dynamic of weight change throughout adulthood provides further information on body fatness. In healthy individuals exposed to chronic overfeeding, it has been shown that the gain and the composition of body mass vary individually, but on average, 2 kg of fat mass is stored for 1 kg of fat-free mass (Bouchard *et al.*, 2014). Weight gain can be predicted by the positive energy imbalance between total energy intake and total energy expenditure minus the energy needed for energy storage in the tissues (Christiansen *et al.*, 2005; Sorensen, 2009). Despite the apparent simplicity of this equation, its components are still not fully understood. Major challenges relate to technical issues and metabolic considerations. Indeed, precise measurement of energy expenditure and intake in real-life conditions and over a long period is extremely difficult (Schutz *et al.*, 2014). Furthermore, the equation described above is a dynamic process and its different components influence the others: weight gain will increase energy expenditure (Christiansen *et al.*, 2005) and storage efficiency varies (Schutz *et al.*, 2014). Another issue relates to the drivers of weight gain or fat mass accretion throughout adult life. This complex question has been the topic of many studies and the underlying mechanisms are not yet fully elucidated. For example, the classical idea that increased intake and decreased energy expenditure are the causes of weight gain leading to obesity needs to be considered in the context of the theoretical possibility that induction of weight gain occurs through active lipid accretion within adipose tissue itself, in particular through a tendency for increased lipid storage (Sorensen, 2009).

Body fat distribution

Several methods are available to measure or estimate the distribution of body fat, with the main objective to distinguish peripheral from abdominal fat and to further discriminate visceral fat from subcutaneous fat. Visceral fat can be assessed by imaging techniques such as computed tomography scan or MRI. However, as these techniques are expensive and not easily available, proxy measures such as waist circumference (WC) and waist-to-hip ratio (WHR) have been used extensively in clinical settings and epidemiological studies. WHR is WC divided by hip circumference and distinguishes fatness in the lower trunk from fatness in the upper trunk (Gibson, 2005a, 2005b). WC and WHR are correlated strongly with total body fat (Gibson, 2005a, 2005b) and reflect both total and regional fatness (Willett, 2013). However, WC has been found to be a better surrogate for abdominal fat as it is more strongly correlated with total abdominal fat and with visceral fat, as assessed by computed tomography scan, than WHR (Pouliot *et al.*, 1994; Clasey *et al.*, 1999). As WC is also associated with body size, WHR and waist-to-height ratio have been considered by some as markers of abdominal adiposity partly adjusted for body size. Distribution of body fat is a critical variable when considering health risk. Indeed, many epidemiological studies have shown that abdominal obesity, particularly excess visceral fat accumulation on anatomical structures such as the mesentery and greater omentum, is a strong risk factor for chronic diseases such as diabetes, cardiovascular diseases, or cancers (Tchernof and Despres, 2013). WC, WHR, and waist-to-height ratio have been shown to be correlated with the metabolic syndrome, cardiometabolic risk (Sun *et al.*, 2010; Kodama *et al.*, 2012; Borne *et al.*, 2015; Nazare *et al.*, 2015), and cancer risk, including breast cancer (World Cancer Research Fund, American Institute for Cancer Research, 2010; Vongsuvanh *et al.*, 2013).

Adiposity and breast cancer risk

Studying the association between adiposity and a specific pathology is a challenge as the marker chosen to reflect adiposity can, *per se*, be a cause of heterogeneity in the results. All of the parameters described above have been used in studies on breast cancer risk, but the most commonly used are BMI, WC, WHR, and weight gain (World Cancer Research Fund, American Institute for Cancer Research, 2010). Among postmenopausal women, positive associations with breast cancer risk have been found for BMI (convincing evidence), weight gain during adulthood, WC, and WHR (probable evidence) (World Cancer Research Fund, American Institute for Cancer Research, 2010). These associations are less consistent in premenopausal women in whom a protective effect of body fatness has been described (World Cancer Research Fund, American Institute for Cancer Research, 2010). However, the underlying pathophysiological mechanisms are not understood as yet and the protective effect is currently questioned by contrary results, indicating possible differences according to the type of cancer, ethnicity, risk level of breast cancer in the population under study, and other methodological factors (Anderson and Neuhouser, 2012). For instance, in a cohort of women at high breast cancer risk in North America including 5864 premenopausal women, Cecchini *et al.* (2012) found an increased risk of invasive breast cancer among premenopausal women within increasing categories of BMI, and a meta-analysis carried out by Pierobon and Frankenfeld (2013) showed a clearly positive association between obesity (BMI > 30 kg/m^2) and the risk of triple-negative breast cancer status among premenopausal women. Furthermore, a recent publication from the EPIC cohort (European Prospective Investigation into Cancer and Nutrition) reported a positive association between weight gain during middle adulthood and breast cancer, especially for women aged 50 years or younger (Emaus *et al.*, 2014). Ethnicity is also important. Indeed, in their meta-analysis, Amadou *et al.* (2013) showed that after stratification by ethnicity, BMI was significantly and inversely associated with breast cancer risk only among African and White premenopausal women, but not among Asian premenopausal women, in whom it was associated positively with breast cancer risk. With respect to body fat distribution, they showed that WHR, but not WC, was associated positively with breast cancer risk in premenopausal women and that this association was stronger among Asian women.

Body fatness and body fat distribution seem to represent significant determinants of breast cancer risk, particularly among postmenopausal women. Considering that fat is also a major component of the breast, what about its local role in breast cancer risk? Macroscopically, this relation can be studied through breast density features, of which percent density is a well-recognized risk factor for breast cancer (Huo *et al.*, 2014).

Breast density features and breast cancer risk

Determination of breast density is based on the radiological properties of breast tissue and reflects breast tissue composition. Indeed, fibroglandular tissue attenuates on radiography more than adipose tissue and appears white on a mammogram. On this basis, breast density can be assessed quantitatively or qualitatively by several methods (Assi *et al.*, 2012). Nowadays, quantitative assessment, usually computer assisted, is the most frequently used in research. However, qualitative methods with visual categorization are also used, for example in the classification proposed by Wolfe (1976) and in the Breast Imaging-Reporting and Data System (American College of Radiology, 2014). Quantitatively, three density features are mainly considered: the absolute dense area (mainly fibroglandular tissue), the absolute nondense area (mainly adipose tissue), and the percent density, which is the proportion of dense tissue in the total breast area. Recently, three-dimensional techniques have been developed to assess total and absolute volumes, but most are still in the process of validation.

With respect to breast cancer risk, percent density is the most studied mammographic density feature. It has constantly been shown to be strongly and positively associated with breast cancer risk among premenopausal and postmenopausal women (Kato *et al.*, 1995; Nagata *et al.*, 2005; Boyd *et al.*, 2009; Pettersson *et al.*, 2014). In a meta-analysis, McCormack and dos Santos Silva (2006) calculated that a breast density of at least 75% was associated with a four-fold relative risk of breast cancer compared with a breast density less than 5%. Absolute dense area has also been studied by many research groups and was found to be associated positively with breast cancer risk (Kato *et al.*, 1995; Nagata *et al.*, 2005; Boyd *et al.*, 2009; Pettersson *et al.*, 2014). Some authors examined whether volume measurements were better predictors of breast cancer risk and found very similar results overall (Boyd *et al.*, 2009; Shepherd *et al.*, 2011). However, the association between volumetric measures of breast density and breast cancer risk still needs confirmation.

The relation between absolute nondense area and breast cancer risk has seldom been studied. To gather the maximum number of studies, we used a systematic method within the PubMed library. We developed and combined the concepts 'nondense' and 'breast cancer' (see Supplementary Text, Supplemental digital content 1, *http://links.lww.com/EJCP/A115*, which presents the search strategy). Among the 118 titles retrieved from the search strategy, six original studies and one meta-analysis presented the relation between nondense breast tissue and breast cancer, and are discussed below. One more study (Torres-Mejia *et al.*, 2005) was added by reviewing bibliographies.

Paradoxically, despite the fact that adiposity has been shown to be associated positively with breast cancer risk (World Cancer Research Fund, American Institute for Cancer Research, 2010), several studies (Torres-Mejia *et al.*, 2005; Pettersson *et al.*, 2011; Olson *et al.*, 2012; Yaghjyan *et al.*, 2013; Baglietto *et al.*, 2014; Pettersson *et al.*, 2014), although not all (Stone *et al.*, 2010; Lokate *et al.*, 2011), have found a negative association between the amount of adipose tissue in the breast, reflected by the absolute nondense area, and breast cancer risk. It is only recently that absolute nondense area has been considered in studies on breast cancer risk. Recently, Pettersson *et al.* (2014) had the opportunity to reanalyze the pooled data of 13 case–control (including 12 nested within cohorts) studies from the DENSNP consortium collaborators, an international network of epidemiological studies on breast density and genetic variants that includes 1776 case patients and 2834 control participants. They found that absolute nondense area was strongly and negatively associated with breast cancer risk in models adjusted for usual confounders including BMI, and this result was maintained after controlling for absolute dense area with an OR per 1-SD increase of 0.82 [95% confidence interval (CI) 0.71–0.94] and 0.85 (95% CI 0.75–0.96) for premenopausal and postmenopausal women, respectively. Similarly, in a prospective cohort not included in this meta-analysis that included 3211 healthy UK women, with 111 developing breast cancer during a median follow-up time of 15 years, Torres-Mejia *et al.* (2005) found that absolute nondense area was associated negatively with breast cancer risk in analyses adjusted for usual confounders including BMI and 10-year change in BMI (hazard ratio per 1-SD increase, 0.76; 95% CI 0.57–1.02). In a matched case–control study nested within cohorts recruited at screening mammography in the UK and including 634 cases and 1880 controls, Stone *et al.* (2010) also found a negative association between absolute nondense area and breast cancer risk, but this association was lost after adjusting for absolute dense area (Q5 vs. Q1 OR 1.08; 95% CI 0.79–1.49). Unfortunately, the analyses carried out in the latter study could not be adjusted for usual confounders or for BMI as these data were not available. However, in a case–control study nested in the EPIC cohort of the Netherlands including 358 postmenopausal breast cancer cases and 859 postmenopausal controls, Lokate *et al.* (2011) found no association between absolute nondense area and breast cancer risk in analyses adjusted for usual confounders including BMI, whereas a positive association was observed when they further adjusted for absolute dense area (Q5 vs. Q1 OR 2.4; 95% CI 1.3–4.2). The technique used to measure mammographic density was very similar between studies: a computer-assisted method (mainly cumulus) on digitized film, but it has been hypothesized that the divergent results found by Lokate and colleagues could be partly due to the mammographic view chosen to evaluate absolute nondense area. Indeed, the mediolateral oblique projection used is more likely to overestimate nondense area because of the inclusion of some subcutaneous fat in the breast adipose tissue, and the evaluated risk could be partly attributed to adiposity instead of breast nondense area (Shepherd and Kerlikowske, 2012). Overall, studies are inconsistent even if a protective effect of breast fat seems to emerge. Many studies remain to be carried out and a better understanding of the association between adiposity and breast density could help increase understanding of the relation between adiposity and breast cancer risk.

Adiposity and breast density features

To review the relation between adiposity and breast density features, we used a systematic approach within the PubMed library. We developed and combined the concepts 'adiposity' and 'breast density' (see Supplementary Text, Supplemental digital content 2, *http://links.lww.com/EJCP/A116*, which presents the search strategy). Among the 3028 titles retrieved from the search strategy, 31 original studies were included in our review as they presented the association between one measure of adiposity and at least one absolute measure of breast density or presented the association between weight or BMI change and breast density (see Supplementary Fig., Supplemental digital content 3, *http://links.lww.com/EJCP/A117*, which present the process of selection in a PRISMA flow chart).

Static measures of adiposity and breast density features

In contrast to the inconsistent results for the association between absolute nondense area and breast cancer risk, cross-sectional analyses on the association between absolute nondense area, or volume, and adiposity have shown a constant positive association for BMI (Boyd *et al.*, 1998; Maskarinec *et al.*, 2001; Heng *et al.*, 2004; Haars *et al.*, 2005; Boyd *et al.*, 2006; Guthrie *et al.*, 2007; Irwin *et al.*, 2007; Stone *et al.*, 2009; Sung *et al.*, 2010; Harris *et al.*, 2011; Tseng and Byrne, 2011; Woolcott *et al.*, 2011; Eng *et al.*, 2014; Nayeem *et al.*, 2014; Schetter *et al.*, 2014; Soguel and Diorio, 2016), with correlation coefficients ranging from 0.41 to 0.77, percentage (Boyd *et al.*, 1998; Sung *et al.*, 2010; Woolcott *et al.*, 2011) or total (Nayeem *et al.*, 2014) body fat, and WC or WHR (Sung *et al.*, 2010; Tseng and Byrne, 2011; Woolcott *et al.*, 2011; Nayeem *et al.*, 2014; Soguel and Diorio, 2016). These results are not surprising because when adiposity is high, it can be expected that breast fat is also found in high amounts. However, it strengthens the apparent paradox in the relation between breast cancer risk and adipose tissue depending on its localization. Indeed, absolute nondense area, reflecting breast adipose tissue, and body fatness are associated positively with one another, but they seem to have opposite associations with breast cancer risk.

Percent density, whether calculated with areas or volumes or estimated by subjective visual scales, has been consistently and negatively associated with measures of body fatness such as BMI (Boyd *et al.*, 1998; Maskarinec *et al.*, 2001; Heng *et al.*, 2004; Haars *et al.*, 2005; Tamimi *et al.*, 2005; Boyd *et al.*, 2006; Ursin *et al.*, 2006; Guthrie *et al.*, 2007; Irwin *et al.*, 2007; McCormack *et al.*, 2007; Jeffreys *et al.*, 2008; McCormack *et al.*, 2008; Reeves *et al.*, 2009; Stone *et al.*, 2009; Lokate *et al.*, 2010; Sung *et al.*, 2010; Harris *et al.*, 2011; Maskarinec *et al.*, 2011; Tehranifar *et al.*, 2011; Tseng and Byrne, 2011; Woolcott *et al.*, 2011; Dorgan *et al.*, 2012; Pollan *et al.*, 2012; Eng *et al.*, 2014; Gierach *et al.*, 2014; Nayeem *et al.*, 2014; Schetter *et al.*, 2014; Soguel and Diorio, 2016), with correlation coefficients ranging from -0.41 to -0.61, percentage (Boyd *et al.*, 1998; Caire-Juvera *et al.*, 2008; Sung *et al.*, 2010; Woolcott *et al.*, 2011) or total (Nayeem *et al.*, 2014) body fat, or estimated by somatotypes (Samimi *et al.*, 2008) and with measures of abdominal body fat distribution such as WC or WHR (Sung *et al.*, 2010; Tseng and Byrne, 2011; Woolcott *et al.*, 2011; Dorgan *et al.*, 2012; Pollan *et al.*, 2012; Nayeem *et al.*, 2014; Soguel and Diorio, 2016). Again, this is not surprising. Indeed, because the absolute nondense area is usually the main component of the breast among women included in mammographic studies and because percent density is the proportion of dense area in the whole breast including fat, percent density is expected to be associated negatively with absolute nondense area and thus with adiposity. However, here again, as both percent density and adiposity are positively associated with breast cancer risk but negatively associated with one another, an apparent paradox arises in the link between adiposity, breast density, and breast cancer risk.

The association between absolute dense area and adiposity is less clear and cross-sectional analyses have led to inconsistent results (Boyd *et al.*, 1998; Maskarinec *et al.*, 2001; Heng *et al.*, 2004; Haars *et al.*, 2005; Tamimi *et al.*, 2005; Boyd *et al.*, 2006; Ursin *et al.*, 2006; Guthrie *et al.*, 2007; Irwin *et al.*, 2007; McCormack *et al.*, 2007; McCormack *et al.*, 2008; Reeves *et al.*, 2009; Stone *et al.*, 2009; Lokate *et al.*, 2010; Sung *et al.*, 2010; Harris *et al.*, 2011; Tehranifar *et al.*, 2011; Tseng and Byrne, 2011; Woolcott *et al.*, 2011; Eng *et al.*, 2014; Gierach *et al.*, 2014). Breast density features were mainly obtained by the same technique, that is, computer-assisted threshold method (mainly cumulus) on digitized film, and we observed no differences in the association according to the method used. Therefore, the observed discrepancies remain unexplained, but could be caused by important variations in the adjustments performed in the analyses and, to a certain extent, to differences in the population under study, including ethnicity or menopausal status. To show the complexity of available studies, we propose to detail the association between absolute dense area and BMI according to the variables included in the models. In unadjusted analyses or in those adjusted at least for age, studies have shown negative (Boyd *et al.*, 1998; Tamimi *et al.*, 2005; Boyd *et al.*, 2006; Stone *et al.*, 2009; Lokate *et al.*, 2010; Sung *et al.*, 2010; Harris *et al.*, 2011; Gierach *et al.*, 2014), positive (Heng *et al.*, 2004; Reeves *et al.*, 2009; Tseng and Byrne, 2011), or no association (Haars *et al.*, 2005; Ursin *et al.*, 2006; Irwin *et al.*, 2007; Tehranifar *et al.*, 2011). In analyses considering adjustment for the usual potential confounders, but not for any other variables that further characterize adiposity, studies have shown negative (Maskarinec *et al.*, 2001; Stone *et al.*, 2009; Sung *et al.*, 2010; Woolcott *et al.*, 2011; Eng *et al.*, 2014), positive (Tseng and Byrne, 2011), or no association (Guthrie *et al.*, 2007; McCormack *et al.*, 2007; McCormack *et al.*, 2008; Tehranifar *et al.*, 2011). Finally, when the analyses were adjusted for usual confounders and for at least one variable that characterizes body fatness (percent body fat) or body fat distribution (WC, WHR), in the few remaining studies, the association was found to be positive (Heng *et al.*, 2004; Tseng and Byrne, 2011) or null (Haars *et al.*, 2005).

Interestingly, when absolute dense volume is considered instead of area, a positive association between BMI and absolute dense volume has been found in several studies (McCormack *et al.*, 2007; Warren *et al.*, 2007; Jeffreys *et al.*, 2008; Lokate *et al.*, 2010; Eng *et al.*, 2014; Gierach *et al.*, 2014; Schetter *et al.*, 2014), although not all (Woolcott *et al.*, 2011; Dorgan *et al.*, 2012; Nayeem *et al.*, 2014). As volume measurement techniques are still in development and as results vary from one technique to another (Shepherd *et al.*, 2011; Nayeem *et al.*, 2014), further studies are needed to evaluate the relation between adiposity, absolute dense volume, and breast cancer risk. Indeed, in the studies presented here, different techniques have been used to assess breast density features [standard mammogram form, single X-ray absorptiometry, MRI, Volpara (Volpara Health Technologies, Wellington, New Zealand); Quantra (Hologic, Bedford, Massachusetts, USA)], and although the two studies using MRI (Dorgan *et al.*, 2012; Nayeem *et al.*, 2014) did not show a positive association between absolute dense volume and BMI, it is difficult to draw conclusions on the impact of these techniques. However, the positive association found between BMI and absolute dense volume could suggest that volume measurements provide additional information on breast density and its relation to breast cancer risk (Lokate *et al.*, 2010). Indeed, some authors have discussed the fact that, according to the technique used, absolute dense volume reflects not only fibroglandular mass but also part of the fat mass of the breast because of the water content of the latter (Shepherd *et al.*, 2011; Gierach *et al.*, 2014). The associations evaluated with these approaches could be compared with analyses carried out on area measurements partly adjusted for nondense area or for adiposity. This hypothesis is also reported in a recent analysis that we carried out among 1435 premenopausal and postmenopausal White women recruited at screening mammography (Soguel and Diorio, 2016). We computed correlations between BMI, WC, WHR, and absolute dense area and found a negative correlation after adjustment for potential confounders, but not for variables reflecting adiposity ($r=-0.21$; -0.23; and -0.19, respectively, $P<0.0001$). When we further adjusted for absolute nondense area, that is, when breast fat is considered, these three correlations switched from negative to positive ($r=0.16$, 0.12, and 0.06, respectively, $P<0.025$) (Soguel and Diorio, 2016). To our knowledge, this is the only study in which the association between adiposity and absolute dense area was adjusted for absolute nondense area.

Dynamic measures of adiposity and breast density features

The association between adult weight gain and breast density features has seldom been studied. In contrast to the negative association found with static measures of adiposity, adult weight gain was found to be associated positively with percent density in two studies (Pollan *et al.*, 2012; Soguel and Diorio, 2016) (women who had gained more than 25 kg showed an increase > 8.5%): first, in a study among 3584 premenopausal and postmenopausal women recruited at screening mammography in Spain, in which Pollan *et al.* (2012) found a positive association in analyses adjusted for usual confounders including BMI and WHR, and second, in our recent large study, in which we found a positive association between adult weight gain and percent density after adjusting for usual confounders including BMI and WHR (Soguel and Diorio, 2016). Moreover, in this study, BMI variation was also positively associated with percent breast density. However, two studies found a negative association, but without adjusting for current adiposity. Thus, this finding could be due to residual confounding, as shown by Samimi *et al.* (2008) in a study among 1398 premenopausal and postmenopausal US women from the Nurses' Health Study, and by Tseng and Byrne (2011) among 415 US Chinese premenopausal and perimenopausal women. However, in the latter study, the association was lost after adjustment for adiposity (BMI residuals and WC).

The association between weight gain during adulthood and absolute dense or nondense areas is poorly understood. To our knowledge, only two studies have assessed these associations: Tseng and Byrne (2011) evaluated this among premenopausal and perimenopausal Chinese women and our group among premenopausal and postmenopausal White women (Soguel and Diorio, 2016). In terms of absolute dense area, both studies showed a positive association with adult weight gain in models adjusted for adiposity as described above (women who had gained more than 25 kg showed an increase > 7.7 cm^2). Tseng and Byrne (2011) found a positive association, especially in women with a BMI < 23 kg/m^2, and so did we, especially among women with a high nondense area (Soguel and Diorio, 2016). In our study, BMI variation was also found to be associated positively with absolute dense area (Soguel and Diorio, 2016). With respect to absolute nondense area, in contrast to what was observed with static measures of adiposity, we observed a negative association with weight gain that was present among women with low and high absolute dense area in models that included BMI and WHR (Soguel and Diorio, 2016). Meanwhile, in models that included BMI (residuals) and WC, Tseng and Byrne (2011) found no association between adult weight gain and absolute nondense area among all women or by BMI strata.

A few longitudinal studies have examined the association between short-term weight change and breast density features (Boyd *et al.*, 1997; Guthrie *et al.*, 2007; Reeves *et al.*, 2009; Woolcott *et al.*, 2011; Wanders *et al.*, 2015). However, the short follow-up period and small variation in weight or BMI (Boyd *et al.*, 1997; Reeves *et al.*, 2009; Woolcott *et al.*, 2011; Wanders *et al.*, 2015), the changes in menopausal status during follow-up (Guthrie *et al.*, 2007; Reeves *et al.*, 2009; Wanders *et al.*, 2015), and the weight loss intent of the study (Boyd *et al.*, 1997; Woolcott *et al.*, 2011) are major limitations to consider in a comparison with studies on weight gain during adulthood. These studies are not discussed here.

In summary, it is not surprising that static measures of adiposity are associated positively with absolute nondense area. Therefore, the negative association observed with percent density is expected. The association with absolute dense area or volume also seems to be positive, but for area, it seems to depend on the adjustments that are performed in the analysis. Considering adult weight gain, when current adiposity is considered in the models, the association with percent density or absolute dense area seems to be positive, but for the latter, it could be limited to some subgroups. The association with absolute nondense area has been scarcely studied and is still controversial.

The association between static or dynamic measures of adiposity and breast density features has not been elucidated as yet and a number of questions remain. However, dynamic measures of adiposity could better reflect what occurs in term of risk. Indeed, associations evaluated in cross-sectional studies do not address causation and cannot simply be interpreted as a risk. Furthermore, the dynamic measure presumably reflects a long-term exposure to a risk factor that is critical for cancer development. Current knowledge does not enable a straightforward understanding of the apparent paradox of the role of fat tissue in breast cancer development when considering fat in the whole body or in the breast.

Role of adipose tissue in breast carcinogenesis

In the breast, histologically fibroglandular tissue (dense area) is mainly constituted by epithelial and stromal cells and adipose tissue (nondense area) mainly of adipocytes. Fibroglandular tissue represents the population of breast cells at risk of carcinogenic transformation (Trichopoulos *et al.*, 2005). Breast cancer generally arises in epithelial cells (Russo *et al.*, 1990) and an increase in overall cellular mass is believed to increase the risk of breast cancer (Preston-Martin *et al.*, 1990). However, breast adipose tissue, as part of the microenvironment surrounding the fibroglandular zone, seems to considerably influence the epithelial differentiation and proliferation by different mechanisms, not all elucidated as yet (Pettersson and Tamimi, 2012). In particular, it has been shown to contribute toward the development and progression of breast tumors in coculture experiments and animal models (Wang *et al.*, 2012). Moreover, fat tissue dysfunction is considered to generate local and peripheral chronic low-grade inflammation, sex hormone alterations, and insulin resistance (Lumeng *et al.*, 2007; Park *et al.*, 2014; Perez-Hernandez *et al.*, 2014). Inflammation in breast adipose tissue is currently believed to play an important role in the development of breast tumors (Santander *et al.*, 2015). Furthermore, body fat, through its aromatase activity, is a significant source of endogenous estrogens, known to promote breast tissue proliferation (Kulendran *et al.*, 2009). As adipose tissue is almost the exclusive source of estrogens among postmenopausal women, the impact of adiposity on breast cancer risk could be more pronounced in this population and one can hypothesize that this is a reason for the unclear results found among premenopausal women. Aromatase is also present in the breast tissue itself where stromal cells in the dense area, and adipocytes in the nondense area, were shown to present the highest aromatase immunoreactivity (Vachon *et al.*, 2011). It is likely that a large breast adipose tissue accumulation accounts for a non-negligible source of local endogen estrogen and, therefore, could contribute toward breast cancer risk. Although, to our knowledge, only one study has evaluated the association between adult weight gain and absolute dense area according to nondense area, this hypothesis is well illustrated by the fact that weight gain was associated positively with absolute dense area, especially if breast fat was present in larger amounts (Soguel and Diorio, 2016).

However, a potentially protective influence of breast fat has also been described. The ability of fat to store vitamin D, known to exert a protective effect against breast cancer development, could partly explain the protective effect (Narvaez *et al.*, 2014). Involution has also been suggested to play a role through the reduction of fibroglandular tissue in favor of adipose tissue (Pettersson *et al.*, 2014). The protective effect of breast fat is plausible because when nondense area increases, breast cancer risk seems to decrease (Pettersson *et al.*, 2014) and when body weight increases during adulthood, breast fat has been shown to decrease or remain stable (Tseng and Byrne, 2011; Soguel and Diorio, 2016).

Conclusion

The association between breast fat and breast cancer risk deserves further epidemiological and biological investigation. The challenges faced when comparing studies lead us to advocate the need for longitudinal (cohort) studies assessing the impact of body weight history through adulthood on breast density features and breast cancer risk over a long follow-up among premenopausal women and among postmenopausal women separately to avoid specific changes during the menopause transition.

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Conflicts of interest

There are no conflicts of interest.

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