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REVIEW ARTICLE

The impact of lifestyle and reproductive factors on the risk of a second new primary cancer in the contralateral breast: a systematic review and meta-analysis

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Abstract

Purpose The risk of being diagnosed with contralateral breast cancer (CBC) is an important health issue among breast cancer survivors. There is an increasing interest in the effect of lifestyle and reproductive factors on CBC risk, since these factors may partly be modifiable. We performed a systematic review and meta-analysis and aimed to evaluate the impact of lifestyle and reproductive factors on CBC risk in population-based breast cancer studies.

Methods The PubMed electronic database was searched up to 2nd November 2019, for relevant publications. Of the included studies, a meta-analysis per lifestyle or reproductive factor was performed.

Results Thirteen out of 784 publications were used for the meta-analysis. Body mass index (≥ 25 vs. < 25 kg/m^2; RR = 1.22; 95% CI 1.01–1.47) was associated with increased CBC risk. The estimates for alcohol use (ever vs. never; RR = 1.15; 95% CI 1.02–1.31) and age at primiparity (≥ 25 vs. < 25 years; RR = 1.06; 95% CI 1.02–1.10) also showed an association with increased CBC risk. For parity (≥ 4 vs. nulliparous; RR = 0.56; 95% CI 0.42–0.76) and age at menopause (< 45 vs ≥ 45 years; RR = 0.79; 95% CI 0.67–0.93), results from two studies suggested a decreased CBC risk. We observed no association between CBC and smoking, age at menarche, oral contraceptive use, gravidity, breastfeeding, or menopausal status. Overall, the number of studies per risk factor was limited (n = 2–5).

Conclusions BMI is a modifiable risk factor for CBC. Data on the effect of other modifiable lifestyle and reproductive factors are limited. For better counseling of patients on lifestyle effects, more studies are urgently needed.

Keywords Metachronous · Second primary neoplasms · Breast cancer · Risk factors · Life style · Reproductive history · Review (publication type) · Meta-analysis (publication type)

Introduction

Over the last decades, the survival rate of breast cancer patients has been improving as a result of earlier diagnosis and better treatment [1, 2]. This leads to an increasing number of women who have been previously diagnosed with breast cancer, and are at risk for developing a second new malignancy in the opposite breast over time, i.e., metachronous contralateral breast cancer (CBC). Ten-year cumulative risk of CBC is around 4–5% in the general population [3, 4]

The risk of being diagnosed with CBC is therefore an important health issue among breast cancer survivors and often a recurring subject during follow-up at the outpatient clinic. This can also be observed from the increasing number of breast cancer survivors choosing for prophylactic removal of the contralateral breast. However, in a majority of the

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women with breast cancer, no survival benefit has been reported following this procedure [5, 6].

For this reason, it is important to evaluate the risk of developing CBC in individual breast cancer patients in a tailored fashion to provide them with an accurate follow-up strategy. Not only genetic and breast cancer treatment-related factors, but also lifestyle and reproductive factors should be assessed for this purpose.

Nowadays, there is an increasing interest in the impact of lifestyle and reproductive factors on CBC risk among healthcare professionals and breast cancer survivors, since these factors may partly be modifiable. Current available estimates on lifestyle and reproductive factors need to be combined to get estimates that are based on the highest level of evidence.

We therefore conducted a systematic review with meta-analysis and aimed to evaluate the impact of lifestyle and reproductive factors on metachronous CBC risk in population-based breast cancer cohorts.

Methods

This systematic review with meta-analysis is conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7].

Literature search

We searched the PubMed electronic database for publications on 2nd November 2019, by using search terms related to CBC in combination with lifestyle or reproductive factors that are potentially associated with CBC risk. More specific, we were interested in the impact of dietary habits, exercise, body mass index (BMI), alcohol use, smoking, age at menarche, oral contraceptive use, gravidity, age at primiparity, parity, breastfeeding, menopausal status, and age at menopause on metachronous CBC risk in population-based studies, i.e., studies with general, unselected breast cancer populations, without any germline mutation being tested on. Metachronous CBC is defined as a second primary breast cancer developed in the contralateral breast over time, from now onwards referred to as CBC.

Metachronous refers to a certain time lapse between the first primary breast cancer (PBC) diagnosis and the CBC diagnosis, but in literature this has not been clearly defined yet; mainly a time lapse of 3–12 months is being used. Our literature search included search terms for second breast cancer, thereby potentially including publications that studied the risks of developing ipsilateral second PBC, along with CBC. However, the literature states that only 5% of the second PBCs developed in the ipsilateral breast [8].

The literature search was limited to publications written in English from 1st January 1990, onwards. A description of the full search strategy is given in Table S1.

Study selection

Two reviewers (MMK, CZAS) identified potentially eligible publications by reading each title and abstract. From the selected publications, the full text was read. Publications were subsequently excluded if they met at least one of the exclusion criteria, which were defined as publications without pooled data (e.g., narrative review, research report, guideline, comment editorial), publications without relative risk (RR) estimates (i.e., no relative risk, odds ratio or hazard ratio) or publications with less than 20 CBC events reported. Further exclusion concerned publications on high-risk breast cancer patients (e.g., BRCA-related breast cancer, familial/hereditary breast cancer), publications on non-invasive CBC, publications on CBC analyzed in the context of recurrent disease or publications on topics not related to the effect of lifestyle or reproductive factors on CBC risk. When in doubt about including a paper ($n = 17$), a third reviewer was consulted (DA).

In addition, references of the eligible publications were checked for additional records missed by the initial literature search.

Data extraction

The main study characteristics from the included publications were extracted and collected in an overview (Table 1). These study characteristics included the author, year of publication, origin of cancer or hospital registry, study design, date of first PBC diagnosis, selection criteria, number of first PBC and CBC patients, mean/median years of follow-up (including range) and age (including range) of women with first PBC, required time lapse between first PBC and CBC diagnosis, lifestyle and/or reproductive factors of interest, and time of assessment of the risk factor status (e.g., at first PBC or CBC diagnosis).

Additionally, we extracted the relative risk estimates with the corresponding confidence interval (CI) and factors that were adjusted for in the analysis.

Statistical analyses

Relative risk estimates with the corresponding CI were collected, log-transformed, and pooled per lifestyle or reproductive factor. A random-effects model was used for the meta-analyses. If a study did not report an overall risk estimate for a specific factor, subgroup estimates were combined to create an overall risk estimate with the use of a random effects model.

Table 1 Main characteristics of the included studies, ranked by descending year of publication

First author, year of publication	Origin of cancer/hospital registry (study name)	Study design	Date[a]	Selection criteria	Number of 1st (P)BC patients[b]	Number of CBC patients available for analysis	Median years of FU (range)	Mean age (range)[c]	Time lapse required between 1st PBC and CBC (months)	Lifestyle and/or reproductive factors[d]	Assessment risk factor status	Factors adjusted for
Knight, 2017 [24]	USA, CAN, DNK (WECARE)	Case–control	1985–2008	Age < 55 years at 1st PBC diagnosis; Stage I–III 1st PBC	2,212	1,521	N/A	Med. 46 (23–54)	≥ 12 (when PBC diagnosed 1985–1999); ≥ 24 (when PBC diagnosed 1990–2008)	Alcohol use Smoking	1st PBC diagnosis	FH1; Men; BMI; Age; FTP; His; Stage; ER; Ctx; Rtx; Etx; Smok (in analysis for alcohol use); Alc (in analysis for smoking)
Brooks, 2016 [17]	USA, CAN, DNK (WECARE)	Case–control	1985–2008	Age ≤ 55 years at 1st PBC diagnosis; Stage I–III 1st PBC	2,045	1,386	N/A	Med. 46 (23–55)	≥ 12	BMI	1st PBC diagnosis	FH1; Men; FTP; Age; Stage, ER; Ctx; Etx; Rtx
Shankar, 2015 [10]	*IND*	*Cohort*	*1997–2006*	*Stage I–IV 1st PBC*	*532*	*24*	*N/A*	*47 (30–69)*	*> 6*	*Menopausal status*	*1st PBC diagnosis*	*N/A*
Sisti, 2015 [25]	USA, CAN, DNK (WECARE)	Case–control	1985–2009	Age ≤ 55 years at 1st PBC diagnosis; Stage I–III 1st PBC	2,212	1,521	N/A	Med. 46 (23–55)	≥ 12	Menarche Gravidity Age at primiparity[e] Parity[e] Breastfeeding[e] Menopausal status	N/A 1st PBC diagnosis CBC diagnosis 1st PBC diagnosis CBC diagnosis 2 years before 1st PBC diagnosis	FH; Par; Men; Meno; Ht; Age; Stage; His; Ctx; Etx Additionally, Prim, FTP and BF were mutually adjusted for
Brooks, 2012 [11]	**USA, DNK (WECARE)**	**Case–control**	**1985–2000**	**Age ≤ 55 years at 1st PBC diagnosis; Stage I-III 1st PBC**	**999**	**511**	**N/A**	**Med. 45 (23–55)**	**≥ 12**	**BMI**	**1st PBC diagnosis**	**FH1; FTP; Men; Age; Stage; His; ER; Ctx; Etx; Rtx**
Majed, 2011 [18]	FRA	Cohort	1981–1999	Stage I–III 1st PBC	15,166	1,370	10 (≤ 24)	54 (≥ 18)	> 6	BMI	1st PBC diagnosis	FH; Menopausal; Age; Per; N; His; HR, Tx

Table 1 (continued)

First author, year of publication	Origin of cancer/hospital registry (study name)	Study design	Date[a]	Selection criteria	Number of 1st (P)BC patients[b]	Number of CBC patients available for analysis	Median years of FU (range)	Mean age (range)[c]	Time lapse required between 1st PBC and CBC (months)	Lifestyle and/or reproductive factors[d]	Assessment risk factor status	Factors adjusted for
Poynter, 2010 [26]	USA, DNK (WECARE)	Case–control	1985–1999	Only information from non-carriers was used; Age ≤ 55 years at 1st PBC diagnosis; Stage I–III 1st PBC	1,325 (non-carriers)	597	N/A	NR (< 55)	≥ 12	**Menarche** **Age at primiparity[e]** Parity **Breastfeeding[e]** **Menopausal status** Age at menopause	**N/A** **CBC diagnosis** CBC diagnosis **CBC diagnosis** **CBC diagnosis** CBC diagnosis	FTP; Men; Menopausal; Age; Stage, Ctx, Etx
Figueiredo, 2010 [27]	USA, DNK (WECARE)	Case–control	1985–1999	Age ≤ 55 years at 1st PBC diagnosis; Stage I–III 1st PBC	1,325	597	N/A	46 (20–55)	≥ 12	Oral contraceptive use	Before CBC diagnosis	Age (Tested for other potential confounders as well, but no significant influence was observed. Factors tested: FH1; FTP; Men; Meno; Menopausal; Stage; His; Ctx; Etx)
Li, 2009 [12]	**USA (CSS)**	**Case–control**	**1990–2005**	**Stage I-IIIB 1st PBC, ER-positive 1st PBC**	**726**	**365**	**N/A**	**NR (40–79)**	**≥ 6**	**BMI** **Alcohol use** **Smoking**	**1st PBC diagnosis**	**Ctx, Etx** **Matching variables (implicitly adjusted for): County, Race; Age; Per; Stage; ST. Additionally, BMI was adjusted for use of Ht at 1st PBC diagnosis; Alc for BMI at reference date; Smok for FH1**

Table 1 (continued)

First author, year of publication	Origin of cancer/hospital registry (study name)	Study design	Date[a]	Selection criteria	Number of 1st (P)BC patients[b]	Number of CBC patients available for analysis	Median years of FU (range)	Mean age (range)[c]	Time lapse required between 1st PBC and CBC (months)	Lifestyle and/or reproductive factors[d]	Assessment risk factor status	Factors adjusted for
Figueiredo, 2008 [13]	**USA, DNK (WECARE)**	**Case–control**	**1985–2001**	**Age ≤ 55 years at 1st PBC diagnosis; Stage I-III 1st PBC**	**1,399**	**708**	**N/A**	**46 (23–55)**	**≥ 12**	**Oral contraceptive use**	**Before CBC diagnosis**	**FH1; FTP; Men; Menopausal at reference age; Age; Stage; His; Ctx; Etx; Rtx**
Trentham-Dietz, 2007 [19]	USA	Cohort	1987–2000	Age 18–79 years at 1st PBC diagnosis; Stage I–IV 1st PBC;	10,953	488	Mean 7.1 (1–19)	59 (18–79)	> 12	BMI[h] Alcohol use Smoking Menarche Oral contraceptive use Age at primiparity[e] Parity Menopausal status Age at menopause[e]	1st PBC diagnosis	FH, BMI; pack-years of cigarette smoking; recent alcohol intake. FTP; Menopausal; Ht; Per; Stage. Regression model was conditional on age
Largent, 2007 [28]	USA, DNK (WECARE)	Case–control	1985–1999	Age ≤ 55 years at 1st PBC diagnosis; Stage I–III 1st PBC	1,399	708	N/A	46 (23–55)	≥ 12	**Menarche** **Gravidity** **Age at primiparity** Parity **Breastfeeding** **Menopausal status** **Age at menopause**	**N/A** **Before CBC diagnosis** **CBC diagnosis** CBC diagnosis **CBC diagnosis** **CBC diagnosis** **CBC diagnosis**	**FH; FTP; Men; Meno; Age; His; Stage; Tx; Rtx**

Table 1 (continued)

First author, year of publication	Origin of cancer/hospital registry (study name)	Study design	Date[a]	Selection criteria	Number of 1st (P)BC patients[b]	Number of CBC patients available for analysis	Median years of FU (range)	Mean age (range)[c]	Time lapse required between 1st PBC and CBC (months)	Lifestyle and/or reproductive factors[d]	Assessment risk factor status	Factors adjusted for
Kuo, 2006 [20]	TAI	Cohort	1990–1999	Frequently diagnosed with PBC < 50 years	2,022	120[i]	3.21 (NR)	50 (NR)	> 6	Smoking Menopausal status	1st PBC diagnosis	Time to event. Additionally significant factors from the univariable analysis were taken into account. Factors taken into account: Meno; lobular His; Ctx; Etx; Rtx
Dignam, 2006 [21]	USA (NSABP)	Cohort	1981–1998	Stage I–III 1st PBC; ER-negative and lymph node-negative 1st PBC	4,077	242	NR	NR	NR[k]	BMI	1st PBC diagnosis	Race; Age;T; Tx
Dignam, 2003 [22]	USA (NSABP)	Cohort	1982–1987	Stage I–III 1st PBC; ER-positive and lymph node- negative 1st PBC	3,385	193	13.8 (NR)	NR	NR[l]	BMI	1st PBC diagnosis	Race; Menopausal; Age; T; ER; PR; Tx
Li, 2003 [14]	**USA (CSS)**	**Cohort**	**1983–1992**	**Age ≤ 45 years at 1st PBC diagnosis; Stage I–IV 1st PBC**	**1,285**	**77**	**Mean 9.0 (NR)**	**38 (≤ 45)**	**> 6**	**BMI** **Alcohol use** **Menarche** **Oral contraceptive use** **Gravidity** **Age at primiparity** **Parity**	**1st PBC diagnosis**	**Study; Age; Per; Stage; Ctx**
Vaittinen, Hemminki 2000 [29]	SWE	Cohort	1970–1996	Age 20–89 years at 1st PBC diagnosis	72,096	1,675	NR	NR (20–89)	≥ 6	Age at primiparity Parity	NR	FH; FTP; Primi; Age; Yr; Time
Cook, 1996 [15]	**USA (CSS)**	**Case–control**	**1978–1990**	**Age < 85 years at 1st PBC diagnosis; Stage I-III 1st PBC**	**424**	**216**	**N/A**	**NR (< 85)**	**≥ 6**	**BMI** **Gravidity** **Parity** **Menopausal status**	**1st PBC diagnosis**	**FH1; Menopausal; His** **Matched factors: Age; Stage; Time**

Table 1 (continued)

First author, year of publication	Origin of cancer/hospital registry (study name)	Study design	Date[a]	Selection criteria	Number of 1st (P)BC patients[b]	Number of CBC patients available for analysis	Median years of FU (range)	Mean age (range)[c]	Time lapse required between 1st PBC and CBC (months)	Lifestyle and/or reproductive factors[d]	Assessment risk factor status	Factors adjusted for
Bernstein, 1992 [23]	USA	Cohort	1980–1982	Age 20–54 years at 1st PBC diagnosis; Stage I–IV 1st PBC	4,550	136	Mean 4.3 (NR)	44 (20–54)	> 6	Alcohol use Smoking Menarche Oral contraceptive use Gravidity Age at primiparity Parity Breastfeeding Menopausal status	1st PBC diagnosis	FH; Edu; BMI; FTP; Prim; Men; Meno; Menopausal; Age; Stage; Lobular His; History of benign disease

Duplicate studies (i.e., with the same selection of patients) excluded from the meta-analyses are highlighted in bold

Factors excluded from the meta-analyses because only a univariable estimate was provided (6) are highlighted in italics

BC breast cancer, *PBC* primary breast cancer, *CBC* contralateral breast cancer, *BMI* body mass index, *FU* follow-up, *USA* United States of America, *CAN* Canada, *DNK* Denmark, *FRA* France, *IND* India, *TAI* Taiwan, *SWE* Sweden, *Med* median, *Race* race/ethnicity, *FH* family history of breast cancer, *FH1* first degree family history of breast cancer, *Edu* education, *Smok* smoking, *Alc* alcohol use, *BF* breast feeding, *FTP* number of full term pregnancies, *Prim* age at primiparity, *Par* age at parity, *Men* age at menarche, *Meno* age at menopause, *Menopausal* menopausal status, *Ht* postmenopausal hormone therapy, *Age* age at primary breast cancer diagnosis, *Yr* year of birth, *Per* period of recruitment/year of first PBC diagnosis, *Stage* stage of primary breast cancer, *N* number of positive lymph nodes, *T* tumor size, *His* histology of primary breast cancer, *ER* estrogen receptor status of primary breast cancer, *PR* progesterone receptor status of primary breast cancer, *HR* hormonal receptor status, not specified, *Tx* treatment, not specified, *Ctx* chemotherapy, *Etx* endocrine therapy, *Rtx* radiotherapy, *Time* time between primary breast cancer and CBC diagnosis, *ST* survival time, *N/A* not applicable, *NR* not reported

.[a]Date of first PBC diagnosis

[b]Number of first PBC patients or BC patients (i.e., first PBC and CBC patients) for case–control and cohort studies, respectively

[c]Mean age (range) of women with first PBC

[d]Selected lifestyle and reproductive factors per study

[e]Among parous women only

[f]Only the data of non-carrier cases and controls were used for the meta-analysis

[g]The underlying cohort of this study was composed of women with only estrogen receptor-positive first PBC

[h]Among postmenopausal women only

[i]Bilateral BC cases of which 44 synchronous BC, 75 metachronous BC and 1 unknown type of BC

[j]The underlying cohort of this study was composed of women with only estrogen receptor-negative first PBC

[k]No definition for metachronous CBC was provided, but the paper focussed on events occurring over time, therefore assumed that the focus was on metachronous CBC events

[l]No definition for metachronous CBC was provided, but from the figures, we observed the first CBC event to appear at least 3 months after first PBC diagnosis

Relative risk estimates from univariable and multivariable analyses were analyzed separately. If both an adjusted (i.e., using multivariable risk estimates) and a crude meta-analysis (i.e., using univariable risk estimates) could be conducted for a factor, we only selected the papers eligible for the adjusted meta-analysis.

Subsequently, we evaluated whether there was potential overlap in patients from the different papers. In case of overlap, we selected either the most recent or the most relevant (i.e., on topic) paper.

To examine the continuous effects (trend analysis) of BMI and number of full-term pregnancies (FTP), we used the dose–response method described by Greenland et al. [9]. Results from this analysis were subsequently pooled using a random-effects meta-analysis and the *p*-value for trend was extracted from the confidence interval of the pooled estimate.

Additionally, we tested for heterogeneity using the I^2-statistics and reported the *p*-value for heterogeneity for each lifestyle or reproductive factor in the figures.

We used the METAN package of Stata Statistical Software version 14.0 to conduct the statistical analyses.

Results

Search results and study selection

Our PubMed literature search identified 784 publications, of which 707 met the inclusion criteria (Fig. 1). Based on relevance, 41 of the remaining publications were selected for further review. Hereof, 20 publications were eligible for inclusion after applying the exclusion criteria. No additional publications were found by checking the references of the eligible publications. In addition, seven out of these 20 publications were ineligible for the (adjusted) meta-analyses due to non-preferable risk estimates (i.e., solely reporting univariable risk estimates [10]) or overlap in patients [11–16] and were therefore excluded.

From the 13 papers finally used for the meta-analysis, there were between 424–72,096 first PBC and 24–2515 CBC patients available for the analyses. A majority of the studies (9 out of 13) were at least partially performed in the USA.

Meta-analyses

The adjusted estimates for lifestyle and reproductive factors are presented in an overall plot in Figs. 2 and 3, respectively, and per lifestyle or reproductive factor in Supplementary Figs. S1–16.

Heterogeneity will only be reported for risk factor estimates in case of moderate or high heterogeneity (i.e., $I^2 > 50\%$, $p < 0.05$ as reported in the figures).

Lifestyle factors (Fig. 2; Supplementary Figs. S1–5)

Eight publications studied the impact of potentially modifiable lifestyle factors (BMI, alcohol use, and smoking) on CBC risk (Table 1) [11, 17–24].

Overweight and obesity (BMI ≥ 25 kg/m^2) compared to having a normal weight (BMI < 25 kg/m^2) assessed at first PBC diagnosis were associated with an increased CBC risk (RR = 1.22; 95% CI 1.01–1.47); however, heterogeneity was high ($I^2 = 75.4\%$, $p = 0.003$; Fig. S1) [17–19, 21, 22]. The main outlier was the study performed by Brooks et al. [17], possibly due to inclusion of mainly young, premenopausal women at first PBC diagnosis (further elaborated on in "Discussion" section). Excluding this study resulted in a decrease in heterogeneity and a slight increase in CBC risk (RR = 1.31; 95% CI 1.15–1.50; $I^2 = 35\%$). Trend analysis on BMI showed a significant increased CBC risk with increasing BMI (*p*-trend < 0.0001).

The meta-analysis on three studies concerning alcohol use (ever vs. never; assessed at first PBC diagnosis) was suggestive of increased CBC risk (RR = 1.15; 95% CI 1.02–1.31; Fig. S4) [19, 23, 24]. Four studies on smoking did not result in an association with CBC risk (ever vs. never; assessed at first PBC diagnosis; Fig. S5) [19, 20, 23, 24].

There were no data available on the association between dietary habits or physical exercise and CBC risk.

Reproductive factors (Fig. 3; Supplementary Figs. S6–16)

Eight publications studied the impact of reproductive factors (age at menarche, oral contraceptive use, gravidity, age at primiparity, parity, breastfeeding, menopausal status, age at menopause) on CBC risk (Table 1) [19, 20, 23, 25–29].

Older age at primiparity (≥ 25 years vs. < 25 years; assessed at/before CBC diagnosis) was investigated in four studies and was associated with increased CBC risk (RR = 1.06; 95% CI 1.02–1.10; Fig. S9) [19, 23, 25, 29].

The two studies on age at menopause (< 45 years vs. ≥ 45 years; assessed at/before CBC diagnosis) suggested a decreased CBC risk association for this factor (RR = 0.79; 95% CI 0.67–0.93; Figure S16) [19, 26].

Three studies on parity (≥ 1 FTPs vs. nulliparous; assessed at/before CBC diagnosis) showed no significant association with CBC risk (Fig. S10) [19, 25, 29], although trend-analysis resulted in a decreasing risk with increasing numbers of FTPs (*p*-trend < 0.0001). Moreover, subgroup analysis on two papers suggested that having ≥ 4 FTPs compared to being nulliparous (assessed at/before CBC diagnosis) was protective for CBC risk (RR = 0.56; 95% CI 0.42–0.76; Fig. S12) [19, 28]. Having ≥ 2 FTPs compared to 1 FTP (assessed at first PBC diagnosis), which was investigated in three papers, showed a protective effect for

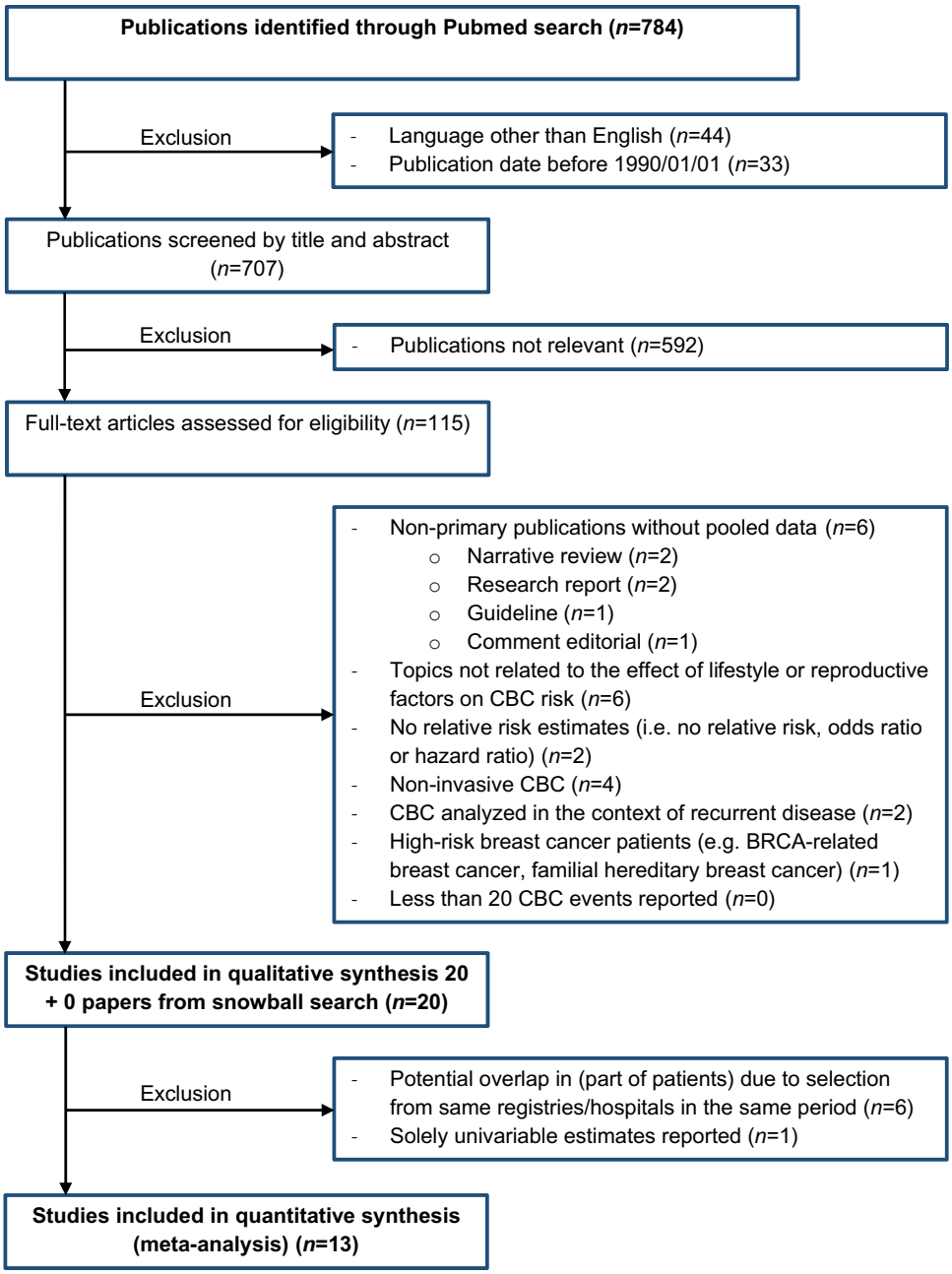

Fig. 1 Flowchart of the literature search for a systematic review with meta-analysis assessing lifestyle and reproductive risk factors for contralateral breast cancer. *CBC* contralateral breast cancer

CBC risk as well (RR = 0.86; 95% CI 0.79–0.94; Fig. S13) [23, 25, 29]. The association between breastfeeding (ever vs. never; assessed at/before CBC diagnosis) and CBC risk was borderline significant, but the meta-analysis was based on two papers only (RR = 0.87; 95% CI 0.74–1.01; Fig. S14) [23, 25].

No significant association was found for age at menarche (≥ 13 years vs. < 13 years; Fig. S6) [19, 23, 27], oral contraceptive use (ever vs. never; assessed before CBC diagnosis; Fig. S7) [19, 23, 27], gravidity (ever pregnant vs. never pregnant; assessed at first PBC diagnosis; Fig. S8) [23, 25], menopausal status (postmenopausal vs. premenopausal; assessed at/before first PBC diagnosis; Fig. S15), and CBC risk [19, 20, 23, 25]. However, for all these factors, the number of papers was limited ($n = 2$–4).

Discussion

In this systematic review and meta-analysis, we studied the impact of lifestyle and reproductive factors on CBC risk in population-based breast cancer cohorts.

We observed a moderately increased CBC risk in women being overweight. Further, alcohol use and older age at

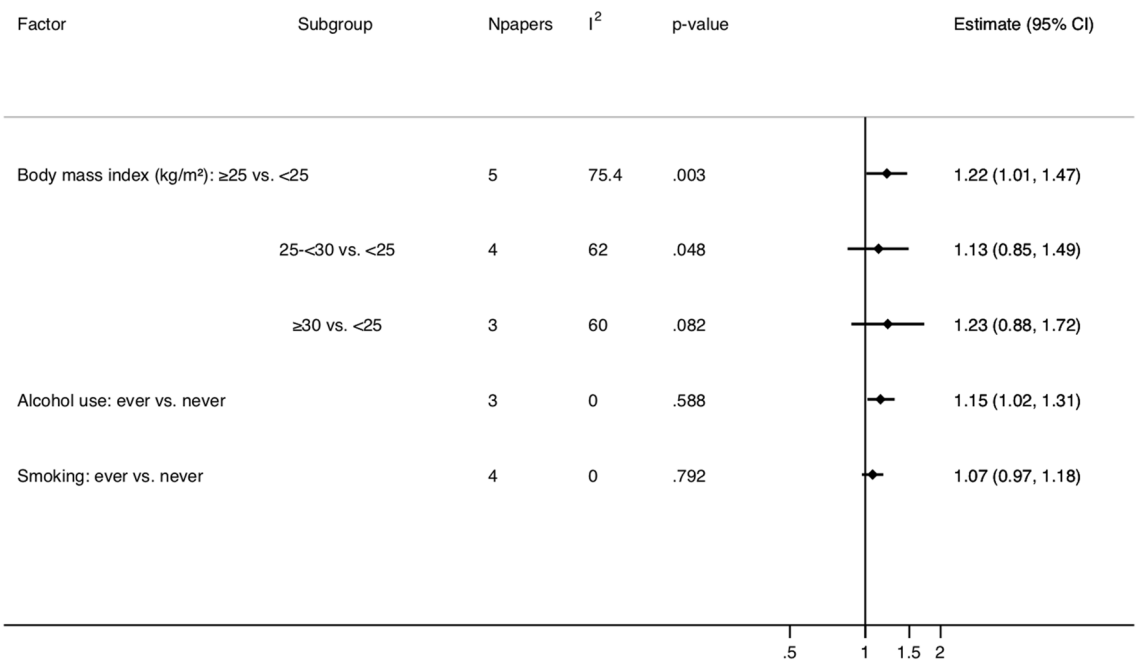

Fig. 2 Forest plot of the overall adjusted meta-analyses per lifestyle factor on the risk of developing contralateral breast cancer in population-based cohorts Npapers = number of papers used for the analysis; I^2 = test for heterogeneity; p-value = p-value for heterogeneity: $p < 0.05$ considered significant; estimate = relative risk estimate combining relative risks, odds ratios, and hazard ratios]

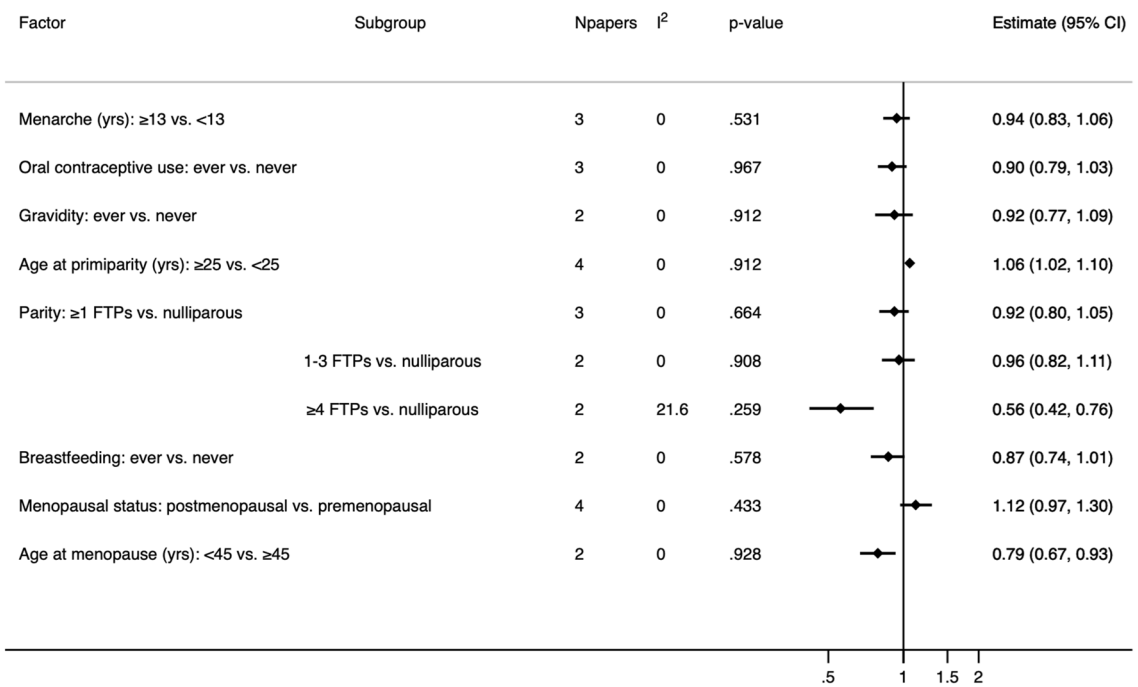

Fig. 3 Forest plot of the overall adjusted meta-analyses per reproductive factor on the risk of developing contralateral breast cancer in population-based cohorts Npapers = number of papers used for the analysis; I^2 = test for heterogeneity; p-value = p-value for heterogeneity: $p < 0.05$ considered significant; estimate = relative risk estimate combining relative risks, odds ratios, and hazard ratios. *yrs* years, *FTP(s)* full-term pregnancy/pregnancies]

primiparity were suggestive of increased CBC risk, whereas a high number of full-term pregnancies and younger age at menopause seemed associated with decreased CBC risk. Overall, the number of papers available for the meta-analyses was limited.

We observed high heterogeneity in the meta-analysis concerning BMI. Difference in menopausal status at first PBC diagnosis could have led hereto, since most women of the lower risk outliers [17, 21] were pre/perimenopausal as opposed to the other studies [18, 19, 22] in which the majority of women was postmenopausal at first PBC diagnosis. It is sometimes hypothesized that high BMI in premenopausal women may lead to anovulation and reduction of circulating estrogen and progesterone and thereby reducing PBC risk [30]. Contrarily, in postmenopausal women, a high BMI is observed to be a risk factor for first PBC [31, 32], likely due to increasing estrogen concentration through adipose tissue production and reduction of sex hormone-binding globulins [33]. These mechanisms may also be applied to the association between BMI and CBC. Still, literature supporting the inverse association between BMI and premenopausal first PBC is scarce and lacks strong evidence [31, 32].

In contrast to the systematic review of Simapivapan et al. [34] in which no conclusive association between alcohol consumption and second PBC was found, we did observe a positive association between alcohol consumption and CBC risk. Simapivapan et al. included the same publications as we did [12, 14, 16, 19, 23], but did not exclude the publications of Li et al. [12, 14] which we considered to overlap in patient cohort with Knight et al. [24]. Consequently, because of the limited number of available publications, we had to use a dichotomous outcome (i.e., ever vs. never), whereas Simapivapan et al. gave a narrative overview of the frequency and/or period of exposure (e.g., pre or post breast cancer diagnosis) to alcohol consumption.

Despite contradicting evidence relating to the impact of parity on CBC risk, it seems that multiple FTPs are protective for developing a CBC as shown by the trend-analysis for an increasing number of FTPs and subgroup analyses for parity (≥ 4 FTPs vs. nulliparous and ≥ 2 FTPs vs. 1 FTP). The fact that some analyses did not show a significantly decreased CBC risk for parity (≥ 1 FTPs vs. nulliparous and 1–3 FTPs vs. nulliparous) could be explained by a lack of power from small contrast in numbers of FTP and from including a small number of studies ($n = 2$–3).

Just as for first PBC [35], having multiple full-term pregnancies seemed protective for developing CBC, whereas primiparity at an older age showed an increased risk of CBC. Pregnancy induces terminal differentiation of mammary luminal cells through exposure to human chorionic gonadotrophin (hCG). This results in changing gene expression in the mammary stem cells, becoming more refractory to carcinogenesis through increased DNA repair pathway and apoptosis control. Older age at primiparity delays the formation of this protective 'genomic signature' and extends the exposure time to carcinogens, thereby making the breast more susceptible to carcinogenesis [36]. We assume that the underlying mechanisms for parity and age at primiparity on first PBC risk may apply for CBC as well.

We observed a decreased CBC risk in women with younger age at menopause (i.e., early/premature menopause), but the number of papers was limited ($n = 2$). Nonetheless, older age at menopause has previously been described as a risk factor for first PBC [37], possibly due to a higher number of menstrual cycles experienced [38], thereby having longer exposure to high estrogen levels [39]. Therefore, it makes sense that a younger age at menopause is associated with a decreased CBC risk. Moreover, first PBC risk increases less for every year older at menopause than for every year younger at menarche, implying that not only the number of menstrual cycles plays a role in the relationship between childbearing years and first PBC risk (and possibly CBC risk) [37] but also the number of reproductive years before the first FTP is even more important. Nonetheless, we did not find any association between age at menarche and CBC risk.

There are several limitations to our study that need to be considered. First, there were only few studies available per studied risk factor (two to five per meta-analysis), underlining that little is known about the impact of lifestyle and reproductive factors on CBC risk. For example, only two publications were included in the meta-analyses for gravidity, subgroups of parity (1–3 or ≥ 4 full-term pregnancies vs. nulliparous), breastfeeding, and age at menopause. In addition, we had to use a dichotomous outcome (i.e., ever vs. never) for the meta-analyses concerning smoking, alcohol use, oral contraceptive use, gravidity, and breastfeeding. The outcomes of these analyses should therefore be interpreted with caution. In addition, the small number of papers that was available per factor inhibited us from being able to inspect the presence of publication bias.

Second, the analyzed data are heterogeneous regarding the timing of assessment of the lifestyle and reproductive factors. All lifestyle factors (BMI, alcohol use, and smoking) were assessed at first PBC diagnosis, whereas most reproductive factors were assessed at or before CBC diagnosis. Factors assessed at first PBC may be useful for risk prediction but are not that helpful for the prediction of risk modification. Although several modifiable factors were included in this meta-analysis, the potential effect of actual changes in lifestyle factors after first PBC diagnosis has not been addressed.

Third, our literature search included search terms for second breast cancer, thereby including publications that studied the risks of developing ipsilateral second breast cancers as well. However, considering that the large majority (95%)

of second PBCs is contralateral as compared to ipsilateral [8], we do not expect large risk alterations.

Fourth, we did not perform a quality assessment of the included studies; instead, we applied our own selection criteria (e.g., selecting only papers with a minimum number of events and evaluating the statistical methods that were used). Moreover, we know from literature that quality assessment tools in meta-analyses do not prevent nor resolve potential bias [40, 41].

Many breast cancer survivors express their concern on developing breast cancer in the other breast during follow-up at the outpatient clinic. In a previous meta-analysis, we assessed the impact of genetic and clinical factors (i.e., pathological characteristics and treatment) on CBC risk [42]. For example, breast cancer patients with a positive mutation status (e.g., *BRCA1*, *BRCA2* or *CHEK2* c.1100delC) have a two to four times higher relative risk of developing a CBC [42]. The contribution of lifestyle and reproductive factors on CBC risk is compared hereto relatively small. Nonetheless, there is a specific interest from breast cancer survivors in factors that can be modified after first PBC diagnosis (e.g., weight, alcohol use), thereby potentially decreasing the risk of developing a CBC.

To our knowledge, this is the first meta-analysis that studied the impact of multiple lifestyle and reproductive factors on CBC risk, thereby seeking for the best possible evidence on this topic. Healthy BMI seems to be associated with a lower risk of developing a CBC as compared to high BMI. However, we could not prove that losing weight after the first PBC actually has a risk reducing effect on developing a CBC. More research on the impact of weight loss after the first PBC on CBC risk is therefore necessary. Nonetheless, losing weight is considered beneficial for breast cancer patients who are overweight or obese, if not for decreasing CBC risk, then either for other health outcomes. Weight loss intervention programs could be considered as part of the rehabilitation program for breast cancer survivors and have already gained some success in weight loss in breast cancer patients [43, 44]. In addition, breast cancer survivors in general may be advised to maintain a healthy lifestyle.

Most importantly, this systematic review and meta-analysis highlighted the current gaps in our knowledge and stressed the importance of further investigations that are needed to improve CBC risk management in breast cancer survivors. The results pointed in a specific direction for alcohol use, number of FTPs, age at primiparity, and age at menopause, but to provide strong conclusions, more research is definitely needed.

Moreover, more research on the impact of modifiable lifestyle factors (e.g., exercise, dietary habits, extent and timing of alcohol use) and known reproductive risk factors for a first PBC (e.g., parity, menopausal status) on CBC risk is necessary to offer breast cancer patients personalized evidence-based CBC risk estimates.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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