Gain de poids à l'âge adulte et densité mammaire

Mémoire

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Résumé

L'adiposité est un facteur de risque connu pour le cancer du sein et le gain de poids à l'âge adulte semble l'être également. Au niveau mammaire, le tissu adipeux peut être étudié au travers des mesures de densité. En effet, la zone non-dense reflète le gras mammaire et le pourcentage de densité, l'un des plus importants facteurs de risque pour le cancer du sein, reflète la proportion de tissu fibroglandulaire. Le premier objectif de ce mémoire était d'évaluer, chez 1435 femmes recrutées lors d'une mammographie de dépistage, l'association entre le gain de poids à l'âge adulte et trois paramètres de mesure de densité mammaire : le pourcentage de densité et les zones dense et non-dense en valeurs absolues. Le second objectif était de présenter un texte de synthèse et de discussion portant sur les interrelations entre l'adiposité, la densité mammaire et le risque de cancer du sein.

Abstract

Adiposity is a known risk factor for breast cancer and weight gain during adulthood also seems to play a role. In the breast, adipose tissue can be studied through breast density features. Indeed, absolute non-dense area reflects breast fat and percent density, one of the strongest risk factor for breast cancer, reflects the proportion of fibroglandular tissue. The first objective of this dissertation was to evaluate the association between weight gain during adulthood and three density features: percent density, absolute dense and non-dense areas, among 1435 women recruited at screening mammography. The second objective was to present a consolidated text of the interrelation between adiposity, breast density and breast cancer risk and to discuss it in an epidemiological and biological point of view.

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Liste des Abréviations

BIA : Bioelectrical Impedance. Impédance bioélectrique

BI-RADS : Breast Imaging-Reporting And Data System. Classification de la densité mammaire en 4 catégories selon « l'American College of Radiology »

BMI : Body Mass Index. Indice de Masse Corporelle

Cérul : Comités d'éthique de la recherche avec des êtres humains de l'Université Laval

CT-scan : Computed-Tomography-Scan. Imagerie par tomodensitométrie

DXA : Dual-energy X-ray Absorptiometry. Absorptiométrie biénergétique à rayons X

EPIC : European Prospective Investigation into Cancer and Nutrition. Enquête prospective européenne sur le cancer et la nutrition

FRQS : Fonds de Recherche du Québec-Santé

HC : Hip Circumference. Tour de hanches

IMC : Indice de masse corporelle

MRI : Magnetic Resonance Imaging. Imagerie par résonnance magnétique

OMS : Organisation Mondiale de la Santé

PRISMA : Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Recommandations minimales pour rendre compte d'une revue systématique ou d'une méta-analyse.

$p_{tendance}$: Valeur p tendance

p_{trend} : Valeur p tendance

r : Coefficient de corrélation

WC : Waist circumference. Tour de taille

WHO : World Health Organization. Organisation Mondiale de la Santé

WHR : Waist-to-Hip Ratio. Rapport taille-hanche

WHtR : Waist-to-Height Ratio. Rapport taille-hauteur

Chercher à connaître n'est souvent
qu'apprendre à douter.
Antoinette Deshoulières (1634-1694)
Femme de lettres Française

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Ce travail a été possible grâce au soutien de nombreuses personnes que j'aimerais remercier ici.

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La famille et les amis qui ont facilité notre vie au Québec par toutes sortes d'attentions que nous avons beaucoup appréciées.

Avant-Propos

L’objectif principal de ce mémoire est d’évaluer l’association entre le gain de poids à l’âge adulte et la densité mammaire, en tant que marqueur intermédiaire du risque de cancer du sein. Pour atteindre cet objectif, j’ai eu la chance d’avoir accès à une banque de données constituée dans le cadre d’une étude transversale menée par Jacques Brisson, Caroline Diorio et Sylvie Bérubé (1, 2), financée par la Société Canadienne du Cancer. Dans ce projet, 1600 participantes avaient été recrutées lors d’une mammographie de dépistage dans deux cliniques radiologiques de la ville de Québec entre février 2001 et mars 2002. En parallèle des mesures de densité mammaire, de nombreux facteurs de risques de cancer du sein, suspectés ou reconnus, avaient été récoltés. Cela m’a permis de réaliser une analyse secondaire de données pour évaluer spécifiquement l’association entre le gain de poids à l’âge adulte et trois paramètres de mesure de densité mammaire : le pourcentage de densité mammaire et les zones dense et non-dense en valeurs absolues. L’aboutissement de ce travail est présenté dans le *chapitre 3* de ce mémoire sous la forme d’un article actuellement en évaluation pour publication dans la revue Cancer Causes & Control. J’ai rédigé de manière autonome cet article sous la supervision de Caroline Diorio. Ce travail a également fait l’objet de deux présentations orales lors de congrès : la première par Caroline Diorio dans le cadre du 9ème « International Conference of Anticancer Research » en Grèce, en octobre 2014 et la deuxième, par moi-même, dans le cadre du Congrès annuel de l’Association Suisse des Diététicien-ne-s (Nutridays ASDD) en Suisse, en mars 2015.

La revue de littérature sur la relation entre le gain de poids à l’âge adulte et la densité mammaire réalisée pour le présent travail a révélé que très peu d’études se sont intéressées à ce sujet et que les résultats ne sont pas probants. Les relations entre l’adiposité, la densité mammaire et le risque de cancer du sein sont, quant à elles, des sujets récurrents dans la littérature mais les conclusions des études, notamment en ce qui concerne l’association entre l’adiposité et la zone dense et l’association entre la zone non-dense et le risque de cancer du sein, restent également encore peu concluantes. Cette constatation m’a menée à proposer une revue de la littérature élargie portant sur l’association entre différentes mesures anthropométriques reflétant l’adiposité et les différents paramètres d’évaluation de la densité mammaire. Ce travail a ensuite été enrichi d’une discussion de la relation entre l’adiposité, la densité mammaire et le risque de cancer du sein, dans une perspective épidémiologique et biologique. C’est ce texte qui fait office de cadre de référence pour ce mémoire. Il est présenté sous la forme d'un article en préparation pour publication dans le *chapitre 2* et il intègre les résultats de l'analyse présentée au *chapitre 3*. Le plan de rédaction, l'orientation à donner et les messages importants de cet article ont été définis avec Caroline Diorio. J'ai réalisé la revue de littérature et j'ai rédigé le texte présenté de manière autonome, toujours sous la supervision de Caroline Diorio. Une méthodologie rigoureuse a été utilisée pour la recherche de littérature. Elle est décrite en introduction du *chapitre 2* et les caractéristiques des études considérées sont présentées dans un tableau en annexe, construit pour être intégré comme matériel supplémentaire dans la publication à venir (*annexe 2*).

Considérations éthiques

Le protocole de l'étude à l'origine de la collecte de données a été approuvé par le Comité d'Éthique à la Recherche du Centre de recherche du Centre Hospitalier Universitaire de Québec de l'Hôpital Saint-Sacrement. Les femmes qui ont accepté de participer ont signé un formulaire de consentement incluant l'autorisation pour toutes les procédures et recueil de données prévus. Les femmes présentant un déficit cognitif ne permettant pas l'obtention d'un consentement éclairé ont été exclues. L'analyse secondaire menée dans le cadre de ce mémoire a obtenu l'approbation des Comités d'éthique de la recherche avec des êtres humains de l'Université Laval (cérul), comme le prévoit la procédure en vigueur.

Financement

Ce mémoire a été réalisé avec le soutien du Centre de recherche sur le cancer de l'Université Laval qui m'a attribué une bourse d'excellence aux études graduées en 2014 et qui a été complétée par Caroline Diorio. La Bourse de développement de capacité en prévention de la Fondation Canadienne du Cancer du Sein et le programme Chercheur-Boursier du Fonds de Recherche du Québec-Santé (FRQS), attribués au Dre Caroline Diorio ont également permis la réalisation de ce projet.

1. Introduction et objectifs

Le cancer du sein est le cancer le plus fréquent chez les femmes dans le monde : en 2012, il a contribué à 25% des nouveaux cas de cancer, touchant 1,67 million de femmes. En 2012, c'est le cancer qui a causé le plus de décès chez les femmes, représentant 14,7% des décès par cancer dans le monde, suivi de près par le cancer du poumon, représentant 13,8% des décès par cancer. Dans les régions les plus développées, la mortalité par cancer du poumon a dépassé celle par cancer du sein (3). Au Canada, on estime qu'en 2014, 24 400 femmes recevront un diagnostic de cancer du sein et que 5000 en mourront (4). De nombreux facteurs de risques probables ou connus pour le cancer du sein ont été identifiés, ils sont d'ordres socio-culturels, environnementaux, comportementaux ou biologiques et génétiques et on estime que 10 à 30% des facteurs contributifs sont d'ordre héréditaire (5).

Le surpoids et l'obésité, définis respectivement par un indice de masse corporelle (IMC) entre ≥25 et <30 kg/m^2 et un IMC ≥30 kg/m^2 par l'Organisation Mondiale de la Santé (OMS) (6), font partie des facteurs de risque reconnus (éléments de preuve convaincants) pour le développement du cancer du sein chez les femmes postménopausées (7). Le gain de poids à l'âge adulte, le tour de taille et le rapport taille-hanche sont quant à eux des facteurs de risques probables dans cette même population (7). Chez les femmes préménopausées, un IMC élevé a été décrit comme un facteur potentiellement protecteur mais cette observation est remise en question par des résultats contradictoires (8-11). L'inquiétant accroissement de la prévalence du surpoids et de l'obésité dans le monde entraîne une augmentation du nombre de femmes concernées par ce facteur de risque. Un récent rapport international montre en effet une augmentation de 29,8% à 38,0% de surpoids et d'obésité chez les femmes, entre 1980 et 2013. Chez les enfants, les plus hauts pourcentages sont observés dans les pays à hauts revenus, où 22,6% des filles sont considérées en surpoids ou obèses, mais la prévalence augmente dans les pays en voie de développement (12). L'étiologie de la prise de poids, jusqu'à constitution d'une obésité, n'est par ailleurs pas élucidée. En effet, le poids corporel est finement régulé et la prise de poids à l'âge adulte est le reflet d'un mécanisme complexe dont le « primum movens » pourrait être une augmentation des apports énergétiques et/ou une diminution de la dépense énergétique mais pourrait également se situer au sein du tissu adipeux et résulter d'une anomalie de la fonction de stockage des adipocytes (13). La raison pour laquelle certains individus entrent dans un processus de prise de poids importante, jusqu'à constituer une obésité, reste peu clair.

Lorsque l'on s'intéresse à l'adiposité en épidémiologie, il faut garder en tête que les mesures anthropométriques visant à la caractériser sont nombreuses et qu'elles sont principalement des mesures indirectes de facteurs qui influencent l'état de santé. Le choix de la mesure ou de l'indice utilisé pour l'évaluation d'une association entre l'adiposité et une pathologie n'est donc pas anodin et il peut, en soi, être la cause d'hétérogénéité importante des résultats observés. Les paramètres les plus utilisées en épidémiologie pour décrire l'adiposité sont l'IMC, qui donne une information sur la corpulence du sujet, et le tour de taille et le rapport taille-hanche, qui donnent des informations complémentaires concernant la répartition corporelle de la masse grasse. D'autres paramètres sont parfois utilisés, notamment en recherche. Une synthèse des principales mesures permettant de caractériser l'adiposité ou son évolution, a été rédigée dans l'article présenté au *chapitre 2*.

Lorsqu'il se situe au niveau du sein, le tissu adipeux peut être étudié par le biais des mesures de densité mammaire qui font référence à la composition histologique du sein telle que visualisée sur une image de mammographie. Le tissu fibroglandulaire absorbe les rayons-X de manière plus importante que le tissu adipeux et apparaît en blanc, donc plus dense, sur l'image. Le tissu adipeux quant à lui, laisse passer plus de rayons-X et apparaît en noir, donc moins dense. Une récente étude publiée par Ghosh et collaborateurs a permis de confirmer les différences de composition histologique des zones denses et non-denses par la réalisation de biopsies chez des femmes volontaires en santé (14). La détermination quantitative de la densité mammaire sur une mammographie peut être effectuée de différentes manière mais actuellement les logiciels de calculs semi-automatiques utilisés sur des mammographies numériques ou sur des films numérisés sont les plus utilisés. Le logiciel Cumulus, développé à Toronto (15) est considéré comme la référence. L'examinateur délimite la zone totale du sein et définit la zone dense. Sur cette base, le programme détermine la valeur absolue de zone dense (cm^2), la valeur absolue de zone non-dense (cm^2) et calcule le pourcentage de densité mammaire en divisant la valeur absolue de zone dense par la surface totale du sein (Figure 1). Des systèmes de détermination totalement automatique existent mais ils sont encore en évaluation (16-18). Reprochant l'utilisation d'approches bidimensionnelles pour l'évaluation d'entités tridimensionnelles, plusieurs équipes de scientifiques ont cherché à développer de nouvelles techniques de mesures volumétriques permettant d'obtenir les valeurs absolues de volumes dense et non-dense et de définir un pourcentage de densité mammaire sur la base des volumes déterminés. Un certain nombre de ces techniques sont en cours d'évaluation actuellement (19-21).

Figure 1 : Image mammographique.

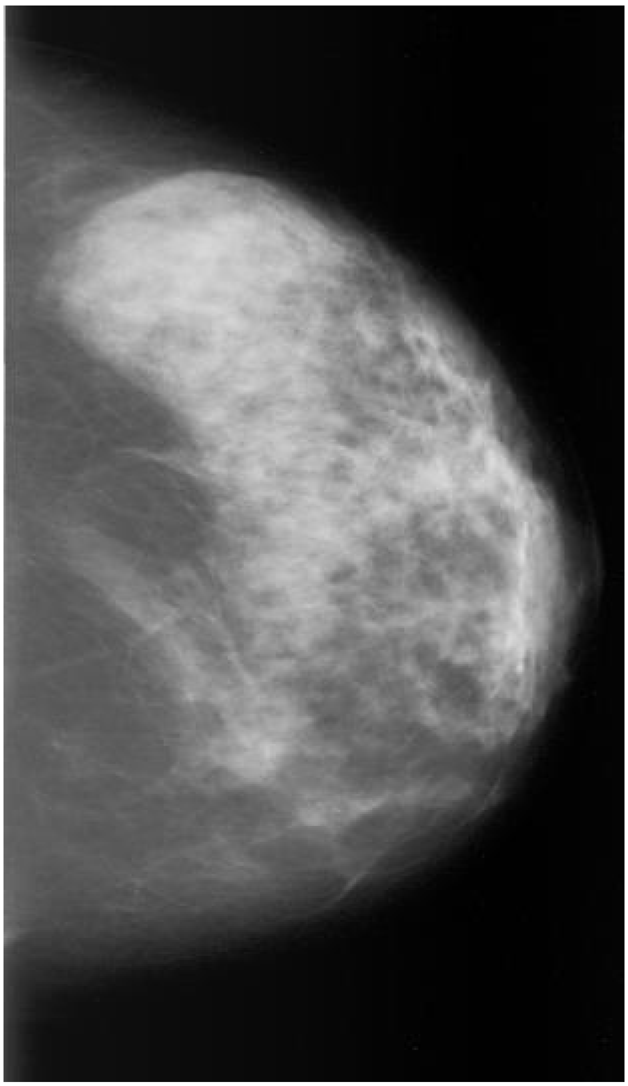


Image mammaire pour laquelle la densité mammaire a été évaluée à 52,2%, la zone dense à 77,0 cm^2 et la zone non-dense à 70.7 cm_2, à l'aide du logiciel cumulus (par C. Diorio).

La densité mammaire est l'un des plus importants facteurs de risque connus pour le cancer du sein (22). Les femmes qui présentent un pourcentage de densité mammaire de ≥75% ont environ 4 fois plus de risque de développer un cancer du sein que celles qui présentent une densité mammaire de <5% (23). Le pourcentage de densité mammaire est régulièrement utilisé comme un marqueur intermédiaire du risque de cancer du sein, notamment dans les études épidémiologiques ou les études d'intervention à visée préventive (24). Depuis quelques années, les chercheurs se sont également intéressés aux rôles spécifiques des zones dense et non-dense, en valeurs absolues, dans le développement du cancer du sein. Comme la zone dense abrite les cellules épithéliales, susceptibles de se différentier en cellules tumorales, et comme la zone non-dense forme le microenvironnement principalement composé de cellules graisseuses qui influence potentiellement le développement tumoral, on s'attend en effet à ce que l'évaluation spécifique de ces zones fournisse un intéressant éclairage pour la compréhension des mécanismes impliqués dans le développement du cancer du sein. Une synthèse de la question a été rédigée pour l'article présentée au *chapitre 2*. Brièvement, la valeur absolue de zone dense semble très certainement positivement associée au risque de cancer du sein (25-29) alors que pour la zone non-dense, les résultats sont moins clairs, même si un rôle protecteur semble se dessiner (27, 30-33).

Plusieurs facteurs héréditaires ou liés au style et au cours de la vie influencent la densité mammaire. Le pourcentage de densité mammaire a notamment tendance à diminuer avec l'âge et avec la ménopause, même si un certain nombre de femmes garde des seins denses à un âge avancé (34). A titre d'exemple, chez les femmes adultes et caucasiennes recrutées lors d'une mammographie de dépistage ou dans la population générale, dans le cadre d'études qui ont évalué l'association entre l'adiposité et la densité mammaire, le pourcentage de densité mammaire médian se situait entre 13 et 45% (35-39). Dans ces mêmes études, la zone dense médiane se situait entre 20 et 43 cm^2 et la zone non-dense médiane, se situait entre 57 et 146 cm^2 (35-39). De manière générale, c'est la zone non-dense, donc le tissu adipeux, qui occupe la plus grande partie du sein. A noter cependant que les espaces interquartiles étaient larges, ce qui démontre une grande variabilité entre les femmes. En 2014, une étude populationnelle incluant 1 518 599 mammographies de contrôle réalisées sur 764 507 femmes âgées de 40 ans et plus et visant à déterminer la prévalence des seins denses à la mammographie aux USA a été publiée (40). Dans cette vaste enquête, la densité mammaire n'a pas été évaluée quantitativement mais catégorisée selon la classification semi-quantitative BI-RADS (41) en quatre types (type I : presque entièrement graisseux ; type 2 : opacités fibroglandulaires éparses ; type 3 : dense et hétérogène et type 4 : extrêmement dense (42)). Les résultats montrent que la proportion de type 4 a tendance à diminuer avec l'âge alors que la proportion de type 1 a tendance à augmenter. Entre 50 et 54 ans, les quatre types BI-RADS se distribuaient ainsi : 12% de type 1, 42% de type 2, 38% de type 3 et 8% de type 4 (40).

L'adiposité est également un facteur important dans la détermination de la densité mammaire. Par exemple, une association négative entre l'IMC et le pourcentage de densité mammaire (19-21, 35-38, 43-63) et positive entre l'IMC et la zone non-dense (19, 21, 35, 44, 46-53, 55, 57, 61, 63) ont été mises en évidence dans de nombreuses études. En ce qui concerne la zone dense, les résultats sont plus contrastés (35, 44, 46-48, 50-52, 54). Le gain de poids à l'âge adulte a été très peu étudié et les résultats ne sont pas concluants en ce qui concerne son association tant avec le pourcentage de densité mammaire (43, 44, 64) qu'avec les valeurs absolues des zones dense et non-dense (44). L'analyse menée dans le cadre de ce mémoire a pour but d'évaluer l'association entre le gain de poids à l'âge adulte et trois paramètres de mesure de densité mammaire : le pourcentage de densité mammaire et les zones dense et non-dense, en valeurs absolues. Elle est présentée au *chapitre 3*.

L'apparent paradoxe autour de la relation entre le risque de cancer du sein et l'adiposité réside dans le fait que le tissu adipeux corporel est positivement associé au risque de cancer du sein mais que lorsqu'il est localisé au niveau mammaire, et donc reflété par la zone non-dense en valeur absolue, il semble négativement associé au risque. C'est précisément autour de ce paradoxe que s'organise l'article présenté au *chapitre 2* qui fait office de cadre de référence pour le présent mémoire. L'objectif est de discuter les interrelations entre l'adiposité, la densité mammaire et le risque du cancer du sein dans une perspective épidémiologique et biologique. Pour ce faire, l'article se présente en cinq parties. La première partie décrit les mesures utilisées pour refléter l'adiposité et la deuxième partie présente leurs associations avec le risque de cancer du sein. La troisième partie décrit les mesures utilisées pour évaluer la densité mammaire et leurs associations avec le risque de cancer du sein. La quatrième partie se présente comme une revue de la littérature portant sur l'association entre l'adiposité et la densité mammaire et finalement, la dernière partie discute le rôle du tissu adipeux dans la carcinogenèse dans une perspective biologique

2. Adiposité et densité mammaire, perspectives épidémiologiques et biologiques

L'article présenté ci-dessous est actuellement en préparation pour soumission en vue d'une publication dans une revue scientifique.

La revue de littérature sur l'association entre les variables anthropométriques reflétant l'adiposité et les différents paramètres d'évaluation de la densité mammaire, est basée sur la méthodologie utilisée pour une revue systématique. Néanmoins, seule la base de données PubMed a été interrogée dans le cadre de cet article et la revue de la littérature présentée ici ne prétend pas être exhaustive. L'angle sous lequel nous avons choisi d'écrire cet article n'est d'ailleurs pas celui d'une revue systématique de la littérature mais plutôt d'une perspective. Cette approche a été favorisée parce qu'elle permet, tout en présentant l'état de connaissances, de formuler des hypothèses et de discuter davantage.

La stratégie de recherche élaborée a combiné les termes associés à la densité mammaire et ceux associés à l'anthropométrie. Pour l'anthropométrie, elle s'est inspirée des termes retenus par la revue systématique de littérature portant sur l'alimentation, la nutrition et l'activité physique en tant que facteurs de risque du cancer du sein menée par le Fonds Mondial de Recherche contre le Cancer et l'Institut Américain de Recherche sur le Cancer (65). Pour la densité mammaire, elle a été construite avec les termes utilisés dans plusieurs recherches de littérature par Caroline Dioro et ses collaborateurs et a été affinée par les mots clés retenus dans diverses publications. La stratégie de recherche retenue et ses résultats sont présentés en annexe (*annexe 1*).

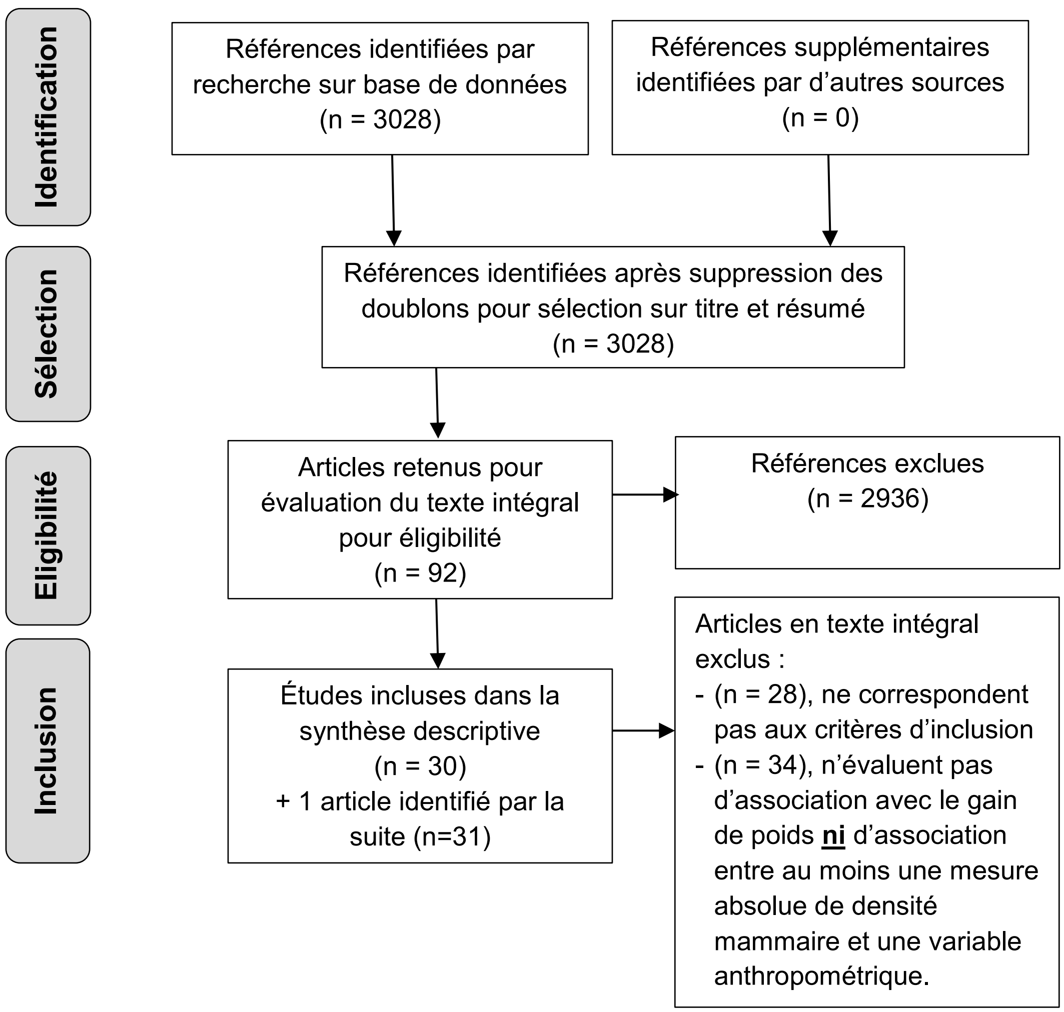
Le processus de sélection est décrit dans un diagramme de flux PRISMA, recommandé pour la rédaction et la lecture des revues systématiques et des méta-analyses (66, 67) (*figure 1*). La base de données PubMed a été interrogée pour la dernière fois le 9 février 2015. Au total, **3028 titres et résumés ont été évalués** pour inclusion dans la revue de la littérature. Ce travail a été réalisé par une seule personne (Ludivine Soguel).

La sélection a été réalisée selon les critères d'inclusion suivants : l'article doit présenter les résultats de l'évaluation d'une association entre au moins une des variables anthropométriques suivantes : IMC, masse grasse (en pourcentage ou en valeur absolue), tour de taille ou rapport taille hanche et au moins un des paramètres de mesure de la densité mammaire suivants : pourcentage de densité mammaire (défini par une méthode en deux ou en trois dimension), zone ou volume dense en valeur absolue, zone ou volume non-dense en valeur absolue, catégories de densité mammaire, évaluation qualitative de la densité mammaire (critères de Wolf ou de Tabar). Sur cette base, **92 articles ont été retenus pour évaluation sur texte complet**.

Par la suite, 28 articles ont été exclus parce qu'ils ne correspondaient finalement pas à ce critère et **64 articles ont été retenus**. A ce stade, il a été décidé de présenter la synthèse des résultats de tous les articles qui présentaient une association avec le changement de poids ou d'IMC à l'âge adulte (3 articles (43, 44, 64)) ou le changement de poids ou d'IMC à court terme (4 articles (45, 46, 63, 68)) et de tous les articles qui présentaient des associations pour au moins une mesure absolue de densité mammaire (zone ou volume dense ou non-dense), quelle que soit la variable anthropométrique étudiée (29 articles (19-21, 35-38, 43-57, 59, 60, 62-64, 69, 70)). Une étude publiée très récemment et présentant l'association entre le changement de poids à court terme et la densité mammaire a été ajoutée par la suite, sur la base d'alertes paramétrées sur PubMed (1 article (39)).

Les caractéristiques des **31 études retenues** sont présentées dans le tableau en annexe (*annexe 2*) et une synthèse a été rédigée pour l'article présenté ci-après (le total des articles est supérieur puisque certains articles se retrouvent dans plusieurs catégories).

Figure 2 : Diagramme de flux PRISMA présentant le processus de sélection des articles portant sur l'association entre l'adiposité et la densité mammaire.



2.1. Titre et résumé en français

Titre : Adiposité, densité mammaire et risque de cancer du sein : considérations épidémiologiques et biologiques.

L'adiposité peut être définie par différents paramètres qui reflètent la graisse corporelle totale ou sa répartition. Une masse grasse corporelle importante et une répartition abdominale de celle-ci sont des facteurs de risque connus pour les maladies chroniques et certains cancers, dont le cancer du sein. Le tissu adipeux joue probablement un rôle dans le développement du cancer du sein à différent niveau : par un effet systémique et local, directement dans le sein. Le gras situé dans le sein peut être étudié macroscopiquement au travers des densités mammaires. En effet, la zone non-dense représente le gras mammaire et le pourcentage de densité la proportion de tissu fibroglandulaire sur l'ensemble du sein. Comme la densité mammaire est l'un des facteurs de risque les plus importants pour le cancer du sein, les relations entre l'adiposité, les mesures de densité mammaire et le risque de cancer du sein sont importantes à considérer mais sont complexes et peuvent sembler paradoxales. En effet, l'adiposité et la zone non-dense en valeur absolue semblent positivement associées malgré le fait que l'adiposité soit reconnue comme un facteur de risque et que la zone non-dense semble jouer un rôle protecteur. Le présent article discute les interrelations entre l'adiposité, la densité mammaire et le risque de cancer du sein en commençant par exposer les mesures utilisées pour définir l'adiposité ainsi que la densité mammaire et leurs associations avec le risque de cancer du sein. Par la suite, une revue de la littérature est proposée sur l'association entre l'adiposité et la densité mammaire et finalement, le rôle du tissu adipeux dans la carcinogenèse est discuté dans une perspective biologique.

2.2. Title and authors

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

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2.3. Abstract

Adiposity can be defined by several markers reflecting body fatness or body fat distribution. High fat body composition and predominantly abdominal distribution of body fat are risk factors for metabolic diseases and for some types of cancer, including breast cancer. Several biological mechanisms in connection with adipose tissue are thought to be implicated in breast cancer development. They concern a systemic effect of body fat but also a local influence from breast fat. Adipose tissue located in the breast can be studied mammographically through breast density features, in particular through the non-dense area mainly composed of fat or through percent breast density, which is the proportion of fibroglandular tissue in the breast in relation to fat. As breast density is one of the strongest risk factor for breast cancer, the relation between adiposity, breast density features and breast cancer is important to consider and complex. Indeed, adiposity and absolute non-dense area are positively correlated with each other but, despite the fact that

adiposity is recognized as a risk factor for breast cancer, absolute non-dense area seems to be negatively associated with breast cancer risk. In the present paper we will discuss these interrelations through an overview of measures used to reflect adiposity and breast density features and their relation with breast cancer risk. The relation between adiposity and breast density features will then be reviewed and the role of adipose tissue in carcinogenesis will be discussed from a biological perspective.

2.4. Introduction

Breast cancer is the most common cancer in women worldwide, accounting for 25% of the total new cases in 2012, touching 1.67 million of women (1). With 522,000 estimated deaths in 2012, it is one of the leading causes of mortality by cancer in women worldwide (1).

Adiposity is an established risk factor for breast cancer among postmenopausal women and both body fatness and abdominal body fat distribution seem to play a role (2). The association is less consistent in premenopausal women for whom the underlying biological mechanisms remain undetermined (3-8). Furthermore, the role of breast fat in breast cancer development is not well understood yet. Actually, fat tissue has been described as a microenvironment promoting carcinogenesis through different mechanisms, in particular chronic inflammation (9, 10) but it also has a potentially protective role, especially as a source of vitamin D (11).

The relation between fat tissue located in the breast and breast cancer risk can be studied through mammographic density features. In fact, absolute non-dense area reflects breast fat tissue and inversely, percent density represents the proportion of non-fat tissue in the breast. Percent density is one of the strongest identified risk factors for breast cancer and is frequently used as a surrogate for breast cancer risk in epidemiological studies (12). The apparent paradox in the relation between adiposity, breast density and breast cancer risk is that adiposity and absolute non-dense area seem positively correlated but, despite that adiposity is recognized as a risk factor for breast cancer, absolute non-dense area has been shown to be negatively associated with breast cancer risk in a recent meta-analysis (13).

Adiposity can be assessed or estimated by different techniques, and thus can be described with different markers. In addition, breast density can also be defined with different features such as percent density, absolute dense and non-dense areas or volumes. The relation between adiposity, breast density features and breast cancer risk can therefore be evaluated in many different manners. In this article, we aim at discussing this relation with an epidemiological and biological point of view. We will first present currently used techniques and markers of adiposity and describe their association with breast cancer risk. Similarly for breast density features, we will describe these measures and their associations with breast cancer risk. We will then review the link between adiposity and breast density features. Finally, we will briefly discuss the role of adipose tissue in carcinogenesis.

2.5. Adiposity

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

Body fatness

Body fatness can be assessed or estimated by many different techniques (14, 15). The most valid methods are dual-energy x-ray absorptiometry (DXA) and densitometry, though both rarely used in epidemiology. DXA allows 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 allows the calculation of **percent body fat** from the weighting of a subject in the air and under water, or with the easiest air displacement plethysmography technique (16). Percent body fat can also be estimated by bioelectrical impedance (BIA), a cheap and non-invasive technique based on the difference of conductance and resistance of fat and lean tissue (17), or extrapolated from an evaluation of subcutaneous fat performed by the measurement of skinfold(s) thickness with a simple caliper (18).

Several **obesity indices** have also been developed in order to characterize body fatness. The one that is universally used, both in epidemiology and clinical setting, is the **body mass index (BMI)**, which is weight (kg) divided by squared height (m2) (19). Such index has the advantage of being poorly correlated with height and rather highly correlated with total body fat (14). However, it remains an indirect measure of body fatness that could be influenced by different factors such as age, body proportions and body composition (20). The use of BMI as an estimation of body fatness is currently widely discussed by scientists. However, in a public health perspective, even if the correlation between BMI and total body fat is not ideal, the World Health Organization (WHO) recommends this easy-to-use marker to characterize people presenting with a similar level of health risk. According to WHO, overweight and obesity are defined as a BMI between ≥25 and <30 kg/m2, and a BMI ≥30 kg/m2, respectively (21-23). Somatotypes, i.e. images representing silhouettes of different BMI ranged from very thin to obese such as those developed first by Stunkard (24), have also been used in epidemiological studies for **self-reported body shape perception**. The validity of such tools varies mainly according to gender, 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 (25). Of importance is that many tools are not validated for use with obese people. As in this specific population perceived body shape can be submitted to distortion, a special attention should be paid to the choice of a measurement instrument (26).

The dynamic of **weight change throughout adulthood** gives further information on body fatness. In healthy subjects exposed to chronic overfeeding, it has been shown, that the gain and the composition of body mass varies individually but on average, 2 kg of fat mass are stored for 1 kg of fat free mass (27). 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 (28, 29). Despite the apparent simplicity of this equation, its components are still not well understood. Major challenges relate to technical issues and metabolic consideration. Essentially, measuring energy expenditure and intake precisely in real life condition and for a long period is currently impossible (30). Furthermore, the equation described above is a dynamic process and its different components influence the others: weight gain will increase energy expenditure (29), and storage efficiency varies (30). Another issue is why do people gain weight. In fact, it is very difficult to determine the “primum movens” of weight gain and this question is not elucidated yet. The classical idea that increased intake and decreased energy expenditure are the causes of weight gain leading to obesity could be tempered by new findings on the possible induction of weight gain within the adipose tissue itself, in particular through a storage dysfunction (28).

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 technical imaging such as computed-tomography-scan (CT-scan) or magnetic resonance imaging (MRI).

However, as these techniques are expensive and not easily available, proxy measures such as **waist circumference (WC)** and **waist-to-hip ratio (WHR)**, are mainly used in clinical setting and epidemiological studies. WHR is WC divided by **hip circumference (HC)** and distinguishes fatness in the lower trunk from fatness in the upper trunk (31). WC and WHR are strongly correlated with total body fat (15) and reflect both total and regional fatness (14). 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 CT-scan, than WHR (32, 33). As WC is associated with body size, the use of WHR or **waist-to-height ratio (WHtR)**, principally used in research, can also be considered as markers of abdominal adiposity partly adjusted for body size. Distribution of body fat is an important variable when considering health risk. Indeed, many epidemiological studies have shown that abdominal obesity, particularly visceral fat, are risk factors for chronic diseases such as diabetes, cardio-vascular diseases or cancers (34), and WC, WHR and WHtR have been shown to be correlated with metabolic syndrome, cardiometabolic risk (35-38) and cancer risk, including breast cancer (2, 39).

2.6. 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 presented above have been used in studies on breast cancer risk but the mostly used are BMI, WC, WHR and weight gain (2). Among postmenopausal women, positive associations with breast cancer risk has been shown for BMI (convincing evidence), weight gain during adulthood, WC and WHR (probable evidence) (2). These associations are less consistent in premenopausal women in whom a protective effect of body fatness has been described (2). However, the underlying pathophysiological mechanisms are not understood 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 (3). For instance, in a cohort of women at high breast cancer risk in North America including 5,864 premenopausal women, Cecchini and colleagues found an increased risk of invasive breast cancer among premenopausal women within increasing categories of BMI (8), and a meta-analysis performed by Pierobon and Frankenfeld showed a clearly positive association between obesity (BMI >30 kg/m^2) and risk of triple-negative breast cancer status among premenopausal women (6). 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 or younger (7). Ethnicity is also a concern. In fact, in their meta-analysis, Amadou and colleagues showed that after stratification by ethnicity, BMI was statistically significantly inversely associated with breast cancer risk only among Africans and Caucasians premenopausal women but not among Asian premenopausal women in whom it was positively associated with breast cancer risk (5). With respect to body fat distribution, they showed that WHR, but not WC, was positively associated with breast cancer risk in premenopausal women, and that this association was stronger among Asian women (5).

Body fatness as well as body fat distribution seem to play an important role in breast cancer risk, particularly among postmenopausal women. Considering that fat is also a major component of the breast, what about its local role on 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 (40).

2.7. 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 x-ray more than adipose tissue and appears dark on a mammogram. On this basis, breast density can be assessed quantitatively or qualitatively. Nowadays, the quantitative assessment, usually computer-assisted, is the most frequently used in research. However qualitative methods with visual categorization are also performed, as for example the classification proposed by Wolfe in 1976 (41) and the Breast Imaging-Reporting and Data System (BI-RADS) (42). Quantitatively, three density features are mainly considered: the absolute dense area (mainly fibroglandular tissue), the absolute non-dense area (mainly adipose tissue) and the percent density that is the proportion of dense tissue on 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 been constantly shown to be strongly positively associated with breast cancer risk among premenopausal and postmenopausal women (13, 43-46). In a meta-analysis performed in 2006, McCormack and colleagues calculated that a breast density of ≥75% was associated with a four-fold relative risk of breast cancer when compared with a breast density <5% (47). **Absolute dense area** was also studied by many research groups and was found to be positively associated with breast cancer risk (13, 43-45). Some authors examined whether volumes measurements were better predictors of breast cancer risk and found very similar results overall (43, 48). However, the association between volumetric measures of breast density and breast cancer risk still needs confirmation.

Paradoxically, even if adiposity has been shown to be positively associated with breast cancer risk (2), several studies found a negative association (13, 49), although not all (50, 51), between adipose tissue in the breast, reflected by the absolute non-dense area, and breast cancer risk. It is only lately that **absolute non-dense area** has been considered in studies on breast cancer risk. Recently, Pettersson and colleagues had the opportunity to reanalyze the pooled data of 13 case-control studies from the DENSNP consortium collaborators, an international network of epidemiological studies on breast density and genetic variants, which include 1,776 case patients and 2,834 control participants (13). They found that absolute non-dense area was strongly 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. Similarly, in a case-control study nested in a cohort of 3,211 UK women with 111 cases of breast cancer, Torres-Mejia and colleagues found that absolute non-dense area was negatively associated with breast cancer risk in analyses adjusted for usual confounders including BMI and 10 years change in BMI (49). In a matched case-control study nested within cohorts recruited at screening mammography in UK and counting 634 cases, Stone and colleagues also found a negative association between absolute non-dense area and breast cancer risk, but this association was lost after adjusting for absolute dense area (51). Unfortunately, the analyses performed in the latter study could not be adjusted for usual confounders nor for BMI as these data were not available. On the other hand, in a case-control study nested in the EPIC cohort of Netherland counting 358 postmenopausal breast cancer cases, Lokate and colleagues found no association between absolute non-dense area and breast cancer risk in analyses adjusted for usual confounders including BMI, while a positive association was observed when they further adjusted for absolute dense area (50). 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 non-dense area. Actually, the medio-lateral-oblique projection used, is more likely to overestimate non-dense area due to the inclusion of some subcutaneous fat to the breast adipose tissue and the evaluated risk could be partly due to adiposity instead of breast non-dense area (52). A better understanding of the association between adiposity and breast density could help to better understand the relation between adiposity and breast cancer risk.

2.8. Adiposity and breast density features

Static measures of adiposity and breast density features

Contrary to the inconsistent results for the association between absolute non-dense area and breast cancer risk, studies on the association between **absolute non-dense area**, or volume, and adiposity have shown a constant positive association for: BMI (53-68), percent (54, 56, 61) or total body (65) fat, and WC or WHR (53, 54, 56, 65, 67). These results are not surprising as when adiposity is high it can be expected that breast fat is also high. However it strengthens the apparent paradox concerning the relation between breast cancer risk and adipose tissue depending on its localization. Indeed, absolute non-dense area, reflecting breast adipose tissue, and body fatness are positively associated with one another but they seem to have opposed associations with breast cancer risk.

Percent density, whether calculated with areas or volumes or estimated by subjective visual scales, has consistently shown to be negatively associated with measures of body fatness such as BMI (53-80), percent (54, 56, 61, 81) or total body (65) fat or estimated by somatotypes (82) and with measures of abdominal body fat distribution such as WC or WHR (53, 54, 56, 65, 67, 69, 71). Again, this is not surprising. Actually, as the absolute non-dense area is usually the main component of the breast among women included in mammographic studies, and as percent density is the proportion of dense area on the whole breast, including fat, percent density is expected to be negatively associated with absolute non-dense area and so, with adiposity. However, here again, as percent density and adiposity are both positively associated with breast cancer risk but are 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 studies have led to inconsistent results (53-62, 64, 66, 68, 70, 72, 73, 75-79). The observed discrepancies remain unexplained but could be due to important variations in the adjustments performed in the analyses and, to a certain extent, to differences in the population under study such as ethnicity or menopausal status and to technical issues in the acquisition of mammographic images. To illustrate the complexity of current knowledge, we propose to detail the association between absolute dense area and BMI according to variables included in the models. In unadjusted or adjusted at least for age analyses, studies have shown negative (55, 56, 58, 61, 64, 72, 73, 76), positive (53, 59, 70) or no association (57, 62, 75, 78). In analyses considering adjustment for usual potential confounders but not for any other variable that further characterize adiposity, studies have shown negative (54-56, 60, 66), positive (53) or no association (68, 75, 77, 79). 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 (among: WC, WHR), in the few remaining studies, the association was found to be positive (53, 59) or null (57).

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 (63, 66, 73, 76, 77, 80, 83) although not all (54, 65, 71). Since volumes measurements techniques are still on development and since results vary from one technique to another (48, 65), further studies are needed to evaluate the relation between adiposity, absolute dense volume and breast cancer risk. 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 (73). 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, due to the water content of the latter (48, 76). The associations evaluated with these kind of measures could be compared to analyses performed on area measures partly adjusted for non-dense area or for adiposity. This hypothesis is also illustrated in a recent analysis we achieved among 1435 premenopausal and postmenopausal Caucasian women recruited at screening mammography (67). We performed correlations between BMI, WC, WHR and absolute dense area and we found a negative correlation after adjustment for potential confounders but no other variables reflecting adiposity ($r= -0.21$; -0.23 and -0.19 respectively, $p<0.0001$). When we further adjusted for absolute non-dense area, i.e. when breast fat is considered, these three correlations switched from negative to positive ($r= 0.16$; 0.12 and 0.06 respectively, $p<0.025$) (67). To our knowledge, this is the only study in which the association between adiposity and absolute dense area was adjusted for absolute non-dense area.

Dynamic measures of adiposity and breast density features

The association between adult weight gain and breast density features has been seldom studied. In contrast to the negative association found with static measures of adiposity, adult weight gain was found to be positively associated with **percent density** in two studies (67, 69). First in a study among 3584 premenopausal and postmenopausal women recruited at screening mammography in Spain, in which Pollan and colleagues found a positive association in analyses adjusted for usual confounders including BMI and WHR (69). And secondly, 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 (67). Moreover, in this study, BMI variation was also positively associated with percent breast density. On the other hand, two studies found a negative association but without adjusting for current adiposity, thus this finding could be due to residual confounding: Samimi and colleagues, in a study among 1,398 premenopausal and postmenopausal US women from the Nurses' Health Study (82), and Tseng and Byrne, among 415 US Chinese premenopausal and perimenopausal women (53). However, in this latter study, the association was lost after adjustment for adiposity (BMI as residues and WC).

The association between weight gain during adulthood and **absolute dense or non-dense area** is poorly understood. To our knowledge, only two studies have assessed these associations: Tseng and Byrne evaluated it among premenopausal and perimenopausal Chinese women (53), and our group among premenopausal and postmenopausal Caucasian women (67). Regarding **absolute dense area**, the two studies showed a positive association with adult weight gain in models adjusted for adiposity as described above. Tseng and colleagues found a positive association especially in women with a BMI<23 kg/m2 (53) and so did we especially among women with a high non-dense area (67). In our study, BMI variation was also found to be positively associated with absolute dense area (67). With respect to **absolute non-dense area**, in contrast to what is observed for 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 (67). Meanwhile, in models that included BMI (residuals) and WC, Tseng and Byrne found no association between adult weight gain and absolute non-dense area among all women or by strata of BMI (53).

A few studies have examined the association between short term weight change and breast density features (54, 68, 70, 84, 85). However, the short follow-up period with very little variation in weight or BMI (54, 70, 84, 85), the changes in menopausal status during follow-up (68, 70, 85) and the intervention intended to lose weight performed for the purpose of the study (54, 84) are major limitations to consider them for comparison with studies on weight gain during adulthood and therefore, are not discussed here.

To summarize, it is not surprising that **static measures of adiposity** are positively associated with absolute non-dense area. Therefore, the negative association observed with percent density is expected. The association with absolute dense area or volume also seems positive but for area, it seems to depend on adjustments. Considering **adult weight gain**, when current adiposity is considered in the models, the association with percent density or absolute dense area seems positive, but for the latter it could be limited to some subgroups. The association with absolute non-dense area was seldom studied and is still controversial.

The association between static or dynamic measures of adiposity and breast density features is not elucidated yet and a number of questions are still open. However, dynamic measures of adiposity could better reflect what happens in term of risk. Indeed, associations evaluated in cross sectional studies do not address causation and cannot be simply interpreted as a risk. Furthermore, the dynamic measure reflects a long term exposure to a risk factor that is critical for cancer development. The apparent paradox regarding the role of fat tissue in breast cancer development, whereas considering fat in the whole body or in the breast is still unsolved. To complete this issue, we will discuss the role of fat tissue in carcinogenesis.

2.9. Role of adipose tissue in breast carcinogenesis

In the breast, histologically fibroglandular tissue (dense area) is mainly constituted by epithelial and stromal cells, and the adipose tissue (non-dense area) mainly of adipocytes. Fibroglandular tissue represents the population of breast cells at risk of carcinogenic transformation (86). Breast cancer generally arises in epithelial cells (87), and an increase in overall cellular mass is believed to increase the risk of breast cancer (88). However, breast adipose tissue, as part of the microenvironment surrounding the fibroglandular zone, seems to greatly influence the epithelial differentiation and proliferation by different mechanisms, not all elucidated yet (89). In particular, it has been shown to contribute to the development and progression of breast tumors in co-culture experiments and animal models (90). Moreover, fat tissue dysfunction is thought to generate local and peripheral chronic low-grade inflammation, sex hormones alterations and insulin resistance (9, 10, 91). Inflammation in breast adipose tissue is currently thought to play an important role in the development of breast tumor (92). Furthermore, body fat, by its aromatase activity, is an important source of endogen estrogens, known to promote breast tissue proliferation (93). 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 it is a reason of 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 non-dense area, were shown to present the highest aromatase immunoreactivity (94). It is likely that a large breast adipose tissue account for a non-negligible source of local endogen estrogen and therefore that a large amount of breast fat could be a risk factor for breast cancer. Although to our knowledge, only one study evaluated the association between adult weight gain and absolute dense area according to non-dense area, this hypothesis is nicely illustrated by the fact that weight gain was positively associated with absolute dense area especially if breast fat was present in a larger amount (67).

On the other hand, a potentially protective influence of breast fat has also been described. The ability of fat to store vitamin D, known to have a protective effect against breast cancer development, could partly explain the protective effect (11). Involution has also been suggested to play a role by the reduction of fibroglandular tissue in favor of adipose tissue (13). The protective effect of breast fat is plausible as when non-dense area increases, breast cancer risk seems to decrease (13), and when body weight increases during adulthood, breast fat has been shown to decrease or remain stable (53, 67).

2.10. Conclusion

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

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3. Gain de poids à l'âge adulte et paramètres de mesure de densité mammaire

L'article présenté ci-dessous est actuellement en évaluation pour publication dans la revue Cancer Causes & Control.

3.1. Titre et résumé en français

Titre : Gain de poids à l'âge adulte et paramètres de mesure de densité mammaire.

Introduction. La densité mammaire et l'obésité sont positivement associées au risque de cancer du sein. L'objectif de ce projet est d'évaluer l'association, peu étudiée, entre le gain de poids à l'âge adulte et les paramètres de mesures de densité mammaire auprès de 1435 femmes recrutées lors d'une mammographie de dépistage à Québec.

Méthodes. La corrélation entre les variables anthropométriques et les paramètres de mesure de la densité mammaire (pourcentage de densité et valeurs absolues des zones dense et non-dense) a été évaluée à l'aide de corrélations partielles de Spearman. Des modèles de régression linéaire multivariés ont été utilisés pour évaluer l'association entre le changement de poids à l'âge adulte, en catégories, et les paramètres de mesure de densité mammaire.

Résultats. Presque 80% des femmes ont pris >5kg durant leur âge adulte. L'indice de masse corporelle (IMC) est inversement corrélé avec le pourcentage de densité (r= -0.49, p<0.0001) et avec la zone dense (r= -0.21, p<0.0001) mais positivement corrélé avec la zone non-dense (r= 0.69, p<0.0001). Après ajustement pour la zone non-dense, l'IMC est cependant positivement associé avec la zone dense (r= 0.16, p<0.0001). Dans un modèle multivarié, incluant l'IMC et le rapport taille-hanche, le pourcentage de densité mammaire et la zone dense augmentent de manière linéaire avec les catégories croissantes de gain de poids ($p_{tendance}<0.0001$ et 0.025 respectivement) alors que la zone non-dense diminue ($p_{tendance}<0.0001$). Après stratification pour la médiane de la zone non-dense, l'association positive entre le gain de poids et la zone dense n'est maintenue que chez les femmes présentant une zone non-dense > médiane.

Conclusion. Nos résultats suggèrent une zone dense plus importante chez les femmes qui ont pris le plus de poids et qu'une quantité minimale de tissu adipeux mammaire pourrait être nécessaire pour promouvoir la prolifération du tissu fibroglandulaire.

3.2. Title and authors

Title: Adult weight gain and mammographic features

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3.3. Abstract and key words

Background. Breast density and obesity are both positively associated with breast cancer risk. However, the association between weight gain during adulthood and mammographic features remains unclear. Therefore, we aimed to evaluate this association among 1435 women recruited at screening mammography.

Methods. Spearman's partial coefficients were used to evaluate the correlation of anthropometric variables 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. Almost 80% of the women gained >5 kg during their adulthood. Body mass index (BMI) 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, BMI was positively correlated with absolute dense area when adjusting for absolute non-dense area (r= 0.16, p<0.0001). Within increasing categories of weight change, percent density ($p_{trend}<0.0001$) and absolute dense area ($p_{trend}=0.025$) increased while absolute non-dense area decreased ($p_{trend}<0.0001$). 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.

Conclusion. 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

3.4. Introduction

Overweight and obesity, respectively defined as a body mass index (BMI) between ≥25 and <30 kg/m^2 and a BMI ≥30 kg/m^2 [1], are global major public health issues. Worldwide, the prevalence of obesity and overweight among women has increased from 29.8% to 38.0% between 1980 and 2013 [2]. Among children, the highest rates are observed in developed countries where 22.6% of girls are considered overweight or obese and prevalence is increasing in developing countries [2]. This has major consequences, for overweight and obesity are associated with many chronic diseases [3, 4] and several cancers [5]. Particularly, body fatness and weight gain during adulthood are well-recognized risk factors for postmenopausal breast cancer development [6], but it is still unclear for premenopausal women [7-11].

Breast density is also a well-recognized breast cancer risk factor [12]. 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 ≥75% of their breast occupied by dense tissue compared with <5% have a more than four-fold relative risk of developing breast cancer [13]. Lately, scientists get 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 showed a positive association with breast cancer risk [14-18]. As of yet, results are less clear for the non-dense area. In a recent meta-analysis, Pettersson and colleagues found a strong inverse association between absolute non-dense area and breast cancer risk, independent of dense area [16]. This observation is supported by other studies [19, 20], although not all [21, 22].

BMI has been shown to be negatively associated with percent density [23-32] or absolute dense area [26-28, 31, 32], although not consistently for the latter [23, 29, 30], while positively associated with absolute non-dense area [23, 26-32]. Meanwhile, the association between weight gain during adulthood and breast density was seldom studied and led to inconsistent results [23-25]. Only one study, among Chinese women, evaluated the association between adult weight gain and absolute areas and observed a positive association for dense area and no association for non-dense area, when variables reflecting current adiposity were included in the models [23]. Further studies to understand this association could help to understand the pathophysiological mechanisms linking obesity to breast cancer risk. Therefore, we aimed to evaluate the association between weight change or BMI variation during adulthood and mammographic features among Caucasian women recruited at screening mammography.

3.5. Materials and Methods

Study population

Study design and methods were described elsewhere [33]. Briefly, 1574 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 [34]), not pregnant, to have no personal history of any cancer or breast surgery, no endocrine or hepatic disease, never used tamoxifen or raloxifene, and not used hormone medication in the past three months. Of the 1574 women recruited, 114 were excluded because of missing values for weight at the age of 18. Among the remaining 1460 women, 25 were excluded because of missing or aberrant 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 (±SD) age of 58.3 ±9.4 years 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-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 [35]) and dietary intake (semiquantitative food frequency questionnaire (97GP copyrighted at Harvard University [36])).

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 was measured using a soft tape midway between the lowest rib margin and the iliac crest in a standing position, while hip circumference was measured over the widest of the gluteal region. Next, BMI (kg/m^2) and waist-to-hip ratio (WHR; an indicator of central body fat distribution) 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, and BMI variation as BMI at mammography minus BMI at the age of 18.

Mammographic features were blindly assessed on batches of 100 digitalized mammograms (Kodak Lumiscan85 digitizer) of the randomly selected left or right craniocaudal view, by one trained reader (CD) using a computer-assisted thresholding program (Cumulus) [37]. The number of pixels in the identified dense area and total breast area were translated in cm2. Absolute non-dense area was calculated as total area minus absolute dense area, and percent density was calculated as dense area divided by total breast area. The reproducibility of the mammographic features determinations was very high, as shown by 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 the percent density, the absolute dense and non-dense areas, respectively.

Statistical analyses

Spearman correlation coefficients were used to evaluate the association between anthropometric variables (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/BMI variation 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/BMI variation. 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 kg; >15 to ≤25 kg; >25 to ≤35 kg; >35 kg). Likewise, BMI variation was also grouped in six categories: one decreased BMI (≥2 kg/m^2), one stable BMI (loss of <2 to gain of ≤2 kg/m^2) and four increased BMI (>2 to ≤6 kg/m^2; >6 to ≤10 kg/m^2; >10 to ≤14 kg/m^2; >14 kg/m^2). Tests for trends (p_{trend}) were based on the F test of the linear contrast of mammographic features across categories of weight change/BMI variation. 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 2-sided and a p-value <0.05 was considered statistically significant.

3.6. Results

Study population

Details of the population characteristics were previously presented [33]. 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 (±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 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 and mean BMI variation 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 areas (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).

Correlation between anthropometry and mammographic features

Spearman correlations between anthropometric variables 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. However, these anthropometric variables 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.

Association between weight change and mammographic features

Results of the multivariate linear models testing the relation of weight change or BMI variation with mammographic features are presented in the Figure 1 (a-f). 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_{trend}<0.0001, Figure 1a). Dense area also increased linearly from 28 to 39 cm^2 (p_{trend}=0.025, Figure 1b), while non-dense area decreased from 115 to 63 cm^2 (p_{trend}<0.0001, Figure 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_{trend}=0.93) but not the association between weight gain and absolute non-dense area (p_{trend}<0.0001). Similar results were observed for increasing categories of BMI variation with higher percent density (p_{trend}<0.0002, Figure 1d), higher absolute dense area although not statistically significant (p_{trend}=0.080, Figure 1e) and lower absolute non-dense area (p_{trend}<0.0001, Figure 1f). Further adjustments for the two absolute areas similarly led to a loss of the positive association between BMI variation and absolute dense area (p_{trend}=0.70) and a maintenance of the negative association between BMI variation and absolute non-dense area (p_{trend}<0.0001).

To gain knowledge on these associations, we stratified the population by the median of absolute non-dense (89.3 cm^2) or dense areas (30.3 cm^2) (Figure 2, a-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_{trend}=0.01, Figure 2c). However, this association was not present among women with an absolute non-dense area below the median (p_{trend}=0.43, Figure 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 ≥ median (p_{trend}=0.0001, Figure 2b and p_{trend}=0.007, Figure 2d respectively). Similar results were observed for BMI variation (data not shown).

3.7. Discussion

In our study population, 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. To date, few studies have examined the relation between adult weight gain and percent density [23-25] or dense area [23]. In line with our results, Pollan and colleagues reported a positive association between adult weight gain and percent density among 3584 premenopausal and postmenopausal women in Spain [24] while Tseng and Byrne found no association among 415 US Chinese premenopausal or perimenopausal women, when variables reflecting current adiposity were included in the model [23]. In the latter study, a positive association was observed between adult weight gain and dense area, particularly among women with low BMI [23]. Conversely, Samimi and colleagues found a negative association between adult weight gain and percent density among 1398 premenopausal and postmenopausal women selected in the Nurses' Health Study in the USA but their association was not adjusted for current body fatness [25]. In a two-years low fat diet intervention study among women with percent density >50%, Boyd and colleagues [38] 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 our: weight loss has the opposite effect as weight gain on dense area. The positive association between weight gain and percent density or dense area we observed in our study is 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 ≥ 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 [39, 40], however not all [41].

We found that weight gain during adulthood was negatively associated with absolute non-dense area. To our knowledge, Tseng and Byrne are the only authors to have assessed this association and found no association when variables reflecting current adiposity were included in the model [23]. As weight gain is a probable risk factor for breast cancer, according to our results, a lower non-dense area is expected to be associated with a higher breast cancer risk. Till date this remains a matter of debate although a protective effect of breast fatness seems to arise. In a recent meta-analysis performed within 19 studies taking part in the international DENSNP consortium (involving 10 countries in Europe, North America and Australia), Pettersson and colleagues found a strong inverse association between non-dense area and breast cancer risk, independent of dense area [16]. They had the opportunity to reanalyze all the data with similar adjustment so their results seem pretty robust, even if the included studies were selected from a closed consortium. The same authors had already found a similar inverse association in a nested case-control study published in 2011 [19]. Moreover, in a prospective study, Torres-Meija and colleagues found that women in the highest non-dense area quartile had lower hazard ratio for breast cancer compared to those in the lowest quartile, although the association was not statistically significant [20]. No adjustment for the dense area was tested in this study. Stone and colleagues also found, in a raw analysis, an inverse association that was lost once they adjusted for dense area [21]. This result should, however, be interpreted with caution since no adjustment for other potential confounders were performed. Lastly, Lokate and colleagues found a positive association between non-dense area and breast cancer risk in a nested case-control study of postmenopausal women [22]. Discussing the controversial results obtained for the association between non-dense area and breast cancer risk, Shepherd and Kerlikowske proposed that discrepancy across results could 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 breast cancer risk compared to those who used the craniocaudal views. The mediolateral projection is more likely 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 [42].

Our results 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 negatively associated with non-dense area, and therefore probably positively associated with breast cancer risk, but positively associated with the well-known risk indicator, dense area, only among women with high fat breasts. It seems that it is a matter of equilibrium between fibroglandular and adipose tissues. The mechanism by which non-dense area could be protective is not elucidated yet. Fat tissue is capable of storing vitamin D, known for its protective effect against breast cancer development [43]. On the other hand, breast adipose tissue has been shown to contribute to the development and progression of mammary tumors in co-culture experiments and animal models [44] and its dysfunction is believed to cause chronic low-grade inflammation, sex hormones alterations and insulin resistance [45, 46]. 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 and colleagues 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 [47]. 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 act on the fibroglandular tissue proliferation.

In our study, anthropometric variables reflecting body fatness (BMI, WHR and waist circumference) were negatively associated with percent density and dense area. These findings are consistent with the literature [23-32], although more conflicting results are reported for dense area [23, 26-32], 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 body fatness 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 the non-dense area, body fatness is positively associated with dense area. The strong positive correlation between body fatness and non-dense area we found is in line with the current scientific knowledge [23, 26-32] and did not reverse when controlling for dense area.

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 of 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 [48] this could have led to increase or decrease the association in these two subgroups respectively.

In conclusion, we found that weight gain during adulthood was positively associated with percent density, possibly meaning a higher breast cancer risk. 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.

3.8. Authors contributions and conflict of interest

Conception and design: C. Diorio, **Development of methodology**: C. Diorio, L. Soguel, **Acquisition of data**: C. Diorio, **Analysis and interpretation of data**: C. Diorio, L. Soguel, **Writing, review, and/or revision of the manuscript**: C. Diorio, L. Soguel, **Administrative, technical, or material support**: C. Diorio, **Study supervision**: C. Diorio.

The authors declare that they have no conflict of interest.

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3.11. Table 1

Table 1. Correlations of anthropometric variables 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	
	r [b]	*p* value	r [b]	*p* value	r [b]	*p* value	r [b]	*p* value	r [b]	*p* 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.

3.12. Figure 1

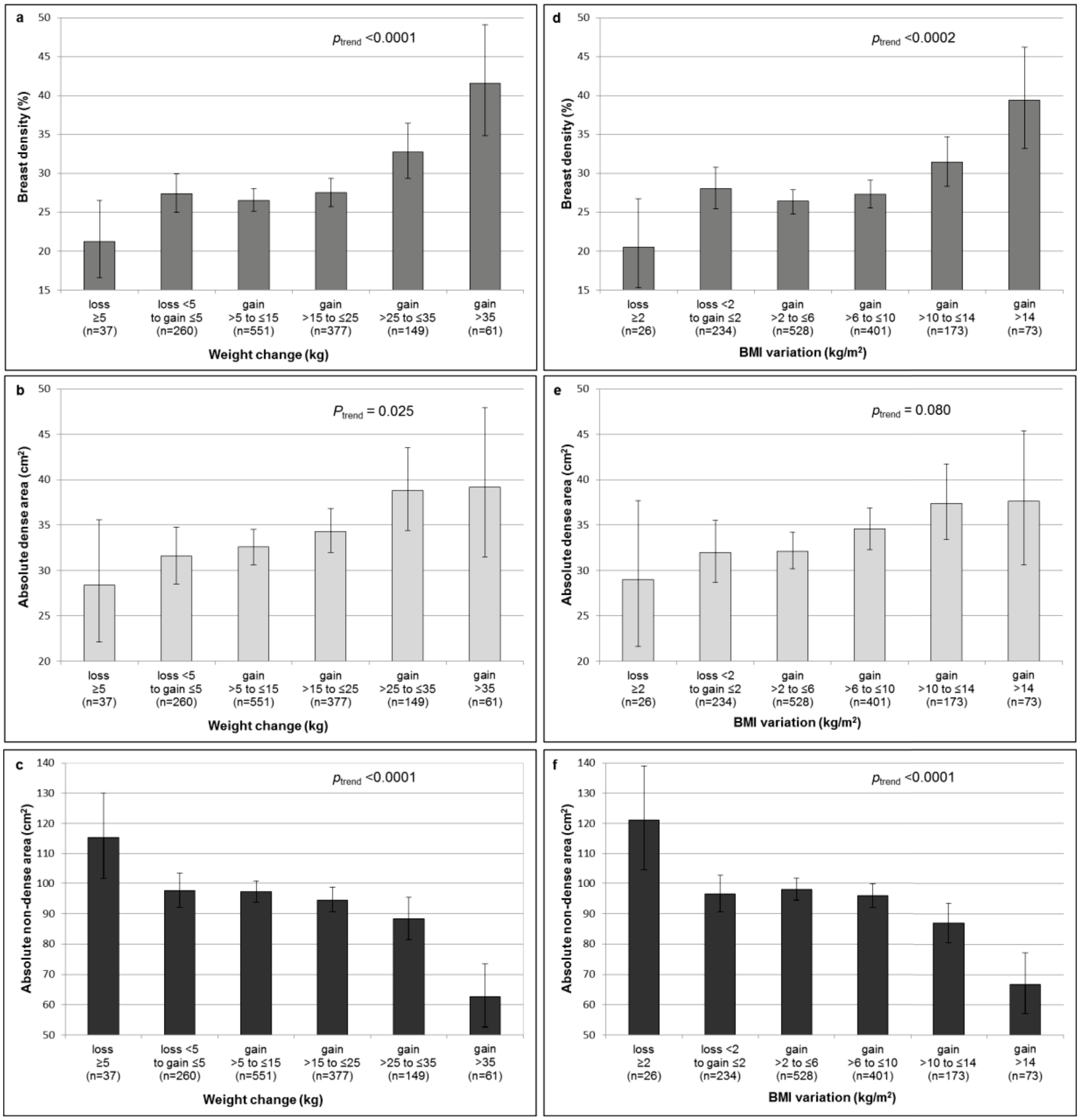

Figure 1. Associations between weight change (a-c) or body mass index (BMI) variation (d-f) and mammographic features.

Adjusted means and 95% confidence intervals of percent density (a, d), absolute dense area (b, e) and absolute non dense area (c, f). Multivariate generalized linear models adjusted for: age at mammography, menopausal status, BMI, 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.

3.13. Figure 2

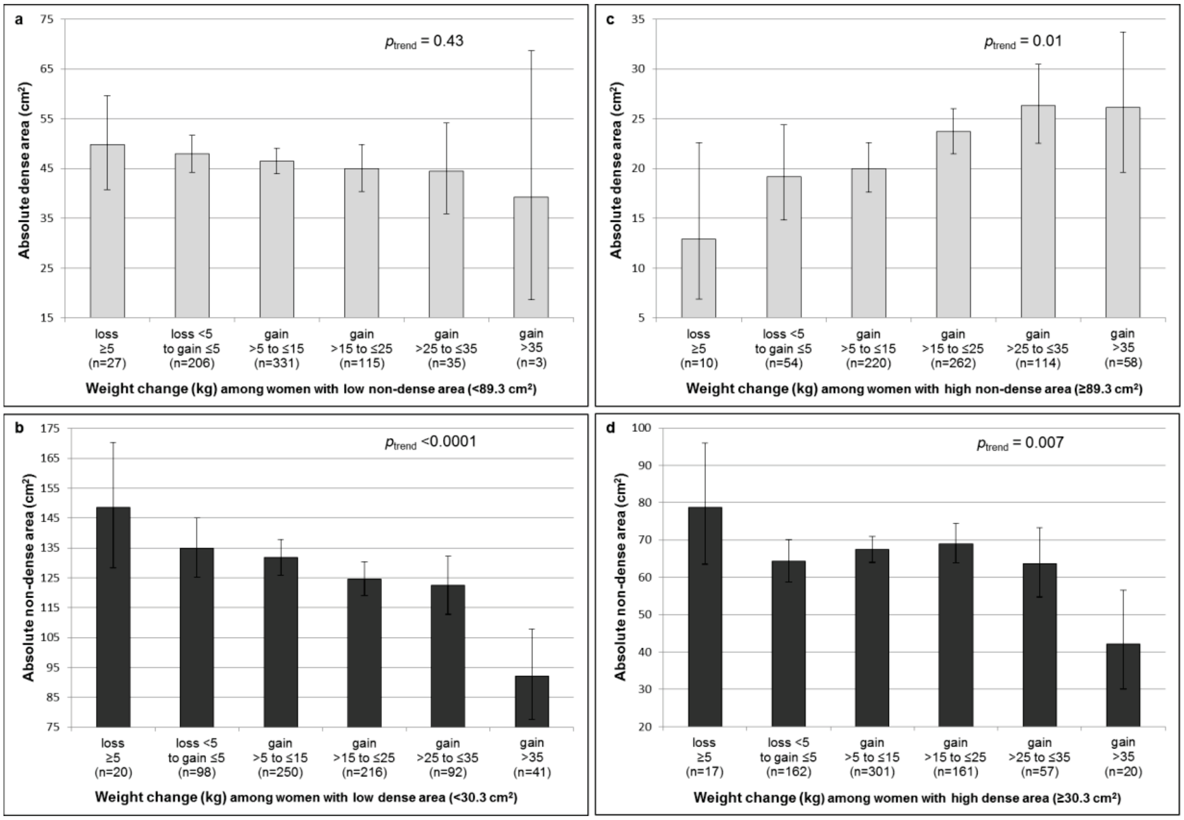

Figure 2. Associations between weight change and mammographic features, stratified by the median of absolute non-dense (a, c) or absolute dense area (b, d).

Adjusted means and 95% confidence intervals of absolute dense area (a, c) and absolute non dense area (b, d). Multivariate generalized linear models adjusted for: age at mammography, menopausal status, BMI, 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.

4. Discussion et conclusion

L'étude présentée au *chapitre 3* a permis de mettre en évidence une association linéaire positive entre le gain de poids à l'âge adulte et la densité mammaire, exprimée en pourcentage ou en valeur absolue. Après stratification de la population en fonction de la quantité de tissu adipeux présent dans le sein, l'association entre le gain de poids et la zone dense en valeur absolue ne restait vraie que pour les femmes ayant une zone non-dense égale ou supérieure à la médiane. Cette intéressante modification de l'effet du gain de poids en fonction de la quantité de gras mammaire suggère qu'une certaine quantité de tissu adipeux pourrait être nécessaire pour que le gain de poids stimule le développement de la zone dense dans laquelle se trouvent les cellules à risque de carcinogenèse. Ce résultat pourrait expliquer certaines incohérence dans les conclusions des études qui s'intéressent au rôle du tissu adipeux dans le sein et qui lui attribuent tantôt un rôle positif tantôt un rôle négatif (27, 30-33).

Cette étude a également permis de montrer que, lorsque l'on tient compte, en plus des facteurs de confusion habituels, de l'adiposité actuelle, plus le gain de poids est important, plus la zone non-dense est faible. A notre connaissance, c'est la première fois qu'une telle association est évaluée chez les femmes caucasiennes et elle mérite certainement d'être testée dans de futures études longitudinales prospectives. Si le tissu adipeux mammaire joue effectivement un rôle protecteur jusqu'à un certain niveau, la diminution de sa quantité avec le gain de poids pourrait faire partie des mécanismes d'augmentation du risque de cancer du sein observés avec le gain de poids à l'âge adulte.

L'importante variation des résultats mise en évidence dans l'article qui discute les interrelations entre l'adiposité, la densité mammaire et le risque du cancer du sein (*chapitre 2*), illustre extrêmement bien le défi que les chercheurs doivent relever lorsqu'ils s'intéressent à un phénomène complexe d'un point de vue épidémiologique. Les facteurs d'ajustements inclus dans le modèle et la manière dont les chercheurs ont modélisé l'effet de ces différents facteurs sur l'issue principale mais également sur les autres facteurs influencent grandement les résultats. Dans l'étude présentée au *chapitre 3*, l'importance de l'ajustement est très bien révélée dans les analyses de corrélation entre les mesures anthropométriques et les mesures de densité mammaires. En effet, la corrélation entre l'IMC et la zone dense en valeur absolue s'inverse si l'on tient compte de la zone non-dense en valeur absolue dans le modèle. Dans une étude évaluant l'association entre les mesures de densité mammaires, l'IMC et le risque de cancer du sein, Baglietto et collaborateurs ont très joliment montré que selon le schéma causal défini pour construire les modèles statistiques, la zone non-dense pouvait être inversement associée au risque de cancer du sein ou non-associée (71). Respectivement, dans le premier modèle causal, les tissus adipeux corporel et mammaire étaient tous deux considérés comme des causes de cancer du sein, agissant de manière indépendantes, et dans le second modèle, ils étaient tous deux considérés comme des représentants (proxy) d'un même facteur de risque, c'est-à-dire de l'adiposité.

Dans l'étude que nous avons menée, le risque de cancer du sein n'a pas été mesuré mais estimé, notamment au travers du pourcentage de densité mammaire, considéré comme un facteur intermédiaire reflétant très bien ce risque (22, 24). Le risque du cancer du sein semble également bien reflété par la zone dense en valeur absolue, même si les études sont moins nombreuses (25-29). Pour la zone non-dense par contre, les résultats sont moins clairs (27, 30-33) et nous ne pouvons donc pas formellement lier la diminution de tissu adipeux mammaire observée avec le gain de poids, à une augmentation du risque du cancer du sein. L'étude de la densité mammaire comme facteur de risque intermédiaire permet de gagner un temps précieux dans le recueil des données puisqu'il n'est pas nécessaire de suivre les femmes jusqu'au développement d'un cancer chez certaines d'entre elles. Néanmoins, ce type d'étude ne remplace pas les études de cohortes qui permettent l'évaluation plus directe de l'influence des facteurs d'intérêt sur le développement du cancer du sein.

Dans l'article présenté au *chapitre 2*, nous avons plaidé pour la réalisation d'études de cohortes avec un long suivi pour évaluer de manière prospective l'effet de l'histoire pondérale à l'âge adulte sur les différentes mesures de densité mammaire et sur le cancer du sein chez les femmes préménopausées et postménopausées séparément. L'étude séparée des femmes selon leur statut ménopausique a été proposée afin d'éviter la confusion entre l'effet du changement de poids et de la transition vers la ménopause sur la densité mammaire. Le suivi prospectif à long terme permettrait quant à lui de directement mesurer le risque de cancer du sein ainsi que d'éviter le risque de biais lié à l'auto-déclaration du poids à 18 ans. Ce biais a été discuté en détail dans l'article présenté au *chapitre 2*. On peut cependant encore dire quelques mots d'un autre aspect important lié aux études s'intéressant à l'histoire pondérale. Le choix des variables d'intérêt est extrêmement complexe et devra être pensé avec soin. En effet, si l'on s'intéresse aux études qui ont évalué le risque de cancer du sein, de nombreuses variables ont été utilisées pour représenter le gain de poids comme par exemple l'IMC ou le poids à différents âges, l'IMC maximal atteint, le changement de poids entre le début de l'âge adulte et le moment de la mesure d'intérêt, le changement de poids entre deux bornes de temps définies (65). De plus, en sus des variations liées à des facteurs environnementaux, comportementaux et de style de vie, le poids dans la vie d'une femme est également sujet à des variations biologiques liées aux grossesses. Faire état de l'histoire pondérale d'une vie à l'aide d'une seule variable est sans doute réducteur et des modèles plus complexes devraient probablement être pensés.

Le fait que le gain de poids à l'âge adulte semble être un facteur de risque du cancer du sein indépendant de l'IMC, est important pour la prévention, notamment chez les femmes en surpoids ou obèse. En effet, perdre du poids de manière durable est difficile et les interventions pour soutenir cette démarche sont complexes (72). Même si la perte de poids reste recommandée, l'objectif intermédiaire de ne pas prendre de poids supplémentaire, plus réaliste dans certaines situations, permettrait déjà de diminuer le risque de cancer du sein. C'est un important message dont les praticiens de premier recours et les gynécologues-obstétriciens qui voient les femmes régulièrement en consultation pourraient se faire écho. En valorisant le maintien du poids, ils pourraient ainsi véhiculer un message positif et favoriser l'estime de soi et la motivation, importants paramètres dans la prise en charge du surpoids et de l'obésité (73).

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Annexe 1 : stratégie de recherche PubMed

Stratégie de recherche retenue pour la base de données PubMed et résultats obtenus.

#1 Anthropometrie (anthropometry)

(anthropometry[tiab]) OR (anthropometry[MeSH Terms]) OR (adiposity[tiab]) OR (adiposity[MeSH Terms]) OR (body weight[MeSH Terms]) OR (weight loss[tiab]) OR (weight loss[MeSH Terms]) OR (weight gain[tiab]) OR (weight gain[MeSH Terms]) OR (body composition[tiab]) OR (body composition[MeSH Terms]) OR (body constitution[MeSH Terms]) OR (DEXA[tiab]) OR (bio-impedance[tiab]) OR (BIA[tiab]) OR (skinfold measurement*[tiab]) OR (skinfold thickness[tiab]) OR (skinfold thickness[MeSH Terms]) OR (waist circumference[tiab]) OR (waist circumference[MeSH Terms]) OR (hip circumference[tiab]) OR (waist hip ratio*[tiab]) OR (waist-hip ratio*[tiab]) OR (waist-hip ratio[MeSH Terms]) OR (BMI[tiab]) OR (body mass[tiab]) OR (Body mass index[MeSH Terms]) OR (obesity[tiab]) OR (obese[tiab]) OR (obesity[MeSH Terms]) OR (overweight[tiab]) OR (over-weight[tiab]) OR (over weight[tiab]) OR (overweight[MeSH Terms])

#2 Densité mammaire (breast density)

(((breast[MeSH Terms]) OR (breast[tiab])) AND ((absolute[tiab]) OR (dense[tiab]) OR (non-dense[tiab]) OR (nondense[tiab])) AND ((area[tiab]) OR (region[tiab]))) **OR** (((breast[MeSH Terms]) OR (breast[tiab])) AND ((density[tiab]) OR (densities[tiab]))) **OR** (((breast[MeSH Terms]) OR (breast[tiab])) AND (parenchymal[tiab]) AND ((pattern[tiab]) OR (patterns[tiab]))) **OR** (Mammographic Density[Supplementary Concept]) **OR** ((mammographic[tiab]) AND ((density[tiab]) OR (densities[tiab]))) OR (((mammographic[tiab]) **OR** (breast[MeSH Terms]) OR (breast[tiab])) AND ((tissues[MeSH Terms]) OR (tissues[tiab]) OR (tissue[tiab]))))

#3 Population humaine, exclusion des études animales (human studies)

NOT (animals[MeSH Terms]) NOT (humans[MeSH Terms])

Résultats de la stratégie de recherche testée dans PubMed le 9.02.2015.

#	Concepts	Nombre de références
#1	Adiposity	741942
#2	Breast density	66739
#3	Animals studies	3972537
#4	#1 AND #2	3683
#5	**#1 AND #2 NOT #3**	**3028**

Annexe 2 : caractéristiques des études, tableau de synthèse

Études sélectionnées pour la revue de littérature portant sur l'association entre adiposité et densité mammaire.

Author Year (ref) Country	Objective of the study	Type of study	Recruitment, Population	Menopausal status (or age)	N included	Mammogram and density features assessments	Breast density features considered	Current anthropometry measures considered (assessment)
Boyd1997 (1) Canada	to determine whether the adoption of a low-fat, high-carbohydrate diet for 2 years would reduce breast density	longitudinal	High-risk of breast cancer population (>50% breast density) included in a RCT (low fat, high carbohydrates diet)	pre (75%) post (25%)	817 (403 interven-tion, 414 control)	digitized CC computer assisted evaluation	PDA ADA TBA	**2-years weight change** (measured)
Boyd 1998 (2) Canada	to examine the association between body weight and percent breast density.	cross-sectional	Screening mammography: purpose sample with wide range of density	pre	273	digitized CC computer assisted evaluation	PDA ADA ANDA	**BMI** **body fat** (skinfolds) (measured)
Boyd 2006 (3) Canada	to examine the associations of body size and mammographic density on breast cancer risk.	cross-sectional	Screening mammography: cases (invasive breast cancer) and controls from 3 nested case-control studies	pre post (75%)	1,114 matched case-control pairs	digitized CC computer assisted evaluation	PDA ADA ANDA	**BMI** (self-reported)
Caire-Juvera 2008 (4) USA (Arizona)	to evaluate the associations of body composition, with mammographic density	cross-sectional	Mammography clinics or community health centers Hispanic (63%) and non-hispanic white women (37%)	pre (58%) post (42%)	238	digitized CC computer assisted evaluation	PDA ADA	**% body fat** (DXA) **% trunk fat** (DXA) (measured)
Dorgan 2012 (5) USA	to evaluate associations of height, adiposity and body fat distribution with percentage dense breast volume and absolute dense breast volume	cross-sectional	Young women with elevated LDL during childhood, included in a RCT (dietary intervention to reduce LDL-choloesterol)	pre	174	non-contrast MRI (Magnetic Resonance Imaging) for each breast	PDV ADV	**BMI** **Androïd/Gynoïd fat ratio** (DXA) **% body fat** (DXA) **WC** (measured)
Eng 2014	to evaluate estimation methods	cross-	Screening	pre/peri (13%)	685	FFDM	PDA	**BMI**

Author Year (ref) Country	Objective of the study	Type of study	Recruitment, Population	Menopausal status (or age)	N included	Mammogram and density features assessments	Breast density features considered	Current anthropometry measures considered (assessment)
(6) UK	of mammographic density for full-field digital mammography (FFDM)	sectional	mammography: controls from a case-control study Caucasian (77%) and other	post (87%)		CC and MLO computer assisted evaluation and fully-automated	ADA ANDA PDV ADV ANDV	(self-reported)
Gierach 2014 (7) USA (Vermont)	to explore the relation between volumetric and area measures of mammographic density with epidemiologic risk factors.	cross-sectional	Women referred for a diagnostic image-guided breast biopsy Non-hispanic white (92.7%)	pre (60.5%) post	413	digitized CC (breast without biopsy) computer assisted evaluation	PDA ADA PDV ADV	**BMI** (measured (98%) or self-reported (2%))
Guthrie 2007 (8) Australia (Melbourne)	to investigate hormonal and other factors associated with mammographic density during the menopausal transition and in postmenopause.	longitudinal (8 years follow-up)	Population based cohort Australian-born women aged 45-55 years	menopausal transition during follow-up	255 mammograms of 114 women	digitized CC computer assisted evaluation	PDA ADA ANDA	**BMI** **2-years BMI change** (measured)
Haars 2005 (9) Netherland	to determine which of the established determinants of relative measurements of density indeed influence the absolute amount of dense tissue	cross-sectional	Population based cohort	post	418	digitized CC computer assisted evaluation	PDA ADA ANDA	**BMI** (measured)
Harris 2011 (10) USA (NHS)	to investigate the association between body fatness during childhood and adolescence, BMI at age 18 years, BMI and breast cancer risk after adjustment for mammographic density. to examine whether there was an interaction between body size and mammographic density.	cross-sectional	Controls from breast cancer studies nested in the Nurses' Health Study (NHS and NHS)	pre	574	digitized CC computer assisted evaluation	PDA ADA ANDA	**BMI** (self-reported)
Heng 2004 (11) Singapore	to determine the demographic, menstrual, reproductive, and anthropometric factors that are associated with quantitative variations in percentage mammographic densities and to examine the association of these factors with the dense and non-dense areas.	cross-sectional	Screening mammography Chinese	pre post (62%)	803	digitized CC view computer assisted evaluation	PDA ADA ANDA	**BMI** (measured)
Irwin 2007	to investigate the association	cross-	Breast cancer patients	post	522	digitized CC	PDA	**BMI**

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(12) USA (New Mexico, California, Washington DC)	between physical activity, body mass index (BMI), and mammographic density	sectional	White (59%), Black (17%), Hispanic (14%)			computer assisted evaluation	ADA ANDA	(measured)
Jeffreys 2008 (13) UK (Glasgow)	to explore the use of the Standard Mammogram Form tool to investigate relationships between breast cancer risk factors and volumetric breast density.	cross-sectional	Glasgow Alumni Cohort	pre (24%) post (76%)	590	digitized MLO visual assignment of 6 area categories fully automated algorithm (volumes)	6 categories classification (0%; 1–10%; 11–24%; 25–49%; 50–74%; ≥75%) PDV ADV	**BMI** (self-reported)
Lokate 2010 (14) Netherland	to investigate whether volumetric density measurements on full-field digital mammography (FFDM) are more strongly related to breast cancer risk factors than measurements with a computer-assisted threshold method.	cross-sectional	Screening mammography	pre/peri (49.2%) post (50.8%)	370	digital, processed, medio-lateral left view computer assisted quantitative evaluation	PDA ADA PDV ADV	**BMI** (self-reported)
Maskarinec 2001 (15) Hawaii	to investigate ethnic differences in and determinants of mammographic densities	cross-sectional	Screening mammography Caucasian (35%), Chinese (14%), Filipino (5%), Japanese (30%), Native Hawaiian (12%)	pre (41%) post (59%)	514	digitized CC computer assisted evaluation	PDA ADA ANDA	**BMI** (self-reported)
McCormack 2007 (16) UK (London)	to compare a new and existing method of mammographic density measurement: intramethod reliability and associations with known risk factors	cross-sectional	Screening mammography	post (98%)	250	digitized CC and MLO computer assisted evaluation	PDA ADA PDV ADV	**BMI** (self-reported)
McCormack 2008 (17) UK (London)	to determine if the lower breast cancer incidence rates in first-generation South Asian and	cross-sectional	Screening mammography	pre post	5277 mammo-grams	digitized CC (28%) and MLO (72%)	PDA ADA	**BMI** (self-reported)

Author Year (ref) Country	Objective of the study	Type of study	Recruitment, Population	Menopausal status (or age)	N included	Mammogram and density features assessments	Breast density features considered	Current anthropometry measures considered (assessment)
	Afro-Caribbean women relative to Caucasian women in the United Kingdom are reflected in mammographic density		Caucasian (41% of women) Afro-Caribbean (33%), South Asian (26%)		from 645 women	computer assisted evaluation		
Nayeem 2014 (18) USA (Texas)	to compare the similarities among patterns of biological predictors of breast density measured by two breast images (MRI and mammography) and five breast density estimation methods	cross-sectional	Healthy women of all major races/ethnicities, living within 80 km of Galveston, Texas White (54%), Hispanic (30%), Black (16%)	pre	137	digital CC and MLO 2D methods: HSM, MATH, FFDM 3D methods: MRI-3DGRE, MRI-STIR.	PDA PDV ADV ANDV TBV	**BMI** **total body fat** (DXA) **WC** **HC** (measured)
Pollán 2012 (19) Spain	to analyze the influence of adult weight gain and fat distribution on mammographic density	cross-sectional	Screening mammography	pre (23%) post (77%)	3574	digitized CC Boyd's visual semi-quantitative classification	Boyd's classification: A (0%), B (<10%), C (10-25%), D (25-50%), E (50-75%), F (>75%)	**BMI** **WC** **HC** **WHtR** **WHR** (measures) **adult weight change** (self-reported)
Reeves 2009 (20)	to study the longitudinal relationships between anthropometry and breast density	longitudinal (8 years follow up)	Study of Women's Health Across the Nation (SWAN) cohort Caucasian (49%), Chinese (22%), Japanese (22%), African American (7%)	at enrollment: pre (58%) early peri (52%)	3746 mammo-grams from 834 women	CC manual evaluation (planimeter)	PDA ADA	**BMI** **1-year weight change** **1-year BMI change** (measured)
Samimi 2008 (21) USA	to examine the associations between current physical activity, childhood and adulthood body fatness, weight change since age 18 and mammographic density	cross-sectional	Nurses Health Study: controls of a case-control study on breast cancer.	pre post	1398	digitized CC computer assisted evaluation	PDA	**BMI** **adult body fatness** (somatotype) **adult weight change** (self-reported)

Author Year (ref) Country	Objective of the study	Type of study	Recruitment, Population	Menopausal status (or age)	N included	Mammogram and density features assessments	Breast density features considered	Current anthropometry measures considered (assessment)
Schetter 2014 (22) USA	to compare the correlation between percent breast density and absolute breast density with baseline demographics and dietary and physical activity variables	cross-sectional	Women with breast density >25%, enrolled in a clinical trial, measures at baseline Caucasian (97%), African (2%), Asian (2%)	post	169	FFDM CC fully-automated	PDV ADV ANDV	**BMI** (measured)
Stone 2009 (23) International	to compare the associations between breast cancer risk factors and the components of percent dense area, absolute dense area and absolute non-dense area, separately	cross-sectional	Women at high risk of breast cancer (at least twice the population), enrolled in the International Breast Cancer Intervention Study I trial, measures at baseline	pre (49%) peri (5%) post (46%)	799	MLO computer assisted evaluation	PDA ADA ANDA	**BMI** (not specified)
Sung 2010 (24) Korea	to examine the association and to explore the possible shared genetic factors influencing between body size measurements and measures of mammographic density	cross-sectional	Women members from the Healthy Twin study (twins and their first-degree adult family members) Korean	pre post (37%)	730 from 341 families (122 pairs monozygotic twins, 28 pairs dizygotic twins, 430 family members)	digital CC computer assisted evaluation	PDA ADA ANDA TBA	**BMI** **% body fat** (DXA) **WC** **WHR** (measured)
Tamimi 2005 (25) USA	to examine the relation between circulating sex hormones and mammographic density	cross-sectional	Nurses' Health Study	post	520	digitized CC computer assisted evaluation	PDA ADA	**BMI** (self-reported)

Author Year (ref) Country	Objective of the study	Type of study	Recruitment, Population	Menopausal status (or age)	N included	Mammogram and density features assessments	Breast density features considered	Current anthropometry measures considered (assessment)
Tehranifar 2011 (26) USA (Brooklin)	to investigate the associations between reproductive and menstrual risk factors for breast cancer and mammographic density	cross-sectional	Screening mammography African American (42%), African Caribbean (22%), White (22%), Hispanic Caribbean (9%), Hispanic non-Caribbean (3%), other (2%)	pre/peri (65%) post (35%)	200	digitized CC computer assisted evaluation	PDA ADA	**BMI** (self-reported)
Tseng 2011 (27) USA	to examine the associations of BMI, waist circumference and adult weight change with breast density	cross-sectional	Convenience sample through local community organizations US Chinese women (immigration ≤ 20y)	pre (68%) peri (31%) not specified (1%)	415	digitized (99%) or digital (1%) CC computer assisted evaluation	PDA ADA ANDA	**BMI** **WC** (measured) **adult weight change** (self-reported)
Ursin 2006 (28) Singapore	to examine the association between mammographic density and reproductive factors and soy intake	cross-sectional	two population-based cohort studies (Singapore Chinese Health Study, Singapore Breast Screening Project) Chinese	pre (14%) post (86%)	380	digitized CC and MLO computer assisted evaluation Tabar classification	PDA ADA Tabar classification (I-IV)	**BMI** (not specified)
Wanders 2015 (29) Netherland	to investigate how percent density, absolute dense area and absolute nondense area change over menopause and whether these changes differ between women who lose weight, maintain stable in weight or gain weight over menopause	longitudinal (follow-up 5 years)	Screening mammography, Prospect-EPIC study cohort	menopausal transition during follow-up	591	digitized MLO computer assisted evaluation	PDA ADA ANDA	**5-years percentage weight change** (self-reported)

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Warren 2007 (30) UK, Italy	to demonstrate the use of grid technology to produce a database of mammograms and supporting patient data, specifically using breast density as a biomarker of risk for breast cancer, for epidemiological purposes	cross-sectional	Screening mammography	pre post	1737	digitized CC and MLO fully-automated	PDV ADV ANDV TBV	**BMI** (measured)
Woolcott 2011 (31) Canada	to examine the association between adiposity and mammographic measures	cross-sectional and longitudinal	RCT (aerobic exercise intervention) Causcasian (90%)	post	302	digitized CC computer assisted evaluation	PDA ADA ANDA PDV ADV ANDV	**BMI** **total body fat** (DXA) **% body fat** (DXA) **WC** **total abdominal adipose tissue** (CT-scan) **subcutaneous abdominal adipose tissue** (CT-scan) **intra-abdominal adipose tissue** (CT-scan) **and 1-year change in all these variables** (measured)

Legends:

RCT: randomized control trial; PRE: premenopausal women; POST: postmenopausal women

CC: cranio-caudal mammographic view; MLO: medio-lateral oblique mammographic view; MRI: magnetic resonance imaging; FFDM: Full-field digital mammogram

BMI: body mass index; WC: waist circumference; HC: hip circumference; WHR: waist to hip ratio; WHtR: waist to height ratio

CT-scan: computerized tomography-scan; DXA: dual-energy X-ray absorptiometry

PDA: percent density area; ADA: absolute dense area; ANDA: absolute non-dense area; TBA: total breast area

PDV: percent density volume; ADV: absolute dense volume; ANDV: absolute non-dense volume; TBV: total breast volume

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