Submitted: 09 November, 2022 Accepted: 08 December, 2022 Published: 15 April, 2023 DOI:10.22514/ejgo.2023.016

SYSTEMATIC REVIEW

European Journal of Gynaecological Oncology

Age at first full-term pregnancy and mammographic breast density in postmenopausal women: a systematic review

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Abstract

While mammographic breast density (MBD) is a well-established independent risk factor for breast cancer and age at first full-term pregnancy (FFTP) has been identified as a protective factor, there are very few high-quality studies that address the relationship between these two variables. The goal of this work was to generate a systematic review of published studies that addresses the association between age at FFTP and MBD based on objective mammographic findings in postmenopausal women. The English-language literature published with a cutoff date 31 August 2022 in the PubMed, EMBASE, Scopus, Web of Science, and Cochrane Library databases was searched using relevant keywords. The Newcastle-Ottawa Quality Assessment Scale was used to assess the quality of all relevant studies identified in this search. Our search yielded 12 original publications (including one conference abstract) that focused on the impact of age at FFTP on MBD in studies that objectively evaluated this condition in women without any form of breast pathology. Of these, six studies revealed a direct association between older age at FFTP and higher MBD in postmenopausal women. The remaining six studies reported either no relationship between these parameters or revealed an inverse association between MBD and older age at FFTP. We concluded that half of the currently-published findings supported an association between older age at FFTP and higher MBD. However, substantial heterogeneity between FFTP and MBD might be explained by different racial clusters, lacking specific information of other reproductive factors and differences in methodology utilized. The goal of this work was to examine whether age at FFTP is associated with MBD in postmenopausal women.

Keywords

First full-term pregnancy; Menopause; Mammographic breast density; Breast cancer risk

1. Introduction

Breast cancer (BC) has been identified as the most common cancer in women worldwide and the second leading cause of cancer-related mortality in the United States and Western Europe. The incidence rate of BC is currently increasing [1, 2]. More than two million women were diagnosed with BC in 2020 which led to 685,000 deaths. By the end of 2020, the five-year prevalence of BC rose to 7.8 million women. At this time, BC became the most prevalent cancer across the globe [3, 4].

The biological and molecular mechanisms associated with age at first full-term pregnancy (FFTP) and the contributions of these factors to protection against BC include the activation of genes that control chromatin remodeling [5, 6]. An FFTP that occurs at or before 25 years of age reduces a woman's lifetime risk of developing BC by as much as 38% to 50%. This risk is further reduced in 7% increments by each subsequent pregnancy [1, 7–11]. By contrast, women who experience an FFTP after the age of 30 are at an increased risk for developing BC [1, 8, 12].

Mammographic breast density (MBD) is determined based on the percentage of dense tissue, (*i.e.*, adipose, epithelial, and/or stromal tissue) detected on a mammogram of an entire breast [2]. MBD is frequently evaluated by subjective visual assessment [13]. The categorization system used most frequently to assess MBD is the Breast Imaging Reporting and Data System (BI-RADS) [2, 14]. BI-RADS classifies MBD into one of four categories: (1) the breast is entirely fatty (<25% of dense tissue); (2) scattered fibroglandular densities can be detected within the breast (25–50% dense tissue); (3) the breast density is heterogeneous (50–75% dense tissue); or (4) the breast is very dense overall (>75% dense tissue) [14–19].

Several fully-automated methods have recently been introduced that provide objective assessments of MBD [20]. Automated methods that objectively assess breast density have been utilized with increasing frequency largely due to the

introduction of digitizing film-screen mammography (FSM) and full-field digital mammography (FFDM). Among these methods are area-based Cumulus and volumetric techniques, for example, VOLPARA (VolparaDataManager®, Version 1.0, Volpara Solutions Limited, Rochester, NY, USA). New algorithms introduced by computational methods such as VOLPARA facilitate non-subjective BI-RADS-based determinations of MBD [12, 21].

Various risk factors have been established for BC. Early menarche, increased height and weight, obesity (in postmenopausal women), late FFTP, nulliparity, older age at menopause, advanced age, and use of hormonal replacement therapy (HRT) are all significant risk factors for this disease [19, 22]. MBD was first identified as a risk factor for BC in 1976 by Wolfe [23]. His description of the relationship between dense breasts and a higher risk of developing BC was confirmed in numerous subsequent studies [13, 16, 18, 19, 24–33]. Two extensive meta-analyses concluded that increased breast density was associated with an increased overall relative risk of BC in all women [34, 35].

The relationship between breast density and the risk of developing BC has been attributed to nutrition, lifestyle factors, and environmental exposures (*i.e.*, air quality, including inhalation of particulate materials and other pollutants) [36–38]. Results from other studies suggest that higher breast densities may be associated with more aggressive tumors [39–41]. Of note, MBD decreases after a woman reaches menopause. For example, while a mean breast density of 38% was determined for women between the ages of 40–44 years, this percentage is reduced by 18–20% in women at 55–59 years of age [42]. Postmenopause is defined as the time after which a woman has experienced 12 consecutive months without menstruation [43]. To date, the relationship between age at FFTP and objective measurements of MBD after menopause has received little attention [39, 40]. Therefore, this review aims to analyze the association between age at FFTP and MBD in postmenopausal women.

2. Materials and methods

2.1 Research aims

We performed a systematic review of published studies that address the relationship between age at FFTP and MBD using objective mammographic methods. To be included in this review, at least 10% of the study population must be described as postmenopausal. Considering the limitations of visual density assessment, we focused on studies that provided quantitative measures of MBD.

2.2 Search strategy

This systematic review article was undertaken in accordance with PRISMA Guidelines [44]. Two independent research librarians performed independent searches using the search terms listed in Table 1 and a cutoff date 31 August 2022. Both librarians searched the English-language literature included in PubMed, Scopus, Web of Science, EMBASE, Scopus, and Cochrane Library databases. The two searches resulted in identical sets of 125 studies (Fig. 1).

2.3 Selection criteria

Studies were identified as eligible for the literature review if they included original data focused on an association between age at FFTP and MBD and included objective determinations of percent and volumetric breast density in postmenopausal women. Most of the studies included in this systematic review included both premenopausal and postmenopausal women, due to lack of studies in only postmenopausal women.

2.4 Quality assessment

The quality of the data and the risk of bias in each publication were critically evaluated by two reviewers. Quality assessments were performed using the Newcastle-Ottawa Quality Assessment Scale which has been validated for observational studies [45]. This scale includes eight items designed to assess patient selection, study comparability, and outcomes (for cohort and cross-sectional studies) or exposures (for cohort studies) with a total of nine points. Scores for each outcome were rated as follows: low quality, $\leq$5; medium quality, 6–7; and high quality, 8–9.

3. Results

3.1 Search results

Our database search using the search terms listed in Table 1 yielded 125 potentially relevant references. Twenty-one duplicate publications were excluded. An additional 46 studies were excluded after a review of the abstracts. Based on the inclusion criteria established for this systematic review, we excluded another 46 studies because (1) they included premenopausal women only, (2) they provided only subjective measures of MBD, (3) they referred to age at FFTP as a risk factor but did not examine its association with MBD in postmenopausal women, or (4) no English-language version of the article was available. Of note, we found no review articles that addressed age at FFTP together with objective measurements of MBD in postmenopausal women. After the exclusion of the aforementioned publications, we identified 12 studies that could be included in our systematic review. Additional details regarding our search strategy are illustrated in the flowchart in Fig. 1. The studies included in this systematic review are summarized in Table 2.

3.2 Quality assessment

We used the Newcastle-Ottawa Quality Assessment Scale to evaluate the quality of papers included in this review. Four of the papers (including one abstract) received scores of 8. Six and two papers received scores of 7 and 6, respectively. The details of these scores are shown in Table 3.

TABLE 1. Search terms (keywords) used to explore PubMed, Scopus, Web of Science, EMBASE, and Cochrane Library databases. Within a column, the operator "OR" was used. Between columns, we used the operator "AND".

Terms used to identify studies of FFTP and Pregnancy	Terms used to identify studies of age at FFTP	Terms used to identify studies of Breast Density	Mammographic Techniques	Terms used to identify studies of Breast Cancer
FFTP	Maternal age	Mammographic density	VOLPARA	Breast cancer
First pregnancy	Age at first birth	Mammographic breast density	BI-RADS	Breast neoplasms
Primigravid	Age menarche	Mammogram	BI-RADS	Breast tumor
Term birth	Age menopause	Dense breast volume	CAD	Breast tumour
Nulliparous	Age first breastfeeding	Breast/anatomy & histology	FFDM	
Childbearing	Onset of menses	Breast parenchyma	Film screened	
		Glandular tissue		
		Fibroglandular tissue		

BI-RADS, Breast Imaging Reporting and Data System; CAD, Computer-Aided Detection; FFDM, Full-Field Digital Mammography; FFTP, First Full-Term Pregnancy; VOLPARA, VolparaDataManager®, USA.

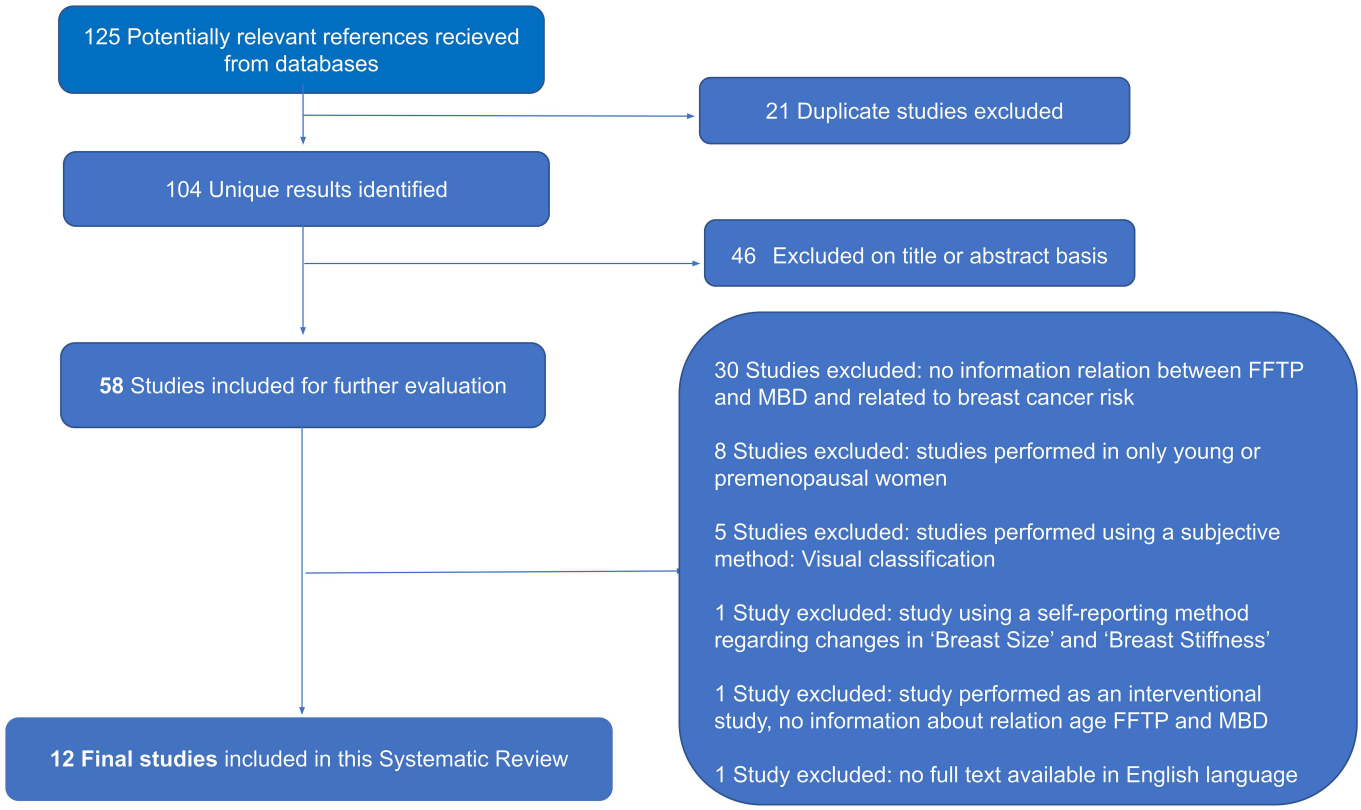

FIGURE 1. Flowchart documenting the method used to identify studies that were included in this systematic review. FFTP, first full-term pregnancy; MBD, mammographic breast density.

TABLE 2. Overview of 12 studies included in this review that describe the relationship between age at FFTP and MBD in postmenopausal women.

Author (yr, Country)	Study design	No. of cases	Age (yr)	Reproductive status	MBD measurement	Study Findings
Case-Control Studies						
Heusinger *et al.* [46] (2011, Germany)	Case-Control	1545 Pre-: 450 (29.1%) Post-: 1095 (70.9%)	46.9–68.7	Pre- and Post-menopausal	Computer-assisted thresholding method, "Madena" software	MBD increased with older age at FFTP Average MBD was positively associated with age at FFTP and inversely associated with BMI, age, and parity [42].
Sung *et al.* [47] (2011, Korea)	Case-Control	244 Pre-: 217 (88.9%) Post-: 27 (11.1%)	29.0–73.0	Pre- and Post-menopausal	Computer-assisted thresholding method, "Cumulus" software	MBD decreased with older age at FFTP Percent breast density (area) was inversely associated with age at FFTP and the number of children, although the associations were only marginally significant after adjustment for BMI [43].
Yaghjyan *et al.* [48] (2016, USA)	Case-Control	4110 Pre-: 1860 (45.3%) Post-: 2250 (54.7%)	30.0–84.0	Pre- and Post-menopausal	Full-field digital mammogram (FFDM), "Cumulus" software	MBD increased with older age at FFTP Percent breast density was positively associated with age at FFTP, while the number of children was inversely associated with percent breast density [44].
Rice *et al.* [25] (2018, USA)	Case-Control	12,274 Pre-: 4297 (35.1%) Post-: 7977 (64.9%)	40.8–70.8	Pre- and Post-menopausal	Computer-assisted thresholding method, "Cumulus" and "UCSF" software	No significant associations between age at FFTP and MBD BMI and the number of live births among parous women were inversely associated with the percent MD. Nulliparity, age at menarche, prior breast biopsy, and current use of postmenopausal HRT were positively associated with percent MD [23].
Cohort Studies						
Rice *et al.* [49] (2013, Mexico)	Cohort	1531 Pre-: 972 (63.5%) Post-: 959 (36.5%)	≥35.0	Pre- and Post-menopausal	Computer-assisted thresholding method, "Mamgr" software	MBD increased by early adult body fatness (*i.e.*, before FFTP and ages 25–35) A modest positive association was observed between body fatness (adipose tissue) immediately before the FFTP and between the ages of 25 and 35 years after adjustment for current BMI [45].
Rice *et al.* [37] (2015, Mexico)	Cohort	1607 Pre-: 1007 (62.7%) Post-: 600 (37.3%)	≥35.0	Pre- and Post-menopausal	Computer-assisted thresholding method, "Mamgr" software	Age at FFTP was not significantly associated with MBD Age at FFTP, age at menarche, and the number of births were not associated with MBD. Age, current BMI, BMI at age 18 years, and weight change since age 18 years were inversely associated with percent breast density [34].

TABLE 2. Continued.

Author (yr, Country)	Study design	No. of cases	Age (yr)	Reproductive status	MBD measurement	Study Findings
Alexeeff *et al.* [26] (2019, USA)	Cohort	24,840 Pre-: 4835 (19.5%) Post-: 20,005 (80.5%)	40.0–74.0	Pre- and Post-menopausal	FFDM and FSM, "Cumulus" software	Older age at FFTP associated with higher MBD Older age at FFTP was associated with higher MBD. Women who first gave birth at age 40 years or more were estimated to have 2.4% higher PD and 3.3 cm^2 higher DA than women who first gave birth before age 20 years. Nulliparity was associated with increased MBD. Both PD and DA decreased as the number of children increased. Older age at menarche was associated with higher PD [24].
Moran *et al.* [29] (2019, Canada)	Cohort	156 Pre-: 97 (62.2%) Post-: 59 (37.8%)	27.0–68.0	Pre- and Post-menopausal	Computer-assisted thresholding method, "Cumulus" software	No significant association between age at FFTP and MBD Women with two or more live births displayed higher adjusted mean non-dense areas compared with women who had one live birth. No other significant associations were observed between the reproductive and hormonal exposures [27].
Cross-Sectional Studies						
Mariapun *et al.* [50] (2015, Asia)	Cross-Sectional	542 Pre-: 228 (42.1%) Post-: 314 (57.9%)	40.0–74.0	Pre- and Post-menopausal	Fully-automated thresholding method, "Cumulus" software	MBD increased with older age at FFTP Percent density decreased with BMI, parity status, earlier age at FFTP, multiple 12-month breastfeeding cycles, and postmenopausal status [46].
Prebil *et al.* [51] (2014, USA)	Cross-Sectional	2440 Pre-: 940 (38.5%) Post-: 1500 (61.5%)	≤45.0 >65.0	Pre- and Post-menopausal	Full-field digital mammogram (FFDM), "Single-energy X-ray absorptiometry" (SXA) software	MBD reduced later in life among women with PIH during FFTP PIH was associated with a decrease in MBD. Breastfeeding was associated with an increase in MBD [47].
Hjerkind *et al.* [52] (2018, Norway)	Cross-Sectional	46,234 Pre-: 12,252 (26,5%) Post-: 33,982 (73.5%)	49.0–71.0	Pre- and Post-menopausal	Full-field digital mammogram (FFDM), "VOLPARA" software	MBD increased with older age at FFTP Percent and absolute VMD increased with age at menarche, age at FFTP, age at menopause, and increasing educational level. Both percent and absolute VMD decreased with an increasing number of pregnancies [48].

TABLE 2. Continued.

Author (yr, Country)	Study design	No. of cases	Age (yr)	Reproductive status	MBD measurement	Study Findings
Vandeloo *et al*. [53] (2021, Belgium)	Cross-Sectional	1034 Post-: 1034 (100%)	50.0–69.0	Postmenopausal	Full-field digital mammogram (FFDM), "VOLPARA" software	MBD (GLAND, VBD, and BI-RADS) is significantly increased with older age at FFTP MBD is significantly increased in women with an FFTP at >25.7 years of age. Older age at menarche was associated with increased MBD. The use of oral contraceptives was associated with reduced MBD at menopause [49].

BI-RADS, Breast Imaging-Reporting and Data System; BMI, Body Mass Index; DA, Dense Area; FSM, Film-Screen Mammography; FFDM, Full-Field Digital Mammography; FFTP, First Full-Term Pregnancy; GLAND, Glandular Tissue; HRT, Hormone Replacement Therapy; MBD, Mammographic Breast Density; MD, Mammographic Density; PD, Percent Density; PIH, Pregnancy Induced Hypertension; SXA, Single-energy X-ray Absorptiometry; UCSF, University of California, San Francisco; VBD, Volumetric Breast Density; VMD, Volumetric Mammographic Density; VOLPARA, VolparaDataManager®, USA.

TABLE 3. Quality of the publications included in this systematic review based on results from the Newcastle-Ottawa quality assessment scale.

Author/yr	Study design	Selection (score)	Comparability (score)	Exposure (score)	Outcome (score)	Total (score)
Heusinger *et al.* [46] (2011)	Case-Control	4	1	2	N/A	7
Sung *et al*. [47] (2011)	Case-Control	4	1	2	N/A	7
Yaghjyan *et al*. [48] (2016)	Case-Control	4	2	2	N/A	8
Rice *et al*. [25] (2018)	Case-Control	3	1	2	N/A	6
Rice *et al.* [49] (2013)	Cohort	3	1	N/A	3	7
Rice *et al.* [37] (2015)	Cohort	3	1	N/A	3	7
Alexeeff *et al.* [26] (2019)	Cohort	4	2	N/A	2	8
Moran *et al.* [29] (2019)	Cohort	3	0	N/A	3	6
Mariapun *et al*. [50] (2015)	Cross-Sectional	4	1	N/A	2	7
Prebil *et al.* [51] (2014)	Cross-Sectional	4	1	N/A	2	7
Hjerkind *et al.* [52] (2018)	Cross-Sectional	4	1	N/A	3	8
Vandeloo *et al.* [53] (2021)	Cross-Sectional	4	1	N/A	3	8

The quality of each study included in this review is represented by the total points.
Aggregate scores greater than five points indicate high quality.
N/A: not applicable.

Of the 12 studies included in this systematic review, 11 evaluated outcomes in both premenopausal and postmenopausal women; only one study focused on postmenopausal women alone. Seven of the 12 studies were performed in North America (USA, Canada and Mexico); three of the studies were performed in Europe, and two in Asia. Regarding study design, four were case-control, four were cohort, and four were cross-sectional studies. Various mammographic density measurement techniques were used. In Table 2, these studies are grouped by study design followed by the mammographic density measurement technique used.

3.3 Mammographic density measurement techniques

The findings shown in Table 2 document the variety of mammographic density measurements used in the studies included in this review. Computer-assisted density methods were used in all 12 studies evaluated [25, 26, 29, 37, 46–54]. Three of the 12 studies used Cumulus software (Canto Software, Inc, San Francisco, CA, USA) to evaluate full-field digital mammogram (FFDM) images [26, 48, 50]; by contrast, two of the studies used area-based approaches (*i.e.*, semi-automated Cumulus and fully-automated ImageJ-based approaches) [25, 47] and two used fully-automated volumetric methods, including VOLPARA [52, 53] and Single-energy X-ray absorptiometry (SXA) Version 6.5 (CIRS Inc., Norfolk, VA, USA) [51]. SXA is a valid alternative to VOLPARA, Cumulus, Quantra, and ImageJ-based methods, as well as BI-RADS [51, 55]. A computer-assisted thresholding method was used in four of the studies [29, 37, 46, 49]. Heusinger *et al*. [46] evaluated their findings using Madena X software version X (Eye Physics, LLC, Los Alamitos, CA, USA). Mamgr® software (London School of Hygiene and Tropical Medicine, London, United Kingdom) was used in two studies [37, 49]. Moran *et al*. [29] performed their analyses using Cumulus software (University of Toronto, Toronto, Canada)

3.4 Relationship between age at first full term pregnancy and mammographic breast density

3.4.1 Positive associations: older age at FFTP is associated with higher MBD

Heusinger *et al*. [46] conducted a case-control study of 1545 women in Germany, including 29.1% who were premenopausal and 70.9% who were postmenopausal (Table 2). In this study, 1025 of the women were BC patients (31.5% premenopausal and 68.5% postmenopausal) and 520 were healthy controls (25.1% premenopausal and 74.9% postmenopausal). The authors reported significantly increased MBD in women diagnosed with BC compared to healthy controls (38% versus 32%, $p < 0.01$). In both groups (BC and controls), the average MBD was inversely associated with age ($p < 0.0001$ and $p < 0.001$, respectively) and body mass index (BMI) ($p < 0.001$ and $p < 0.001$, respectively). Parity and younger age at FFTP were both associated with decreased MBD ($p < 0.01$ and $p = 0.04$, respectively) [46].

Yaghjyan *et al*. [48] evaluated 4110 cancer-free women in a nested case-control study using the Nurses' Health Study and Nurses' Health Study II cohorts in the United States. In this study group, 45.3% of the women were premenopausal and 54.7% were postmenopausal (Table 2). Correlations of

MBD and reproductive factors related to childbearing and menopausal status were evaluated. The researchers concluded that in postmenopausal parous women, older age at FFTP was positively correlated with percent density ($\beta = 0.03$, 95% confidence interval (CI) 0.01; 0.05) and inversely associated with the non-dense area ($\beta = -0.10$, 95% CI −0.13; −0.06). Of note, the positive association of the age at FFTP with percent density and its inverse correlation with the non-dense breast area were both limited to postmenopausal women. Also, in this same group of parous women, having more children was positively associated with lower percent density ($\beta = -0.07$, 95% CI −0.12; −0.02) and smaller absolute values of dense areas ($\beta = -0.14$, 95% CI −0.21; −0.06) and non-dense areas ($\beta = -0.10$, 95% CI −0.20; −0.01). The authors of this study concluded that women who were younger at their FFTP and had more children exhibited more favorable patterns of breast density; this might explain the subsequent reduction in BC risk [48].

Alexeeff *et al.* [26] compared the results of full-field digital mammography (FFDM) with those from previous studies that used traditional film-screen mammography (FSM). The study cohort included 24,840 non-Hispanic white women of whom 19.5% were premenopausal and 80.5% were postmenopausal (Table 2). The authors reported that reproductive factors, including age at FFTP, menopausal status, parity, and age at menarche were all statistically significantly associated with MBD. Nulliparity was associated with increased breast density; both percent breast density (PD) and dense area (DA) measurements decreased as the number of children increased. Older age at first birth was associated with increased MBD; women who first gave birth at age 40 years or more were estimated to have 2.4% higher PD and 3.3 cm^2 higher DA than women who gave birth for the first time before 20 years of age [26].

Mariapun *et al.* [50] conducted a cross-sectional study that included 542 premenopausal and postmenopausal women. MBD was estimated and differences across various ethnic groups were examined in randomly-selected Chinese (n = 205), Malay (n = 138), and Indian (n = 199) women; 42.1% of the women in this cohort were premenopausal and 57.9% were postmenopausal (Table 2). The authors of this study reported that percent breast density decreased with increasing parity ($\beta = -4.31$; $p = 0.001$), younger age at FFTP ($\beta = 0.20$; $p = 0.041$); BMI ($\beta = -1.40$; $p < 0.001$), and postmenopausal status ($\beta = -5.80$; $p < 0.001$) [50].

A cross-sectional study performed by Hjerkind *et al.* [52] included 46,428 women (ages 49–71 years) who participated in "Breast Screen Norway" between 2007 and 2014 for whom information on volumetric mammographic density (VMD) and BC risk factors was available; 26.5% of these women were premenopausal and 73.5% were postmenopausal (Table 2). Means of percent and absolute VMD that were associated with age, menopausal status, BMI, and other factors were estimated. The results of this analysis revealed increases in the percent and absolute VMD with older age at first birth ($p < 0.0001$), older age at menarche ($p < 0.0001$), increasing age at menopause ($p < 0.0001$), and higher educational level ($p < 0.0001$). Both percent and absolute VMD decreased with an increasing number of pregnancies ($p < 0.0001$) [52].

Vandeloo *et al.* [53] conducted a cross-sectional study in Belgium (Table 2) that included 1034 postmenopausal women who participated in the Flemish population-based BC screening program. The authors reported a direct correlation between age at FFTP and MBD. Specifically, the results of their analysis revealed that a younger age at FFTP was associated with reduced MBD at menopause. Among women who were >25.7 years of age at FFTP, each additional year was associated with a 1.3% increase in glandular tissue (GLAND) (95% CI 0.0%; 2.5%) and a 1.5% increase in VBD (95% CI 0.2%; 2.8%). Analysis using BI-RADS provided similar results. Specifically, the odds of moving to a higher BI-RADS classification (*e.g.*, from class 1 to class 2) increased by 5.4% (95% CI, 0.0%; 11.0%) for each year increase in age at FFTP greater than 25.7 years. Older age at menarche was associated with an increase and the use of oral contraceptives in a decrease in MBD at postmenopause [53].

3.4.2 Negative associations: older age at FFTP is associated with lower MBD

Sung *et al.* [47] evaluated 122 pairs of monozygotic female twins in a co-twin control study performed in Korea. Of the 244 women evaluated in this study, 88.9% were premenopausal and only 11.1% were postmenopausal (Table 2). The authors found that MBD decreased with older age at FFTP and a larger number of children and that the absolute dense area was positively associated with the duration of breastfeeding (BF). By contrast, age at menarche was not associated with any mammographic measures. These results suggest that MBD may mediate (at least in part) some of the protective effects of a greater number of childbirths against BC. However, age at FFTP, age at menarche, and duration of BF do not alter the risk of BC via their impact on MBD [47].

3.4.3 No association between age at FFTP and MBD

Rice *et al.* [25] conducted a case-control study that included 12,274 women; 35.1% were premenopausal and 64.9% were postmenopausal (Table 2). This study cohort included 3392 women who were BC patients of whom 32.6% were premenopausal and 67.4% were postmenopausal, and 8882 healthy controls (35.9% premenopausal and 64.1% postmenopausal). The authors concluded that, among postmenopausal women, MBD mediated the positive correlation between older age at FFTP and invasive as well as estrogen-receptor-positive (ER+) BC (16% mediated, $p \leq 0.05$). MBD partially influenced the correlations between nulliparity, age at FFTP, and use of hormonal therapy with the risk of BC. Taken together, these findings suggest that these factors may influence the risk of BC via induction of changes in breast tissue composition [25].

A Mexican Teachers' Cohort study published by Rice *et al.* [37] included 1607 Mexican women, of whom 62.7% were premenopausal and 37.3% were postmenopausal (Table 2). The authors collected information on any history of benign breast disease, 12 months or more of BF, and reproductive history. The researchers reported no significant associations between either parity or age at FFTP and MBD [37].

Moran *et al.* [29] examined the relationship between re-

productive, hormonal, and lifestyle factors and MBD among women with a strong family history of BC who did not carry BRCA1 or BRCA2 mutations. This cohort study included 156 women (62.2% premenopausal and 37.8% postmenopausal). The authors reported no significant association between MBD and age at FFTP. Importantly, they also reported that, among parous postmenopausal women (n = 46), women who had two or more children had higher adjusted mean non-dense areas of 143.0 cm^2 and 146.4 cm^2, respectively, compared to adjusted mean non-dense areas of 95.1 cm^2 among women who had one live birth (both $p = 0.04$) [29].

3.4.4 Other associations between age at FFTP and MBD

Rice *et al*. [49] evaluated 1531 Mexican women who participated in the Mexican Teachers' Cohort study, including 63.5% who were premenopausal and 36.5% who were postmenopausal. Analysis of the latter group revealed a modest positive association between body fatness immediately before FFTP and between the ages 25 and 35 years after adjustment for current BMI, with differences of 4.9 and 3.6 percentage points in MBD, respectively, comparing the heaviest and the leanest women (p-trend = 0.02) [49].

Finally, a cross-sectional study published by Prebil *et al*. [51] enrolled 2440 parous women (38.5% premenopausal and 61.5% postmenopausal) who were diagnosed with hypertension during pregnancy. The authors identified a relationship between pregnancy-induced hypertension (PIH) and percent fibroglandular volume (%FGV). Using multivariate linear regression, significant associations were found between %FGV and parity ($F = 6.66$; $p < 0.001$), age at FFTP ($F = 55.37$; $p < 0.001$), and duration of BF ($F = 37.72$; $p < 0.001$). Interestingly the authors found that a diagnosis of PIH was associated with a decreased %FGV later in life, most notably in women who were over age 30 years at FFTP [51].

4. Discussion

4.1 Summary of main findings

To the best of our knowledge, this review is one of the first to investigate associations between age at FFTP and objective measurements of MBD in postmenopausal women. In six of 12 studies included in this review, the authors reported a positive association between older age at FFTP and higher MBD [26, 46, 48, 50, 52–54]. By contrast, three of the 12 studies reported no association [25, 29, 37], and one study identified decreases in MBD with older age at FFTP [47]. We also identified two studies in which the relationship between age at FFTP and MBD was affected either by early adult body fatness [49] or pregnancy-induced hypertension (PIH) [51]. Thus, the 12 studies included in this systematic review report contradictory conclusions regarding the relationship between FFTP and MBD in postmenopausal women without breast disease.

4.2 Analysis of studies

There was substantial heterogeneity between the studies included in this review. The data collected from the original studies revealed differences in population size, ethnicity, mammographic techniques, and software utilized. Results from these studies suggest that ethnicity may be a confounding factor in this analysis; this issue definitely warrants further research. Other differences among the studies include the reporting of reproductive factors. Some of the studies collected information on BF or age at menarche, while others did not. Furthermore, we recognize that women who are younger at the time of FFTP are likely to have more children and to breastfeed compared with women who were older at FFTP and have only one or two children. BMI clearly increases with the number of pregnancies; this factor is also known to be associated with lower MBD. Other important variables may affect the association between the age of FFTP and MBD. Further research will be needed to determine their overall impact. In addition to the factors already discussed, objective measurements of density introduce important variations with respect to the conclusions that can be reached regarding the relationship between age at FFTP and MBD in postmenopausal women.

Computer-assisted software that can be used to determine breast density in mammography was introduced in the 1990s. Since that time, several computer-assisted tools have been approved for clinical use [56]. However, the interpretation of these images and the results of the software-based analysis remains challenging [57, 58]. The techniques used to measure MBD have evolved over the past 11 years from subjective methods (*i.e.*, visual assessments of mammograms by trained professionals) to computer-assisted methods that use raw data from digital mammography images to evaluate breast density [59].

In this systematic review, we excluded studies that assessed MBD by subjective methods [18, 38, 60–62] (Fig. 1). However, 10 of the 12 studies evaluated in this systematic review did not report which categorization methods were used. Different measurement methods for MBD were used in the various papers. For example, several featured measurements of absolute dense and non-dense areas or presenting findings as percent dense areas. By contrast, Prebil *et al*. [51] presented MBD as percent fibroglandular volume (%FGV) [51]. Likewise, Hjerkind *et al*. [52] used both percent and absolute VMD to measure mammographic density [52]. Further, Caglayan *et al*. [63] concluded that a longer duration of menopause (uninterrupted, smoother gradual) and high progesterone levels were found to cause an increase in breast density [63].

With the introduction of digital mammography, more appropriate MBD measurements were developed [55]. While digital mammography has been used successfully to diagnose intraepithelial neoplasia, there are no studies that feature this technique for primary BC prevention [64, 65]. Results from a study by Vandeloo *et al*. [53] revealed that the three variables contributing to MBD (GLAND, VBD, and BI-RADS) were significantly reduced in women who become pregnant at a younger age [53, 54]. According to the work of the Russo's [66, 67] the pattern of differentiation and involution of the breast that determine MBD and therefore an increased risk of developing BC at menopause are closely related to one another [66, 67].

Reproductive history is consistently and reliably associated

with the risk of developing BC [68]. Epidemiological data worldwide have shown consistently that FFTP at a younger age is associated with a reduction in the risk of developing BC in postmenopausal women [69, 70]; by contrast, late pregnancy and nulliparity are associated with an increased risk [8]. Several mechanisms have been postulated to explain the phenomenon of pregnancy-induced protection [71, 72]. The most plausible explanation has been attributed to the differentiation of the breast [66, 67] in response to the complex hormonal milieu generated by the placenta and the fetus [73]. These developmental events induce morphological, functional, genomic, and transcriptomic changes that may ultimately result in a permanent and specific profile associated with reduced cancer risk [66, 74–77]. These changes may also result in a reduction in MBD in postmenopausal women. Interestingly, insulin-like growth factor 1 (IGF-1) was found to be down-regulated in the parous breast [5, 78]. This observation is consistent with reports of lower levels of IGF-1 in parous compared with nulliparous women [79], thereby supporting the association of this factor with increased BC risk and also increased MBD [79, 80]. The down-regulation of IGF-1 in the parous breast, in association with the significant down-regulation of other related genes, may represent a significant driving force in the reduction of the risk of developing BC conferred by pregnancy. Interestingly, these events might be visualized with appropriate techniques used to measure MBD [77, 81].

This review has several limitations. First, we identified only a few studies that specifically addressed the role of age at FFTP in MBD in postmenopausal women. Most published studies included both premenopausal and postmenopausal women. In addition, the number of cases per study varied widely. It was also difficult to compare results from these publications because of the substantial diversity in the racial and ethnic composition of the study populations. Several studies were themselves limited by poor collection of data on the participants' reproductive histories. Additionally, we were unable to reach a uniform conclusion because MBD results were collected using different methodologies and software analyses. Finally, we were unable to perform a meta-analysis because of the significant cross-study heterogeneity.

5. Conclusions

In this review, we examined the relationship between age at FFTP and objectively-measured MBD in postmenopausal women. Although recent literature provides us with insight into the biological and molecular basis of FFTP and the mechanisms underlying protection against BC, very few studies have investigated whether early FFTP might be associated with lower MBD in postmenopausal women. As part of this systematic review, which covered 11 years of published literature, we found only six (of 12) original studies that reported an association between older age at FFTP and higher MBD. However, due to differences among the study conditions, no conclusions can be drawn regarding the links between age at FFTP, MBD, and BC risk.

ABBREVIATIONS

BC, Breast Cancer; BF, Breast Feeding; BI-RADS, Breast Imaging-Reporting and Data System; BMI, Body Mass Index; BRCA1, BReast CAncer gene 1; BRCA2, BReast CAncer gene 2; CAD, Computer-Aided Detection; CI, Confidence Interval; DA, Dense Area; FGV, Fibroglandular Volume; FSM, Film-Screen Mammography; FFDM, Full-Field Digital Mammography; FFTP, First Full-Term Pregnancy; GLAND, Glandular Tissue; HRT, Hormone Replacement Therapy; IGF-1, Insulin-like Growth Factor 1; MBD, Mammographic Breast Density; MD, Mammographic Density; PD, Percent Density; PDA, Percent Dense Area; PIH, Pregnancy Induced Hypertension; SXA, Single-energy X-ray Absorptiometry; UCSF, University of California, San Francisco; VBD, Volumetric Breast Density; VMD, Volumetric Mammographic Density; VOLPARA, VolparaDataManager®, USA; WHO, World Health Organization.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

MJV, EK, TSN and CVO—conceptualized the current review. MJV—analyzed the data and results obtained from the literature search and elaborated on the conclusions of the manuscript; drafted and finalized the manuscript. CYF and KYN—provided comments and suggestions to the principal author. Each author provided a critical review of the manuscript during the drafting phase. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

The authors thank Beth Lewis, Director of the Talbot Research Library, and Shawn Woodson, Research Librarian of the Talbot Research Library at the Fox Chase Cancer Center (FCCC) for providing us with access to the library resources. We also provide special mention to Paris Grimaldi and Seamus P. Steele, pre-graduate students of Drexel University and interns in the Co-op program of the Breast Cancer Research Laboratory (BCRL) at the FCCC (Philadelphia, USA), for their help with the bibliographic search. We also acknowledge Jose Russo, Director of the BCRL for providing logistic support in conducting this work.

FUNDING

This research was funded by the Breast Cancer Organization "Think Pink" of Belgium; and Fox Chase Cancer Center (FCCC), Philadelphia, USA, NCI Grant U54 CA221705 and

NIH Grant CA06927.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Magda J. Vandeloo, Eliane Kellen, Carolyn Y. Fang, Kristof Y. Neven, Tim S. Nawrot, Chantal Van Ongeval. Age at first full-term pregnancy and mammographic breast density in postmenopausal women: a systematic review. European Journal of Gynaecological Oncology. 2023; 44(2): 1-13. doi: 10.22514/ejgo.2023.016.