REVIEW ARTICLE
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Family history of breast cancer and risk of benign breast diseases: an integrative literature review

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ABSTRACT

Introduction: Some benign breast diseases (BBD) can determine an increased risk of developing breast cancer. Environmental factors related to lifestyle and family history of breast cancer may be associated with BBD development. However, the effect of family history of breast cancer on the risk of benign breast diseases is still unclear. **Objective:** To evaluate the association between family history of breast cancer and benign breast diseases. **Methods:** This is an integrative review that selected observational studies in different databases to analyze the association between BBD and family history of breast cancer, considering the different classification criteria for both benign diseases and family history. All studies were published between 1977 and 2016. A total of 13 studies were selected, among which ten are case-control and case-cohort studies; and three are cohort studies. Most studies received high or moderate quality classification according to the Newcastle-Ottawa assessment scale. **Results:** Family history of breast cancer was associated with the development of proliferative lesions and the presence of atypia, and it was more closely related to the development of benign diseases in young women, with a tendency to decrease with advancing age. **Conclusion:** Studies suggest there may be an association between family history of breast cancer and benign breast diseases; nevertheless, no statistically significant results were found in many case-control studies, and more robust prospective research is necessary to further clarify this association.

KEYWORDS: breast diseases; fibrocystic breast disease; breast neoplasms.

INTRODUCTION

Benign Breast Diseases (BBD) represent a public health issue insofar as they are classified as one of the main risk factors for breast cancer[1] and correspond to one to two million diagnoses of breast biopsies in the United States of America per year[2,3]. BBD encompass a wide range of histological changes[4,5], which attribute variable risk of breast cancer to women[6] and can be classified as nonproliferative, proliferative without atypia, and proliferative with atypia (atypical hyperplasia)[7].

Studies have shown an increase in the risk of breast cancer of 1.45 to 1.9 times higher in women with proliferative lesions without atypia compared with women with nonproliferative lesions, and 3.75 to 5.3 times higher in women with atypical hyperplasia[7-10]. In addition to increasing the risk of breast cancer, certain benign diseases have been associated with the development of both multifocal tumors[11], which are lesions that have a worse prognosis, and of hormone receptor-positive breast cancer, the most incident in the female population[12,13].

Although the process of mammary carcinogenesis is not fully understood, studies support the development of breast cancer in which atypia represents a nonobligate precursor of low-grade ductal carcinoma *in situ* and of invasive carcinoma[14,15]. Still in the 1970s, Wellings et al.[16] described the evolution of some benign diseases, in which hyperplastic epithelial cells of the breast would slowly increase the terminal duct lobular units, progressing to atypical ductal hyperplasia, ductal carcinoma *in situ,* and invasive carcinoma, successively.

Therefore, epidemiological studies on the etiology of benign breast diseases have, in general, evaluated the same risk factors established for breast cancer. Similar to what has been observed regarding invasive lesions, studies show that environmental and lifestyle-related factors, such as diet, alcohol consumption, physical inactivity, and the use of hormone replacement therapy, may be linked to the development of benign lesions[17-21].

Considering that family history of breast cancer is one of the most significant risk factors for the development of

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invasive carcinoma[1], it has also been investigated in the etiology of benign lesions[21-23]. Family history of breast cancer comprises both the effect of the genetic load[24] and environmental exposures[1]. In addition to genetic inheritance, people from the same family nucleus tend to share the same exposures[25], including eating and living habits, exposures to carcinogens at home, such as endocrine disruptors present in household cleaning products[26,27], access to diagnostic and screening services, knowledge of the disease, among others[28]. In this sense, knowledge of the etiology of benign breast diseases and the identification of women at greater risk of developing them could have important implications for preventing breast cancer in high-risk groups through screening and, when indicated, chemoprevention and prophylactic surgery[29].

Although there are literature reviews about the epidemiological factors associated with the development of benign lesions, including family history of cancer, none of them considered the different classification criteria used for family history, and neither the various histological types. The reviews found so far were carried out more than ten years ago and identified risk factors for specific lesions, such as fibrocystic lesions, fibroadenomas, and some lesions with degrees of atypia[30], as well as benign proliferative epithelial disorders[31].

Therefore, the present review aimed to evaluate the effect of family history of breast cancer on the risk of developing benign breast diseases, considering all histological types of BBD and the different criteria for classifying family history.

METHODS

Study design

This is an integrative literature review that sought to answer the following question: do women with family history of breast cancer have a higher risk of developing benign breast diseases than those without family history of breast cancer?

The study was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020156687).

Selection criteria

A search was carried out for observational studies of the types cohort, case-control, and cross-sectional, which assessed the role of family history of breast cancer in women of any age group diagnosed with benign breast diseases. The population of the selected studies consisted of women with diagnostic confirmation of BBD by breast biopsy or breast cytology. Studies published in English, Spanish, and Portuguese languages were eligible for this study. For the selection of articles, there was no restriction on the date of publication of the study. The assessed outcome was any type of BBD. The exposure of interest consisted of family history of breast cancer. For studies that did not present risk estimates, but reported the values necessary to calculate them, the authors of the present review carried out the analyses and reported the estimated risk. The risk estimates extracted from studies included the relative risk, the odds ratio, the hazard ratio, and the prevalence odds ratio.

Research strategy and information sources

An electronic search was conducted in the following databases: PubMed (Medical Literature Analysis and Retrieval System – MEDLINE), Scopus, Google Scholar, and Virtual Health Library (VHL). In addition, aiming at finding all sources for the review, studies in gray literature and in the references of the selected articles were searched. For articles selected in the PubMed database, the terms *benign breast disease OR nonproliferative breast disease* OR *proliferative breast disease* OR *proliferative breast disease without atypia* OR *proliferative breast disease with atypia* OR *benign proliferative epithelial disorders* AND *family history* and its variants were used.

In the first search, 514 articles were identified. After evaluating the titles and abstracts, 26 articles were selected as potentially eligible. In the Scopus database, the search for titles, abstracts, or descriptors using the same terms and search engine resulted in 290 documents. After reviewing the documents, 16 articles were identified with potential for inclusion (Figure 1).

Regarding Google Scholar, the search with the same terms used in PubMed and Scopus generated 12,100 results. Considering the *benign breast disease and family history of breast cancer* terms, 6,080 articles were found. Thus, the search was limited to the title of the articles, and the result showed 23 publications, all selected as potentially eligible. The search for the terms *benign proliferative breast disease and family history of breast cancer*, using the limit option "exact expression anywhere in the article," found 272 results, of which 21 were selected. Regarding the term *benign proliferative epithelial disorders and family history of breast cancer*, 107 results were found, 11 of which were potentially eligible. Finally, 55 potentially eligible articles on Google Scholar were identified.

In the VHL regional portal, the following terms were used for advanced search limited by title, abstract, or subject: *benign breast disease and family history of breast cancer*; *benign proliferative breast disease and family history of breast cancer*; *benign proliferative epithelial disorders and family history of breast cancer*, which resulted in 653, 46, and three publications, respectively. Of this total, 18 were selected as potentially eligible.

Study selection and data extraction

The process of identification and selection of articles followed the recommendations described in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram[32]. First, articles were selected based on their title/abstract, and duplicate articles were excluded.

The second step of the evaluation was based on the content of the articles, which were selected according to the inclusion criteria. For overlapping studies, only the one with the largest number of individuals in the sample was selected. One of the authors of the present study performed the data extraction, and the second author reviewed the gathered information with the aid of a spreadsheet for data extraction. In cases in which there were doubts about the extracted information, the authors made a joint assessment until reaching a consensus.

The authors extracted information on the date of publication of the study, research design, study population (criteria for defining cases and controls), frequency of family history of cancer in the study population (for case-control studies), cumulative risk (for cohort studies), and risk estimates, according to the criteria used in each study (BBD histological characteristic, age, menopausal status, and family history of breast cancer).

The Newcastle-Ottawa scale[33] was used to assess the methodological quality of the included studies. This scale is composed of three categories (selection, comparability, and outcome) and scores up to nine points (stars). It can be applied to cohort and case-control studies and classifies them as high quality (7 to 9 stars), moderate quality (5 to 6 stars), or low quality (0 to 4 stars).

The studies were grouped according to the methodological design into two categories:

- case-control, nested case-control, and case-cohort studies (Chart 1);
- cohort studies (Chart 2).

No cross-sectional study was found within the search period.

RESULTS

Identification of studies

A total of 47 studies were identified in the electronic databases. 14 articles were excluded after the initial screening based on title/abstract. After content evaluation, 13 articles that met the selection criteria were included. Figure 1 summarizes the selection of the included studies.

Study characteristics

Among the 13 included studies, seven were carried out on North American populations; one of Central America; two of South America; one of Oceania; and two of Asia, corresponding to three cohort studies, eight case-control studies, one nested case-control study, and one case-cohort study. The studies were published between 1977 and 2016 and used different criteria for classifying family history of breast cancer. In total, four studies evaluated the family history of breast cancer in first-degree relatives[22,23,34,35] and four others in relatives with any degree of consanguinity[18,36-38]. Hardy et al.[39] and Berkey et al.[21] evaluated the history of the mother, sister, aunt, cousin, and grandmother. The other studies analyzed the family history of breast cancer in the mother and/or sister[40-42]. A summary of the characteristics of each study is presented in Charts 1 and 2.

Assessment of the quality of studies

According to the classification of the Newcastle-Ottawa scale, among the three cohort studies included, Hislop and Elwood[41] and Webb et al.[22] received 6 stars, and were considered studies of moderate quality. The study conducted by Berkey et al.[21] received 4 stars and was considered a study of low methodological quality. The studies were carried out on specific populations, thus not representing the general population. In the cohort study conducted by Berkey et al.[21], the outcome was assessed using a self-administered questionnaire, and it was not possible to guarantee that the outcome was not present at the beginning of the study. Among the case-control, nested case-control, and case-cohort studies, the observed methodological quality was moderate and high (≥6 stars). A total of 60% of the studies did not report whether nonresponse frequency was the same for cases and controls[35-39,42]. Information on the quality assessment of each study can be found in Chart 3.

Only two studies aimed to specifically assess the association between BBD and family history of breast cancer[21,22], and three other studies evaluated several risk factors, including family history of the disease[36,40-42]. The other studies focused on reproductive factors and/or diet[18,23,34,37,39]; composition of fatty acids and breast adipose tissue[38]; and on serum levels of insulin, estradiol, C-reactive protein, and adiponectin[35].

Case-control and case-cohort studies

Among the case-control studies that evaluated the family history of breast cancer in any relative (general), two observed positive associations, with a magnitude of association ranging between 1.1 and 2 ($p>0.05$); however, the results were not statistically significant[18,36]. Conversely, two other studies found a statistically significant difference between the group of women with BBD and the control group concerning the presence of a family history of breast cancer in any relative ($p<0.01$)[37,38].

Among the studies that evaluated the association between family history of breast cancer in first-degree relatives and BBD[23,34,35], there was a positive association ranging from 1.17 (95% confidence interval – 95%CI 0.92–1.48) to 1.97 (95%CI 0.93–4.16), although without statistical significance. Furthermore, Wu et al.[23] observed that the association was strongly positive among women diagnosed with nonproliferative lesions (odds ratio – $OR_{adjusted\ for\ age} = 3.8$; 95%CI 0.9–16.8); proliferative lesion ($OR_{adjusted\ for\ age} = 2.8$; 95%CI 0.6–13.6); and atypical lesion ($OR_{adjusted\ for\ age} = 3.2$; 95%CI 0.04–63.2), but the results were not statistically significant. Minami et al.[42] also evaluated the association according to the presence of histological proliferation, following the criteria of Dupont and Page[7], and found a

Chart 1. Characteristics of case-control, case-cohort, and nested case-control studies regarding family history of breast cancer and risk of BBD.

Authors, year	Location	Population	Family history of BC (definition)	Frequency of family history (%)	OR (95%CI)
Galván-Portillo et al., 2002[18]	Mexico City, Mexico	Cases: 121 women with BBD. Controls: 121 (clinical).	Family history (general)	Cases: 8 (6.7) Controls: 5 (4.13)	FH- =1 FH+ =2 (0.60; 6.64)+
Wu et al., 2004[23]	Shanghai, China	Cases: with atypia (33); proliferative without atypia (181 cases); nonproliferative (175 cases). Controls: 1,070 women with normal self-examination.	Family history in first-degree relatives	Nonproliferative lesions Cases: 6 (3.4) Controls: 17 (1.59) Proliferative lesions Cases: 5 (2.7) Controls: 17 (1.59) Lesions with atypia Cases: 1 (3) Controls: 17 (1.59)	Nonproliferative lesions FH- =1 FH+ =3.8 (0.9; 16.8)+ Proliferative lesions FH- =1 FH+ =2.8 (0.6; 13.6)+ Lesions with atypia FH- =1 FH+ =3.2 (0.04; 63.2)+ All lesions FH- =1 FH+ =1.97 (0.93; 4.16)+
Ingram et al., 1991[34]	Perth, Australia	Cases: 91 women with benign epithelial hyperplasia and 95 women with benign fibrocystic breast disease. Controls: 209 women identified through electoral registers.	Family history in first-degree relatives	Benign epithelial hyperplasia Cases: 9 (10) Controls: 12 (6) Fibrocystic disease Cases: 7 (7.3) Controls: 12 (6)	Both FH- =1 FH+ =1.45 (0.67; 3.15)*a Benign epithelial hyperplasia FH- =1 FH+ =1.80 (0.73; 4.43)*a Fibrocystic disease FH- =1 FH+ =1.30 (0.49; 3.41)*a
Catsburg et al., 2014[35]	United States of America	Cases: 667 women with benign proliferative disease. Controls: 1,321 women without abnormal mammography or abnormal clinical examination.	Family history in first-degree relatives	Cases: 136 (20.4) Controls: 237 (17.9)	FH- =1 FH+ =1.17 (0.92; 1.48)*b
Bright et al., 1989[36]	Boston, United States of America	Cases: 172 women with mammography and BBD biopsy. Controls: 134 women with normal routine mammography.	Family history of breast cancer (general)	–	Both FH- =1 FH+ =1.1 (0.65; 2.0)+ Premenopausal status FH- =1 FH+ =1.1 (0.54; 2.4)+ Postmenopausal status FH- =1 FH+ =1.2 (0.48; 2.8)+
Rohan et al., 1998[37] Case-cohort	Canada	Cases: 545 women with proliferative epithelial lesions. Non-cases: 4,921 selected from a stratified random sample (by selection center).	Family history (general)	Cases: 99 (18.2) Non-cases: 546 (11.1)	FH- =1 FH+ =1.78 (1.40; 2.25)*c
Conceição et al., 2016[38]	Belo Horizonte, Brazil	Cases: 75 with BBD. Controls: 116 women who underwent a routine exam or gynecological surgery and had a recent mammogram result.	Family history (general)	Cases: 13 (17.33) Controls: 0	There was a statistically significant difference between the group of women with BBD and the control group in relation to the presence of FH of BC (p<0.001).

Continue...

Chart 1. Continuation.

Authors, year	Location	Population	Family history of BC (definition)	Frequency of family history (%)	OR (95%CI)
Hardy et al., 1990[39]	Campinas, Brazil	Cases: 257 women with BBD biopsy or cytology Controls: 257 women diagnosed with healthy breasts.	Family history of breast cancer in mother, sister, daughter, aunt, cousin, and grandmother.	Mother Cases: 10 (3.9) Controls: 5 (1.9) Sister Cases: 4 (1.6) Controls: 3 (1.2) Daughter Cases: 0 Controls: 0 Aunt Cases: 15 (5.8) Controls: 12 (4.7) Cousin Cases: 8 (3.1) Controls: 7 (2.7) Grandmother Cases: 6 (2.3) Controls: 3 (1.2)	Mother FH- =1 FH+ =2.04 (0.69; 6.05)*[d] Sister FH- =1 FH+ =1.34 (0.29; 6.05)*[d] Aunt FH- =1 FH+ =1.26 (0.58; 2.75)*[d] Cousin FH- =1 FH+ =1.15 (0.41; 3.22)*[d] Grandmother FH- =1 FH+ =2.02 (0.50; 8.16)*[d]
Nomura et al., 1977[40#]	Washington County, United States of America	Cases: 320 women with cystic disease and fibroadenoma. Controls: 320 women selected through a population census.	Family history of maternal cancer	Cystic disease and fibroadenoma Cases: 14 (4.4) Controls: 7 (2.2) Cystic disease Cases: 12 (4.4) Controls: 6 (2.2) Fibroadenoma Cases: 2 (4.4) Control: 1 (2.2)	Cystic disease and fibroadenoma FH- =1 FH+ =2.04 (0.81; 5.12)*[e] Cystic disease FH- =1 FH+ =2.04 (0.75; 5.51)*[e] Fibroadenoma FH- =1 FH+ =2.04 (0.18; 23.33)*[e]
Minami et al., 1998[42]	Miyagi, Japan	Cases: 382 women with BBD biopsy. Controls: 1,498 women who participated in screening programs, in which the cases were identified, and who did not present changes in the exams.	Family history of mother or sister with breast cancer	Proliferative lesions Cases: 8 (6.1) Controls: 8 (1.6) Nonproliferative lesions Cases: 12 (4.8) Controls: 26 (2.6)	Proliferative lesions FH- =1 FH+ =4.31 (1.55; 11.95)[§] Nonproliferative lesions FH- =1 FH+ =1.80 (0.90; 3.59)[§]

#Cystic disease included fibrocystic disease, chronic cystic mastitis, sclerosis, adenosis, and papillomatosis; [§]OR adjusted for age at menarche and parity; [+]OR adjusted for age; *estimates calculated by the authors of the present review, based on the family history of cases and controls made available in the studies; [a]the study paired cases and controls by age and place of residence; [b]the study paired cases and controls by age, race, blood collection date, and randomization group; [c]a crude estimate was calculated. It was not adjusted by confounding variables; [d]the study paired cases and controls by age, year of diagnosis, and place of consultation; [e]the study paired cases and controls by age; BBD: benign breast diseases; BC: breast cancer; FH: family history; OR: odds ratio; 95%CI: 95% confidence interval.

positive and statistically significant association between family history of breast cancer in the mother or sister and proliferative lesions (OR_{crude} = 4.31; 95%CI 1.55–11.95) (Chart 1).

Studies that assessed the association between family history of breast cancer and BBD (Chart 1) according to menopausal status did not find a statistically significant association for family history of breast cancer in general relatives ($OR_{premenopausal}$ = 1.1; 95%CI 0.54–2.4; $OR_{postmenopausal}$ = OR = 1.2; 95%CI 0.48–2.8)[36], and neither for family history of breast cancer in first-degree relatives ($OR_{postmenopausal}$ = 1.17; 95%CI 0.92–1.48)[35].

On the other hand, the two case-control studies that evaluated the maternal family history of breast cancer[39,40] verified that the maternal history of the disease was strongly associated with the development of benign lesions (OR = 2.04; p>0.05), although the results were not statistically significant. In addition, it was observed that women with a maternal history of breast cancer were 2.04 times more likely to develop cystic disease (95%CI 0.75–5.51) and fibroadenoma (95%CI 0.18–23.33)[40] (Chart 1).

Ingram et al.[34] also assessed the association by specific type of lesion and observed that women with a family history of breast cancer in first-degree relatives were 1.3 times more likely to have fibrocystic disease (95%CI 0.49–3.41) and 1.8 times more likely to have benign epithelial hyperplasia (OR = 1.8; 95%CI 0.73–4.43); nevertheless, the results were not statistically significant.

Figure 2 shows the frequency of family history of breast cancer in the cases and controls of the included studies, according to the different family history classification criteria. Approximately twice as many women with a family history of maternal breast cancer were

verified among cases compared with controls. A total of 11.33% of women had a family history of breast cancer in first-degree relatives between cases, against 7.32% in the control groups, and 16.19% of women had a family history of breast cancer regardless of the relatives' degree in the case groups, against 10.68% in the controls.

Cohort studies

In cohort studies, a positive and statistically significant association was observed between BBD and family history of breast cancer as for: age (25–29 years: relative risk – RR = 2.08; 95%CI 1.09–3.96)[22]; age and sister with breast cancer (30–50 years: RR = 2.9; p≤0.01; >50 years: RR = 2.65, p≤0.01)[41]; first-degree relatives with breast cancer (RR = 1.67; 95%CI 1.47–1.90) [22]; aunt with breast cancer (OR = 2.71; 95%CI 1.16–6.34); mother, aunt, or maternal grandmother with breast cancer (OR = 1.92; 95%CI 1.12–3.27)[21]; two or more affected family members (OR = 4.26, p=0.02)[21]; and atypia compared with proliferative disease without atypia (prevalence odds ratio – $POR_{adjusted\ for\ age}$ = 2.76; 95%CI 1.33–5.74) or any BBD without atypia ($POR_{adjusted\ for\ age}$ = 2.16; 95%CI 1.05–4.35)[22](Chart 2).

DISCUSSION

The results of the present review suggest a positive association between family history of breast cancer and BBD. Family history of breast cancer was strongly associated with the development of BBD in case-control studies that classified lesions according to histological and/or atypical proliferation[23,42]. Women diagnosed with proliferative lesions were 4.3 times more likely to have a family history of breast cancer in the mother or sister (95%CI 1.55–11.95) than those without a family history[42]. Despite the strong association observed between family history in first-degree relatives and nonproliferative lesion, proliferative lesion, and lesion with atypia, none of the estimates were statistically significant and had a wide confidence interval, probably due to the low frequency of family history of breast cancer in the study population[23], verified in the low breast cancer incidence rates historically observed in the population of Shanghai[43].

The study conducted by Webb et al.[22] showed that atypia was significantly associated with a family history of breast cancer in first-degree relatives compared with proliferative lesion without

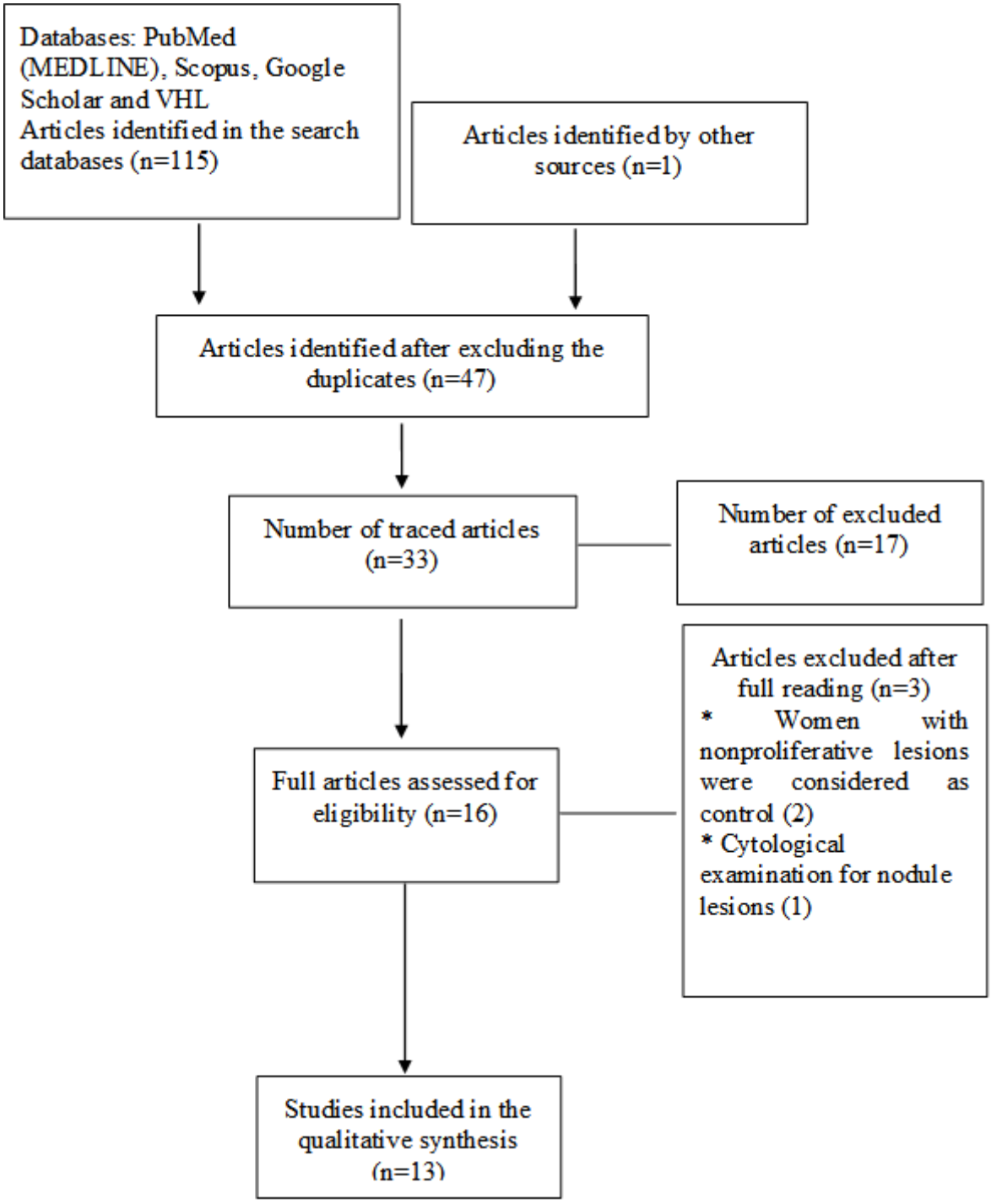
Chart 2. Characteristics of cohort studies regarding family history of breast cancer and risk of BBD.

Authors, year	Location	Population	Family history of BC (definition)	Cumulative risk (%)	HR/RR/OR/POR	
Berkey et al., 2012[21]	United States of America	6,888 young girls (9 to 15 years old), 67 with biopsy of benign disease.	Family history of mother, aunt, maternal grandmother, one family member, and two family members.	–	**OR for mother** FH- =1 FH+ =2.07 (0.83–5.20) **OR for aunt** FH- =1 FH+ =2.71 (1.16–6.34) **OR for mother, aunt or grandmother** FH- =1 FH+ =1.92 (1.12–3.27)	**OR for one family member** FH- =1 FH+ =1.74 (p=0.058) **OR for two or more family members** FH- =1 FH+ =4.26 (p=0.02)
Webb et al., 2002[22]	United States of America	80,995 women in the baseline; 16,849 self-reported a medical diagnosis of BBD; 3,165 had their diagnosis confirmed by biopsy.	Family history in first-degree relatives	–	**BBD confirmed by biopsy** FH- =1 FH+ =1.67 (1.47–1.90) **POR for atypia in the general BBD (with or without proliferation)** FH- 1 FH+ 2.16 (1.05–4.35) **POR for atypia in proliferative BBD** FH- =1 FH+ =2.76 (1.33–5.74)	**25–29 years** FH- =1 FH+ =2.08 (1.09–3.96) **45–50 years** FH- =1 FH+ =1.31 (0.83–2.06)
Hislop and Elwood, 1981[41]	Vancouver, Canada	1,374 women in the baseline, 726 of whom completed the follow-up questionnaires and 107 had biopsy confirming the diagnosis of benign breast disease.	Family history in mother and sister	Mother <30 years: 0 30–50 years: 11 >50 years: 11 Sister <30 years: 14 30–50 years: 36 >50 years: 45	**<30 years** FH- sister =1 FH+ sister =3.1 (p>0.05) **30–50 years** FH- mother =1 FH+ mother =0.8 (p>0.05) FH- sister =1 FH+ sister =2.9 (p=0.005)	**>50 years** FH- mother =1 FH+ mother =0.65 (p>0.05) FH- sister =1 FH+ sister =2.65 (p=0.001)

BBD: benign breast diseases; BC: breast cancer; FH: family history; HR: hazard ratio; RR: relative risk; OR: odds ratio; POR: prevalence odds ratio.

atypia or any BBD without atypia (with or without proliferation). The study was conducted in a large cohort of 80,995 women, 3,165 of whom had diagnostic confirmation of BBD. When assessing the association according to women's age, the authors observed that, in the age group of 25–29 years, the risk of BBD was twice as high (95%CI 1.09–3.96); and in the age group of 45–50 years, the risk was 1.3 times higher (95%CI 0.83–2.06) for those with a family history of breast cancer in first-degree relatives. In Canada, the family history of breast cancer in the sister was positively associated with BBD and varied by age group: 3.1 ($p>0.05$), in women aged <30 years; 2.9 ($p<0.01$), in women aged 30 to 50 years; and 2.65 ($p<0.01$), among those aged >50 years[41].

These results suggest that family history of breast cancer is associated with proliferative breast lesions and the presence of



MEDLINE: Medical Literature Analysis and Retrieval System; VHL: Virtual Health Library.
Figure 1. Flow diagram of the selection of articles.

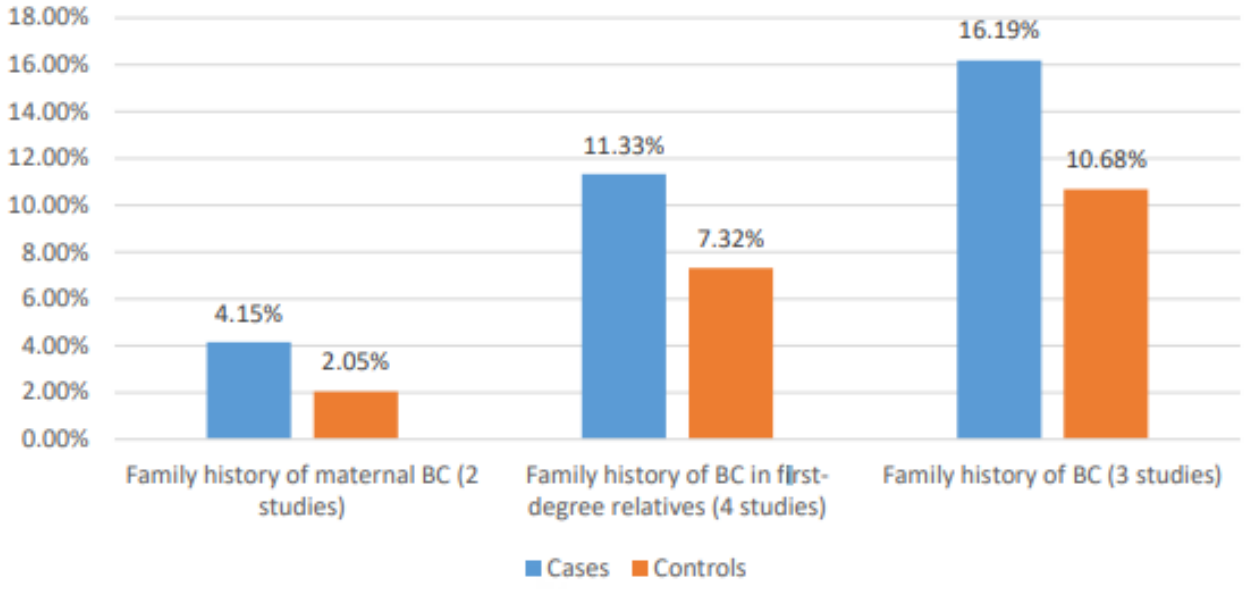
atypia, which are lesions that increase the risk of breast cancer[6]. However, such association is stronger in young women and tends to decrease with advancing age. First-degree relatives, especially sisters, of young women tend to be relatively young, and the breast cancer diagnosis at this stage of life is more likely to be related to genetic factors than to environmental factors[22,44,45].

The results may depict the tendency of women with a family history of breast cancer to seek medical care more frequently than those without a family history[46], if they suspect any change in the breasts. Moreover, breast biopsy has been strongly recommended by doctors for women with a family history of breast cancer, which could represent a selective surveillance bias[47]. However, the cohort and case-control studies on women who were routinely screened as the study population were deemed more appropriate, considering that such studies allowed to overcome this surveillance bias[48,49]. This rationale is supported by the fact that women with and without family history would have equal opportunities for diagnosis in these research designs. Thus, the estimates presented by such research may represent an association closer to the reality in the source population.

The scores obtained using the Newcastle-Ottawa scale reinforce the methodological quality of the research included

Chart 3. Classification of the methodological quality of the selected studies according to the Newcastle-Ottawa scale.

Reference	Study design	Selection	Comparability	Outcome	Total
Galván-Portillo et al., 2002[18]	Case-control	3	1	2	6
Berkey et al., 2012[21]	Cohort	1	1	2	4
Webb et al., 2002[22]	Cohort	2	1	3	6
Wu et al., 2004[23]	Case-control	4	1	2	7
Ingram et al., 1991[34]	Case-control	4	2	3	9
Catsburg et al., 2014[35]	Nested case-control	3	2	2	7
Bright et al., 1989[36]	Case-control	3	1	2	6
Rohan et al., 1998[37]	Case-cohort	3	2	2	7
Conceição et al., 2016[38]	Case-control	3	2	2	7
Hardy et al., 1990[39]	Case-control	3	2	2	7
Nomura et al., 1977[40]	Case-control	4	2	2	8
Hislop and Elwood, 1981[41]	Cohort	2	1	3	6
Minami et al., 1998[42]	Case-control	4	2	2	8



BC: breast cancer. Family history of maternal breast cancer included data from studies conducted by Hardy and colleagues[39], and Nomura and colleagues[40]. Family history of breast cancer in first-degree relatives included data from four studies[23,34,35,42]. Family history of breast cancer (general) included three studies[18,37,38].

Figure 2. Frequency of family history of breast cancer in cases and controls.

in this review, adding greater weight to the estimates found[50]. Most studies (92%) had moderate or high methodological quality (≥6 stars). Only one study was considered of low quality, obtaining 4 stars[21]. One of the main limitations of the cohort study carried out by Berkey et al.[21] is the determination of the outcome, considering that the participants themselves reported breast biopsy diagnosis.

Literature has shown that other large cohort studies have used only the BBD[51] report itself, and the authors also mention a validation study carried out on a large cohort of women, some of whom are mothers of the participants (Nurses' Health Study II), confirming the accuracy of the BBD diagnosis reported by women[52]. Conversely, the limited statistical power of most case-control studies may be due to an insufficient sample to represent the real estimates, considering that the magnitudes of the associations were high.

Case-control studies that used women with nonproliferative lesions as a control group were excluded because the natural history of histological changes that compose benign breast diseases is still unclear. Studies that used this strategy aimed to identify the risk factors for benign lesions that confer a higher risk of breast cancer (proliferative and atypical lesions); nevertheless, it is unknown, for example, whether BBD regress to histological types with less proliferation or progress to types with greater proliferation and/or atypia[53].

Visscher et al.[53] conducted a cohort study on 13,466 women aged between 18 and 85 years who underwent breast biopsy with benign findings, and those with an initial diagnosis of nonproliferative lesion and subsequent proliferative diagnosis had an increased risk of breast cancer (hazard ratio – HR = 1.77; 95%CI 1.06–2.94) compared with those who had no change in diagnosis. Thus, nonproliferative lesions could be part of the causal link that leads both to the development of lesions with more significant oncogenic potential and to breast cancer. In this case, women with such lesions might not be selected as controls in case-control studies. However, further studies are needed to confirm these causal links. Women who perform multiple biopsies with benign changes that progress in subsequent biopsies may have been subjected to the procedure of different breast regions, which in turn could result in hidden undiagnosed lesions instead of injuries that have progressed.

Among the limitations of this review, in case-control studies that presented only the number of women classified in each category (case and control) according to the presence or absence of family history, without having estimated the magnitude of the association, the authors of the present review calculated the risk estimates. The values of crude OR were calculated. More accurate estimates adjusted for potential covariates were not applied to these studies[34,37,35,39,40], although most authors have paired cases and controls for age and other variables, as demonstrated in Chart 1.

In addition, the different BBD classification criteria and family history of breast cancer adopted by the studies made direct comparisons difficult. The oldest studies used specific types of lesions, such as: cystic disease, fibroadenoma, benign epithelial hyperplasia, and fibrocystic disease[34,40]; whereas the most recent ones used the proliferation and atypia degree-based classification model [7]. Furthermore, most studies (53%) were conducted on North American populations, mostly composed of Caucasian women, and studies on European and African populations were not found.

Therefore, further studies on populations covered by screening programs that use a standard BBD classification scheme and family history of breast cancer are necessary. Moreover, many studies that indicated a strong association between BBD and family history of breast cancer did not have enough power to exclude chance as a possible explanation for that result. Thus, studies with larger sample sizes are necessary to obtain more accurate estimates.

A better understanding of the role of family history of breast cancer in the risk of developing BBD will help to understand the factors and biological pathways that lead to the development of breast cancer, in addition to identifying whether women with BBD and family history of breast cancer could benefit from greater adherence to additional breast cancer screening or chemoprevention modalities.

AUTHORS' CONTRIBUTION

M.S.: conceptualization, project management, formal analysis, interpretation, and writing.
I.S.: conceptualization, project management, writing, critical analysis, and review of the study.
Both authors approved the final version of the article.

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