Nutrición Hospitalaria

Revisión

The association between breast cancer and consumption of dairy products: a systematic review

La asociación entre cáncer de mama y el consumo de productos lácteos: una revisión sistemática

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Abstract

Introduction: breast cancer (BC) is the most common cancer in women and its relationship with dietary factors particularly dairy products, has been investigated trough several studies but up to now there are still not enough results to confirm the association between breast cancer and dairy products.

Objective: the purpose of this systematic review was to expand the number of systematic reviews that to date exist on the relationship between dairy products consumption and risk of breast cancer. A comprehensive search of the PubMed, Scopus and Embase was performed from September 2005 to September 2018 in which one case control and cohorts' studies were included.

Results: eighteen studies were finally selected for the review (10 case-control and 8 cohorts' studies). These studies reported several statistically significant associations (OR, HR, RR) between dairy product consumption and the risk of breast cancer. Seven case-control and four cohorts' studies showed that dairy product consumption was inversely associated with the risk of breast cancer, on the other hand, a positive association was found in two case-control and non- significant association was found between dairy product consumption and the risk of breast cancer in the remaining studies (one case-control and four cohorts' studies)

Conclusion: although an inverse association was observed in most studies, it's difficult to draw conclusions when the methodology methods to collect the dairy product intake and the servings or portions measurements were different in each study. On the other hand, not all studies used the same confounding variable to estimate risk.

Resumen

Introducción: el cáncer de mama (BC) es de los cánceres más comunes en mujeres, y su relación con los factores dietéticos y, en particular, con los productos lácteos, ha sido investigada a través de varios estudios, pero hasta ahora no hay resultados suficientes que confirmen la asociación entre cáncer de mama y productos lácteos.

Objetivo: el objetivo de esta revisión fue ampliar y actualizar el número de revisiones sistemáticas que hasta día de hoy existen sobre la relación entre el consumo de productos lácteos y el cáncer de mama.

Metodología: se realizó una búsqueda exhaustiva en las bases de datos PubMed, Scopus y Embase entre septiembre de 2005 y septiembre de 2018 en la que se incluyeron estudios de casos y controles y estudios de cohortes.

Resultados: se seleccionaron 18 estudios (10 estudios de casos-controles y 8 estudios de cohorte). Siete casos-controles y cuatro estudios de cohorte mostraron que el consumo de productos lácteos tenía una asociación inversa con el riesgo de cáncer de mama y, por otro lado, en dos estudios de casos-controles se observó una asociación positiva. No se encontró una asociación significativa entre el consumo de productos lácteos y el cáncer de mama en los restantes estudios (1 caso-control y 4 cohortes).

Conclusión: aunque se observó una asociación inversa en la mayoría de los estudios, es difícil sacar conclusiones cuando los métodos metodológicos para recolectar la ingesta de lácteos y las porciones o las mediciones de las porciones fueron diferentes en cada estudio. Por otro lado, no todos los estudios tienen en cuenta las mismas variables de confusión.

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INTRODUCTION

Breast cancer (BC) is the most common cancer in women, with nearly 1.7 million new cases diagnosed in 2012 and it's the second most common cancer overall. This represents about 12 % of all new cancer cases and 25 % of all cancers in women (1). Notably, only 5-10 % of all cancers are due to genetic defects, while the remaining 90-95 % are associated with a number of risk factors among which are lifestyle factors (2,3).

Within the lifestyle risk factors, nutrition and others factors such as alcohol intake, obesity and physical activity are widely thought to play an important role in cancer (4). Several dietary factors, as consumption of fruit and vegetables (5), meat, poultry and fish (6), high-fat diet patterns (7), and dairy products (8), have been intensively studied in relation to BC risk. Although the relation with dairy products has been widely studied the results remain inconsistent.

Dairy products are important for healthy human nutrition and development throughout life, especially in childhood. However, the value of dairy products in human nutrition has been increasingly questioned in over last years (9,10).

Consumption of dairy products has long been thought to play a role in breast cancer risk through several hypothetical mechanisms (11) such as high dietary intake of total and saturated fat (12-14), presence of carcinogenic pesticides in milk products and presence of growth factors in milk, including IGF-1, which may promote breast cancer cell growth (15). Notably, however, some components of dairy products may protect against breast cancer, such as calcium, vitamin D, rumenic acid, butyric acid, branched chain fatty acids and whey protein (15).

Many epidemiological studies have reported conflicts results about on the association between dairy product consumption and breast cancer risk, with both positive and inverse associations but mostly these studies measured exposure to dairy products in notably different ways, which makes it difficult to compare them (16-18).

Although during the last decade, the number of original studies into the relationship between breast cancer and dairy products has increased, it is important to keep updated databases that provide information on this topic because it is a topic that can cause a lot controversy and for this reason a systematic review was carried out in order to collect and complement the studies published by Dong *et al.* (16) , and Zang *et al.* (17) and to carry on observing whether there is any relationship between the consumption of lactic products and the risk of breast cancer. Taking in account that the relationship between dairy products and breast cancer is being debated for a long time, we thought that it was important to continue to update this kind of review in order to increase the evidence related to this topic.

METHODS

SEARCH STRATEGY

We searched The Cochrane Library, MEDLINE (PubMed), EMBASE (Ovid), and Scopus using the terms "dairy products", "dairy", "cheese", "milk", and "yogurt" in combination with "breast cancer", "breast neoplasm", "breast tumour", "breast adenoma", "breast carcinoma", "breast sarcoma" and "breast adenocarcinoma". We designed the following search string for MEDLINE (PubMed), and modified this strategy to search the other databases: ("breast tumor "[Title/Abstract] OR "tumor breast" [Title/Abstract] or "breast cancer" [Title/Abstract] or "cancer breast"[Title/Abstract] or "breast adenoma" [Title/Abstract] or "breast carcinoma" [Title/Abstract] OR "carcinoma breast" [Title/Abstract] or "breast sarcoma" [Title/Abstract] or "sarcoma breast" [Title/Abstract] or "breast adenocarcinoma" [Title/Abstract] or "breast neoplasms" [MeSH Terms]) and ("cheese" [Title/Abstract] or "yogurt" [Title/Abstract] or "dairy food" [Title/Abstract] or "dairy products" [Title/Abstract] or "cheese" [MeSH Terms] or "cultured milk products" [MeSH Terms] OR "dairy products"[MeSH Terms])". We searched for articles published between September 2005 and September 2018. We also manually checked the reference lists from relevant studies to identify further eligible studies.

STUDY SELECTION AND DATA COLLECTION

We selected studies based on an initial screen of the abstracts and titles, and a second screen of the articles' full text. All reports identified through the electronic searches were scanned independently by two review authors (E.V.G., M.S.S.), and disagreement was resolved by discussion or, if necessary, referred to a third review author (R.P.R.).

We identified eligible studies according to the following criteria: (1) the study was a case-control or prospective cohort design; (2) the main exposure of interest was dairy products consumption including any type of milk, yogurt, cheese, cream, and other dairy products (3) the outcome of interest was breast cancer (BC) incidence; and (4) Relative Risks (RRs), Odd Ratios (ORs) and Hazard Ratios (HRs) and with corresponding 95 % confidence intervals (CIs); (5) English language.

DATA EXTRACTION

We extracted all data using a standardized data-collection form. The following information was extracted from each study by two investigators independently: first author's name, publication year, country in which the study was conducted, sample size age range or mean age at baseline, period of study, dietary assessment method, type of dairy product, risk estimate with corresponding 95 % CI for the highest *versus* lowest category of the total dairy products consumption and specifics types of dairy products, and variables adjusted for each study. Dairy products have been defined as the sum of different dairy product (eg. whole, low-fat and skimmed milk, regular and low-fat cheese, yogurt, and ice cream) and, as far as milk is concerned, both the high fat and skimmed variety are included. The table I and II shows what kind of dairy product has been taken into account in each study.

Table I. Characteristics of case-control studies of dairy intake and breast cancer risk

Study	Subjects (case/control)	Age (yr)	Period	Dietary assessment	Dairy type	Adjusted risk (95 % CI)	Statistical adjustment
Wirfalt, 2005, Sweden (22)	237/673	≥ 50	1991-1996	FFQ+ 24h recall	*Fermented milk products* (means fat intake) 4.6 vs. 0g/week	OR = 0.65 (0.43-0.98); *p* trend 0.012	Energy, past change of food habits, alcohol and smoking habits, physical activity, age at birth of first child, current hormone therapy, height, and education, waist circumference and body mass index, fermented milk products, vegetable oil–based dietary fats, and dried soup powders
Gallus, 2006, Italy (23)	2.569/2.588	Median: Case 55.0 Control 56.0	1991-2002	FFQ	*Milk* (Partly skim or skim milk) 225 *vs.* 0 ml /week	OR = 0.87 (0.77-0.98)	Age, sex, study centre, education, smoking, alcohol, body mass index, physical activity and total energy intake
Knight, 2007, Canada (24)	972/1,135	< 70 y	2003-2004	FFQ	Milk (whole and skim milk) ≥ 10 *vs.* < 5 glass/week	*Vitamin D-related exposures at ages of 10-19 years:* OR = 0.62 (0.45-0.86); *p* = 0.004 *Vitamin D-related exposures at ages of 20-29 years:* OR = 0.63 (0.47-0.83); *p* = 0.006	Reference age, ethnicity, family history in first-degree relatives, ever breast-fed, education, age menarche, and age at first birth
Lima,2008, Brazil (25)	89/94	30-80	2002-2003	FFQ	*DP* (it's not difined) > 14.2 *vs.* ≤ 9.1 portion/week	OR=0.04 (0.01-0.15); *p* trend 0.00	Age group, origin, oral contraceptives, age at menopause, body mass index, and energy
Bessaoud, 2008, France (26)	437/922	25-85	2002-2004	FFQ	*DP* (milk and cheese) > 402.87 *vs.* ≤ 134.34g /day	No statistically significant associations	Energy intake, education, parity, breast-feeding age at first full-term pregnancy, duration of ovulatory activity, body mass index, physical activity, and first-degree family history of breast cancer
Zhang, 2011, China (27)	438/438	25-70	2007-2008	FFQ	*Total DP* (mean) by dry weight. 8,15 *vs.* 2,98 g/d *Total DP* (mean) 2,8g *vs.* 0,79 g protein /d *Low fat DP* (mean) 8,15 *vs.* 2,98 g dry weight/d DP (skim/low-fat milk, skim/ low-fat milk powder, and yogurt)	OR = 0.61 (0.41-0.90); *p* trend 0.016 OR = 0.64 (0.43-0.95); *p* trend 0.031 OR = 0.67 (0.47-0.95); *p* trend 0.033	Age at menarche, live births and age at first live birth, months of breast feeding, body mass index, history of benign breast disease, mother/sister/daughter with breast cancer, physical activity, passive smoking, and total energy intake

Table I (Cont.). Characteristics of case-control studies of dairy intake and breast cancer risk

Study	Subjects (case/control)	Age (yr)	Period	Dietary assessment	Dairy type	Adjusted risk (95 % CI)	Statistical adjustment
Bao, 2012, China (28)	3.443 /3.474	25-70	Phase I: 1996-1998 Phase II: 2002-2004	FFQ	*Milk* (any kind of milk) ≥ 135.72 *vs.* < 7.39 g/day	*All cases:* OR = 0.83 (0.73-0.93); *p* = 0.001 *ER+/PR+ cases:* OR = 0.85 (0.73-0.99); *p* = 0.04	Energy, age, education level, ever diagnosed with benign breast disease, first-degree family history of breast cancer, participation in regular exercise, body mass index, study phase (I and II), age at menarche, menopausal status, parity, total vegetable intake, and total fruit intake
Bahadoran, 2013, Iran (29)	100/175	30-65	2010	FFQ	*DP* (milk, yogurt, yogurt drink, cheese, cream, and kashk) 234 ± 1 *vs.* 57 ± 16 g/day *Low-fat DP* (DP containing < 2.5 % fat) 785 ± 22 *vs.* 126 ± 22 g/day *Fermented DP* (cup/day) (yogurt, yogurt drink and cheese) 565 ± 24 *vs.* 137 ± 24 g/day	OR = 0.14 (0.04-0.38); *p* = 0.004 OR = 0.10 (0.03-0.34); *p* = 0.003 OR = 0.06 (0.02-0.19); *p* = 0.001	Menopause status, family history of breast cancer, physical activity, energy intake, energy density of the diet
Mobarakeh, 2014, Iran (30)	53/40	20-65	2009	FFQ	High fat milk (g/d no available) High fat cheese (g/d no available)	OR = 17,45 (2.19-138.98) OR = 6,88 (1.44-32.77)	Age, body mass index and education
Zahedi,2015, Iran (31)	150/150	Case (mean) 51.61 ± 10.52 Control (mean) 51.55 ± 10.27	2013 - 2014	FFQ No validate	*Yogurt* ≥ 1,5 *vs.* ≤ 1 glass/week	OR = 2.57 (101-6.55)	Education, living place, Occupation status, type of occupation, marital status, walking time, sleeping per day, driving, driving duration, exposure duration to second-hand smoke, physical activity, exercise duration per week, years of doing exercise

Table II. Descriptive study characteristics of cohort's studies of dairy intake and breast cancer risk

Study	Subjects (case)	Age (yr)	Period	Dietary assessment	Dairy type	Adjusted risk (95 % CI)	Statistical adjustment
McCulloug, 2005, USA (32)	68,567 (2,855)	50-74	1993-2001	FFQ	*DP* (whole, low-fat and skim milk, regular and low-fat cheese, yogurt, and ice cream) > 3 *vs.* < 0.5 serving/day *Low fat DP* (low-fat and skim milk, low-fat cheese) > 3 vs < 0.5 serving/day	*All cases:* RR = 0.81 (0.69-0.96); *p trend 0.002* *ER+ cases:* RR = 0.73 (0.57-0.93); *p trend 0.0003* *All cases:* RR = 0.86 (0.74-0.99); *p trend 0.016* *ER+ cases:* RR = 0.76 (0.61-0.94); *p trend* 0.002	All cases: age, energy, history of breast cyst, family history of breast cancer, height, weight gain since age 18, alcohol use, race, age at menopause, age at first birth and number of live births, education, mammography history, and HRT. ER+ cases: age, energy, history of breast cyst, family history of breast cancer, height, weight change from age 18 to 1992
Kesse-Guyot, 2007, France (33)	3,836 (92)	51,2/58,5	1994-2003	24 h recall	*DP* (yogurt, fresh cheese, milk and cheese) > 400 *vs.* < 165 g/day	Premenopausal RR = 0.35 (0.12-0.95); *p* = 0.01	Smoking habits, body mass index, Physical activity and calcium intake
Van der Pols, 2007 England and Scotland (34)	2,215 (97)	4-11	1948-2005	24 h recall	*DP* (milks, infant formulas, cheese, cream, milk pudding, and ice cream) *Milk* (whole milk)	No statistically significant associations	Age, sex, and energy and fruit intakes
Pala, 2009, EPIC (35)	319,826 (7119)	20-70	1992-2003	FFQ	*Milk* (whole-fat, skim, semi skim)	No statistically significant associations	Energy, height, weight, years of schooling, smoking, and menopause; stratified by centre and age
Linos,2010, USA (36)	39,268 (455)	34-53	1991-1995	FFQ	*Milk* (low-fat and high fat milk) (g/week)	No statistically significant associations	Age, total energy intake, family history of cancer, history of benign breast cancer disease, menopausal status, age of menarche, parity, age of first birth, weight gain since age 18, body mass index at age 18, current oral contraceptive and adult alcohol use

Table II (Cont.). Descriptive study characteristics of cohort's studies of dairy intake and breast cancer risk

Study	Subjects (case)	Age (yr)	Period	Dietary assessment	Dairy type	Adjusted risk (95 % CI)	Statistical adjustment
Hjartåker, 2010, Norway (37)	64,904 (1,407)	Mean 56.8	1991-1999	FFQ	*White cheese* ≥ 25.3 *vs.* < 6 g/day	*Premenopausal:* HR = 0.50 (0.29-0.87); *p* = 0.02 *Postmenopausal:* HR = 0.81 (0.66-0.99); *p* = 0.03	Age, energy intake, alcohol intake, height, weight increase since age 18, level of physical activity, years of education, maternal history of breast cancer, mammography practice, age at menarche, number of children and age at first birth, and use of oral contraceptives
Wirfält, 2011, Sweden (38)	15,773 (544)	45-73	1991-2004	FFQ+ 24h recall	*Milk* (regular milk) 239 *vs.* 3.6 g/day (median)	HR = 0.65 (0.48-0.88)	Method version, season of date collection, age, total energy
Genkinger, 2013, USA (39)	52,062 (1,268)	21-69	1995-2007	FFQ	*DP* (milk, whole milk, low-fat milk, hard cheese, yogurt, and ice cream) total milk intake (MVRR = 1.05, 95 % CI = 0.74-1.46 comparing 1,000-0 g/ week)	No statistically significant associations	Energy intake, age at menarche, body mass index, family history of breast cancer, education, parity and age at first live birth, oral contraceptive use, menopausal status, age at menopause, menopausal hormone use, vigorous physical activity, smoking status, and alcohol intake

Yr: year; FFQ: food frequency questionnaire; DP: dairy products; RR: relative risk; HR: harz ratio; CI: confidence interval; HRT: Hormone Replacement Thera.

We performed a systematic review of existing literature according to the Cochrane methodology (19), and followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (20). The Critical Appraisal Skills Programme (CASP) (21) tools was used to assessment the papers and make sense of evidence.

RESULTS

LITERATURE SEARCH

The results of the article selection process are summarised in figure 1. The initial search resulted in 325 articles. After applying the inclusion criteria, we identified 70 potentially relevant studies for full-text review. Two additional publications were identified through the bibliography cited in the original search, giving a total of 72 studies. After reading the full-text article and the details of each study, we selected 18 studies for review, of which ten were case-control studies (22-31), and eight were cohort studies (33-39).

STUDY CHARACTERISTICS

The data extracted from these 18 studies are shown in tables I and II. All studies were published between 2005 and September 2018. Four studies were conducted in North America (EEUU, Canada) (24,32,36,39), eight in European countries (Italy, France, England and Scotland, Sweden, Norway and multicentre) (22,23,26,33-35,37,38), one in South America (Brazil) (25), two in China (27,28), and three in Iran (29-31). Most studies, both case-control and cohort's studies, estimated the dairy food consumption using the Food Frequency Questionnaire (FFQ) as the dietary assessment method (23-30,32,35-37,39), two studies added a day 24 h record (22,38), two studies just used 24 h record (33,34) and one study didn't describe the dietary assessment method (31).

MAIN OUTCOMES

Each dairy products amount (gr or ml) that are shown in tables I and II are the ones that the researchers used to calculate the risk.

Regarding the case control studies three studies (25,27,29) which analysed *dairy products* (DP) *consumption* as a sum of more than one type of dairy products, reported a significant association between DP consumption and risk of breast cancer. Zhang *et al.* (27) reported that higher consumption of total DP and low-fat DP were inversely associated with risk of breast cancer (OR = 0.61; 95 % CI 0.41, 0.90; OR = 0.67; 95 % CI 0.47, 0.95) by dry weight of total dairy and low-fat dairy, respectively and (OR = 0.64; 95 % CI 0.43, 0.95) by the protein weight.

Bahadoran *et al.* (29) observed that total DP consumption was inversely associate (OR = 0.14; 95 % CI 0.04, 0.38) and this protective effect was even greater when considering just low-fat dairy products (OR = 0.10; 95 % CI 0.03, 0.34). The most significant
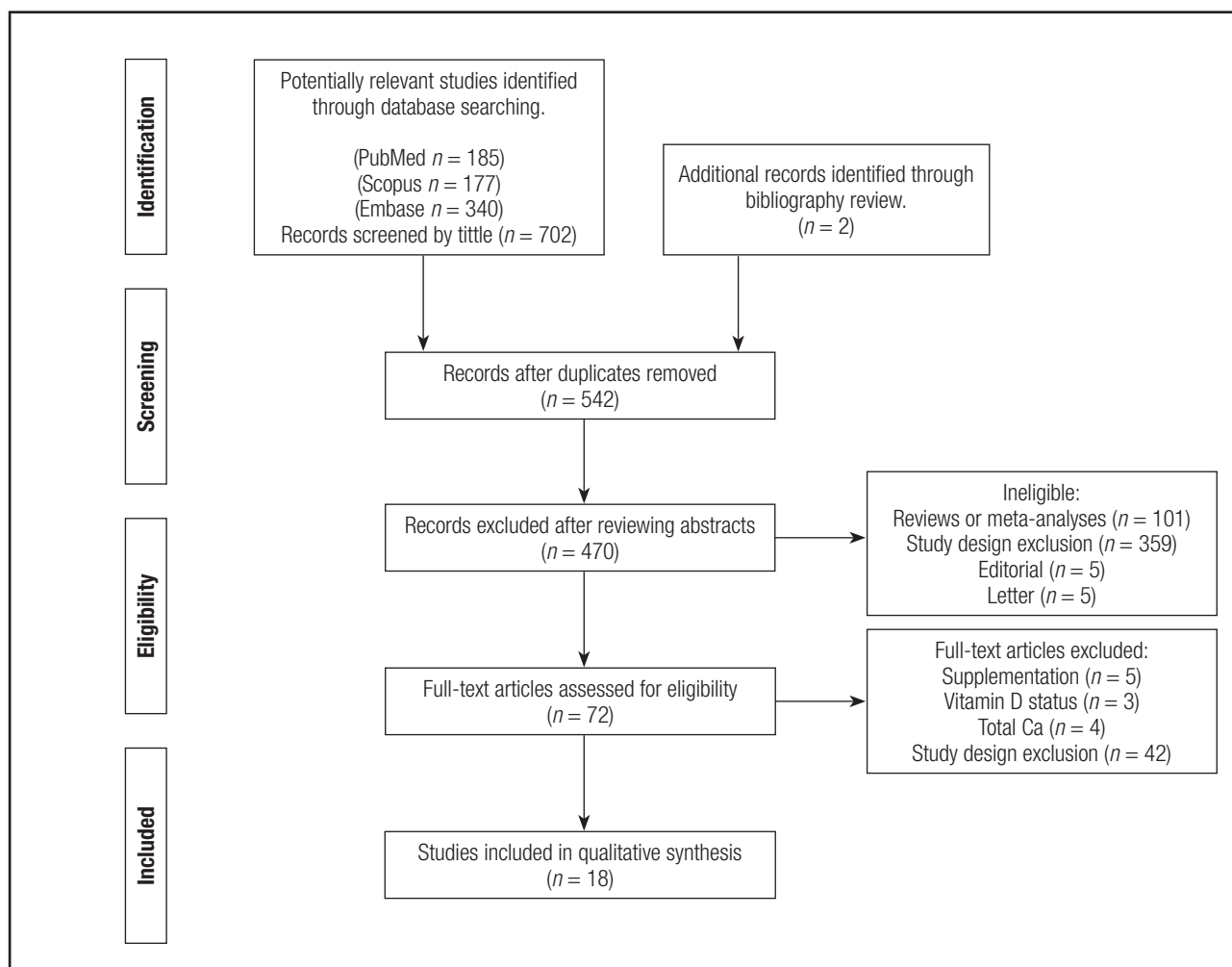
Figure 1.

Flow diagram of the literature search process (From*:* Moher D, Liberati A, Tetzlaff J, et al, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7):e1000097. DOI: 10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org).

association was reported by Lima *et al.* (25) (OR = 0.04; 95 % CI 0.01, 0.15) for the whole fat DP.

For *milk intake,* four studies analysed (23,24,28,30) the association between milk intake and BC risk. The Canada study (24) found a protective effect for the whole fat milk (OR = 0.62; 95 % CI 0.45, 0.86) and (OR = 0.63; 95 % CI 0.47, 0.83) for both vitamin D-related exposures between the ages of 10 to 19 and 20 to 29. A study from China (28) found that whole milk consumption was inversely associated with BC risk (OR = 0.83; 95 % CI 0.73, 0.93), comparing the highest to the lowest tertile of intake, and suggested that milk intake was associated with higher risk of the estrogen receptor positive subtype (ER+) and the progesterone receptor positive subtype (PR+) than the other three BC subtypes (ER+/ER+; PR+/PR+; PR+/ER+) (OR = 0.85; 95 % CI 0.73, 0.99). An Italian study (23) found an inverse association with milk consumption (OR = 0.87; 95 % CI 0.77, 0.98) and a study carried on in Iran (30) was report to a strong risk of breast cancer by the

whole milk consumption when it was just adjusted by age, Body Mass Index and education (OR = 17.45; 95 % CI 2.19-138.98).

Four case-control studies (22,29,30,31) analysed the association between risk of BC and fermentable dairy products consumption, including yogurt and cheese of which two were observed a significantly increased of risk of BC (30,31). Zahedi *et al.* (31) found a positive association (OR = 2.57; 95 % CI 1.01, 6.55) by the low yogurt intake (≤ 1 glass/week), and Mobarakeh *et al.* (30) found that risk of BC was positively associated a for the high fat cheese intake (OR = 6.88; 95 % CI 1.44, 32.77). In contrast Wirfalt *et al.* (22) found an inverse association between risk of BC and fat intake from fermented milk products (OR = 0.65; 95 % CI 0.43, 0.98), and Bahadoran *et al.* (29) reported similar results for fermentable dairy products (yogurt, yogurt drink, cheese) (OR = 0.06; 95 % CI 0.02,0.19). There was just one case-control study carried on by Bessaoud *et al.* (26) which found no significant association between the highest and lowest

quartiles of milk and cheese consumption (OR = 1.00; 95 % CI 0.67, 1.50).

Regarding the cohort studies, two of them found an inverse association between dairy product consumption and risk of BC (32,33). McCullough *et al.* (32), found an inverse association (RR = 0.86; 95 % CI 0.74, 0.99) and (RR = 0.81; 95 % CI 0.69, 0.96) for low-fat and whole fat dairy products respectively and the associations were slightly stronger in women with estrogen receptor-positive tumors in both low fat dairy products (RR = 0.76; 95 % CI, 0.61, 0.94) and whale fat dairy products (RR = 0.73; 95 % CI 0.57, 0.93). Kesse-Guyot *et al.* (33) reported a lower risk of breast cancer (RR = 0,35; 95 % CI 0.12, 0.95) and no association was found in both Vander Pols *et al.* (34) and Genkinger *et al.* (39) studies for whole fat dairy products.

The association between *milk* consumption and risk of BC was inverse in the Wilrfalt *et al.* (38) (RR = 0.65; 95 % CI 0.48, 0.88) and no association was found in Pala *et al.* (35) and Linos *et al.* (36) studies. Hjartaker *et al.* (37) found a statistically significant inverse association in both pre-menopausal and postmenopausal women (HR = 0.50; 95 % CI 0.29, 0.87) and (HR = 0.81; 95 % CI 0.66, 0.99) respectively when compared to those with the lowest consumption.

DISCUSSION

In this systematic review, we summarized the evidence found regarding the association between dairy products consumption and risk of breast cancer from ten case-control and eight cohort studies were published since 2005 to 2018.

We observed that dairy products consumption was inversely associated in seven case-control (22-25,27-29) and four cohorts' studies (32,33,37,38), a positive association was found just in two case-control studies (30,31) and for remaining studies, one case-control (26) and four cohort studies (34-36,39) no significative association was found.

The relationship between DP consumption and the risk of breast cancer has been studied extensively over the last years although the details of the studies are not conclusive (16,17). While some components of milk have been attributed a positive association with the risk of breast cancer other components seem to have a protective factor. The role of the dairy products in the development of breast cancer is thought that it would be able to be explained by different mechanisms along which is the high fat intake.

Some studies indicate that dietary fats have both direct and indirect effects on breast cancer risk, in that some fat types can also affect inflammatory processes, the composition and function of cell membrane, and cell signalling pathways (41-43). While saturated fatty acids have been linked to increased breast cancer risk, no significant association has been demonstrated for total, monounsaturated, or polyunsaturated fats (44-46). The first observation suggesting an association between dietary fat and breast cancer were reported by Tannenbaum *et al.* (47) which was conducted in mice which was followed for others studies which suggests that high fat intake (48) and possibly high intake of specific fatty acids

(49) has been shown to be an important modulator of breast cancer risk in animal studies (50,51) and since then case-control and cohorts' studies have not been able to confirm a relationship between dietary fat and breast cancer (48,52,53) but the relationship between dietary fat and the risk of breast cancer has been controversial for decades. However, several recent cohort's studies have reported results that suggest a modest positive association between fat intake and the risk of breast cancer (54) and more recently, one study carried by Prentice et al, 2006 (55) reported a marginally statistically significant reduction in breast cancer incidence among women in the low fat dietary patterns group compared with women in the control group (56) and when some studies analyse the specific subtype of fat some studies show that when all types of fat were considerate simultaneously only the association for saturated fat remained statistically significant (53). Although there are studies which show this kind of relationship, it's important to note that people who eat healthy fat enjoy a better life style and are more active physically, they don't smoke, and they follow a balanced diet and a good quality of life that is known to protect against breast cancer. On the other hand, there is a relationship between saturated fat with an unbalanced diet and other risk factors (5). That is why it is so important to take into account as many confounding variables as possible.

Although some components in the milk is thought to play a role in the development of breast cancer, in contrast, calcium, vitamin D and conjugated linoleic acid contained in dairy products are associated with decreased risk of breast cancer particularly Vitamin D and calcium have been shown to have an anti-carcinogenic effect (15). Notably, dairy products are an excellent source of calcium and the greatest source of vitamin D for many populations where milk is fortified with this vitamin.

In this systematic review, the positive association was mainly reported in association with high fat dairy products (30), but is important to note that may be because the statistical adjustment was just for age, education and Body Mass Index while the rest of studies took in consideration more adjustment factors such as physical activity (57), energy intake (58) which has an important relation-ship with breast cancer.

Fermented dairy or yogurt are rich in probiotics, microorganisms that are beneficial to the health of the host when ingested in adequate amounts. *Lactobacillus acidophilus*, a probiotic present in yogurt, may modulate the immune response against breast cancer, which may lower cancer risk (59). Two of the studies included in our review showed a protective effect associated with fermented dairy products, including yogurt (30,31).

Other systematic reviews that have evaluated the link between dairy consumption and risk of breast cancer have also found inconsistent results (11,16,17,60). The first meta-analysis was published by Boyd *et al.*, who found a small increase in breast cancer risk in women who consumed more milk (60). Subsequent studies reported different results (18), supporting the conclusion that studies published not provide consistent evidence for an association between consumption of dairy products and breast cancer risk.

Although menopause does not cause breast cancer it's well known that women who start the menopause later may have an

increased risk and that may be because they have more ovulations and that means an exposure to estrogen over long periods of time. There is an article including a review that shows the breast cancer risk of premenopausal women was lower than postmenopausal women eating the same kind of dairy product and after adjustment due to several potential confounders (37).

LIMITATIONS

The review presents several possible limitations, which must be considered when interpreting the results. The main one is no metanalyses was carried out, and on the other hand, the methods *used to assess* dairy product intake amount have some limitations, which could lead to some misclassification so food Frequency Questionnaires have been dietary assessment tools widely used in epidemiological studies investigating the relationship between dietary intake and disease or risk factors since the early '90s it's also important to note that this tool has some limitations such as systematic errors and bias in estimates, efforts are being developed to improve the quality of the information, personal memory of diet in the past may be biased by present diet and the precision in estimates and quantifying food portion sizes. (ref. http://www.nutricionhospitalaria.com/pdf/8751.pdf) and this limitation may well explain some of the results.

The present review aimed to summarize these effective strategies, however, combining the results in a meta-analysis was not possible as the outcome measures and designs among the studies differ tremendously, which may be seen as a limitation of this review.

This limitation means that the weight or volume of rations were not homogeneous, and variability in dairy consumption over time was not considered, especially in the prospective studies, where intake of dairy products could change over the long follow-up period. Another limitation is the adjustment for potential confounding factors differed across studies, and most risk estimates were adjusted for age, body mass index, family history of breast cancer, reproductive factors, hormone replacement therapy, and total energy intake, but some study the adjustment was just for age, body mass index and education but some studies just used a few potential confounding factors. It is well known that some of nutrients in dairy products, such as Vitamin D and calcium, could protect against breast cancer, and should be considered in the adjusted model but just only one was adjustment by calcium.

Finally, it's important to note a common limitation of studies when Food Frequency questionnaire is the only questionnaire to use to collect data from dietary intakes, this kind of methods has some limitations although it has been more used in epidemiological studies (54). It has been recommended the use of FFQs with other methods to do the adjustments required and in this review just three studies used it (22,33,34).

STRENGTHS

This systematic review has several strengths. First of all, we included data from different countries with different patterns of milk consumption on the other hand we considered several types of dairy products, and grouped the results by type and it's important to note that we included some studies more than the last review (16,17). A systematic review carried out by Dong *et al* (16), was report 18 cohort's studies and any case control study from 1984 to 2010 and some years later a new systematic review carried on by Zang *et al.* (17), added 5 cohort's studies and five case-control studies. In order to complete both the last systematic review and incorporate more evidence about dairy products and breast cancer association our review added 7 case-control studies (22-26,30,31) and one cohort's (38). We found a case-control studies which were not incorporated in the Zang *et al.* review and in order to not miss any one our review was carried on from 2005 to 2018.

CONCLUSION

Although it is difficult to reach a conclusion because the meta-analysis was not carried out. Dairy products intake was inversely associated with the risk of breast cancer in most studies although it is important to note that more studies are needed with a clearer and homogenic methodology.

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