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Review

The impact of patient characteristics and lifestyle factors on the risk of an ipsilateral event after a primary DCIS: A systematic review

Sena Alaeikhanehshir [a, b], Ellen G. Engelhardt [a, c], Frederieke H. van Duijnhoven [b], Maartje van Seijen [a], Patrick A. Bhairosing [d], Donna Pinto [e], Deborah Collyar [e], Elinor Sawyer [f], Shelley E. Hwang [g], Alastair M. Thompson [h], Jelle Wesseling [a, i], Esther H. Lips [a, *, 1], Marjanka K. Schmidt [a, c, 1], on behalf of PRECISION

[a] Division of Molecular Pathology, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands
[b] Department of Surgery, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands
[c] Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands
[d] Scientific Information Service, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands
[e] Patient Advocate Involvement Panel (PAIP), PRECISION PROJECT, United Kingdom
[f] School of Cancer and Pharmaceutical Sciences, Guy's Hospital, King's College London, London, United Kingdom
[g] Department of Surgery, Duke University Medical Centre, Duke Cancer Institute, Durham, NC, United States
[h] Dan L Duncan Comprehensive Cancer Centre, Baylor College of Medicine, Houston, TX, United States
[i] Department of Pathology, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

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ABSTRACT

Objective: The majority of 'low-risk' (grade I/II) Ductal Carcinoma In Situ (DCIS) may not progress to invasive breast cancer during a women's lifetime. Therefore, the safety of active surveillance versus standard surgical treatment for DCIS is prospectively being evaluated in clinical trials. If proven safe and selectively implemented in clinical practice, a significant group of women with low-risk DCIS may forego surgery and radiotherapy in the future. Identification of modifiable and non-modifiable risk factors associated with prognosis after a primary DCIS would also enhance our care of women with low-risk DCIS.
Methods: To identify modifiable and non-modifiable risk factors for subsequent breast events after DCIS, we performed a systematic literature search in PUBMED, EMBASE and Scopus.
Results: Six out of the 3870 articles retrieved were included for final data extraction. These six studies included a total of 4950 patients with primary DCIS and 640 recorded subsequent breast events. There was moderate evidence for an association of a family history of breast cancer, premenopausal status, high BMI, and high breast density with a subsequent breast cancer or further DCIS.
Conclusion: There is a limited number of recent studies published on the impact of modifiable and non-modifiable risk factors on subsequent events after DCIS. The available evidence is insufficient to identify potential targets for risk reduction strategies, reflecting the relatively small numbers and the lack of long-term follow-up in DCIS, a low-event condition.

Contents

* Corresponding author. The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066, CX, Amsterdam, Netherlands.
E-mail address: e.lips@nki.nl (E.H. Lips).
[1] Shared last authors.

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1. Introduction

Knowledge about the natural course of disease of women with Ductal Carcinoma In Situ (DCIS) is scarce, but available evidence suggests that if left untreated, not all DCIS will progress to invasive breast cancer (IBC) [1,2]. Treated women diagnosed with primary DCIS have a 5 year risk of developing a subsequent invasive ipsilateral breast cancer of approximately 6% [3]. A Dutch study showed, if treated with surgery (and radiotherapy if indicated) that women with DCIS have a 5-year overall survival probability of about 98% [4], and a US study showed a breast cancer-specific mortality probability of approximately 3% [5]. The modest risks of experiencing an invasive breast event and breast cancer death also mean that many women with DCIS may safely forego immediate treatment, and many are potentially at risk for overtreatment. These women are at risk for therapy-induced side effects, and negative treatment dependent psychological effects without deriving any clear treatment benefit in terms of progression-free, recurrence-free, or overall survival [6–10].

To reduce overtreatment, it is crucial to be able to accurately differentiate between indolent and aggressive DCIS. Evidence on which factors are predictors of progression in DCIS is still limited. Some characteristics of DCIS lesions, such as nuclear grade, tumour size, and detection by palpation have been shown to be associated with a subsequent breast event specifically, ipsilateral Invasive Breast Cancer ($IBC_{ipsilateral}$), or ipsilateral DCIS recurrence (iDCISr) [11]. Further, known risk factors for the development of primary IBC, such as body weight, breast density, and a family history of breast cancer (see for example [12–38]), may or may not be predictors of DCIS progression, but have not been validated. The association between characteristics of women with DCIS and clinical outcomes was studied by Shamliyan et al., synthesizing data from five randomized controlled clinical trials, and 64 observational studies published up to 2009 [39]. They reported statistically significant associations between ipsilateral breast tumour recurrence and a younger age, premenopausal status at diagnosis, obesity, and a high breast density [39]. However, the strength of the evidence they retrieved was modest to weak; it is not yet clear to what degree these factors are associated with DCIS progression.

At present, three international randomized controlled trials (i.e., COMET, LORIS, LORD-trial) [40–42] and one single arm trial (JCORG, LORETTA) [43] are studying whether, and in which patients it is safe to omit surgical treatment (and radiotherapy) for 'low-risk' DCIS (i.e., DCIS grade I and II). These ongoing active surveillance trials have the potential to change the current clinical approach towards the management of DCIS, resulting in an increasingly number of women with DCIS remaining in the breast at risk of experiencing a subsequent breast event. With this future scenario in mind, it becomes increasingly important to identify predictors of DCIS progression to IBC. Insight into predictors of progression can be used to estimate the risk of experiencing a subsequent breast event for an individual patient and can aid tailoring DCIS management strategies. Lifestyle factors (e.g. smoking, alcohol consumption, weight/BMI) possibly associated with an increased risk to develop IBC are potential targets for risk reduction interventions (e.g., smoking cessation or weight loss). Knowledge of the effect of non-modifiable and modifiable factors on the risk of progression to IBC could help women together with their clinician make an informed decision about active surveillance and screening for early detection and lifestyle changes.

In the wake of the ongoing active surveillance trials, we anticipate a shift in thinking towards less invasive management strategies for low-risk DCIS in the coming decades. Therefore, a systematic literature review was performed to evaluate the impact of established breast cancer risk factors on the risk of developing in situ or invasive disease after treatment of primary DCIS.

2. Materials & methods

2.1. Systematic literature search and inclusion/exclusion criteria

Relevant articles were identified by performing a systematic literature search in consultation with an experienced information specialist (P.A.B.). The bibliographic databases PUBMED, EMBASE (Ovid), and Scopus were searched for articles from 1970 till September 19, 2018. During primary review, the study by Shamliyan et al. 2010 was encountered [39], which identified five randomized controlled clinical trials and 64 observational studies published from January 1970 to January 2009 by searching trial registries and American cancer registries. Ten publications reporting results from the Surveillance Epidemiology and End Results (SEER) database were also included [39]. Considering the extent of overlap in the research questions, the current review was amended to focus on articles published after January 2009, and only before January 2009 if not already included by Shamliyan et al. Eligible studies were full-text English language involving women diagnosed with primary DCIS (all grades). Observational studies, case-control studies, and randomized controlled trials were included. Animal studies, case reports/case series, conference abstracts, commentaries and letters to the editor were excluded. See Fig. 1 for the PRISMA flow diagram and Appendix A for the detailed search strategy.

All the articles from the initial search were independently reviewed by E.G.E and S.A. based on title and abstract. Any discrepancies were resolved by consensus, and if consensus could not be reached, the full-text was reviewed. Full-text assessment was reviewed by E.G.E. and S.A., and any disagreement during this phase was settled by a third reviewer (M.v.S.).

2.2. Data extraction

Data extracted from the articles by one of the reviewers included: patient cohort used; population source; the period of recruitment; number of patients included; the number of patients with the studied outcomes: ipsilateral invasive breast cancer recurrence; in situ recurrence in the ipsilateral breast; development of a regional and/or distant metastasis ≥6 months after DCIS diagnosis; median follow-up time (years); type of treatment; patient age; Hazard Ratios (HR), Odds Ratios (OR), and Relative Risks (RR) with their concomitant 95% confidence intervals (CI). A complete overview of the risk factors of interest for this review are listed in Table 1.

Table 1
Factors of interest for a breast event after primary DCIS[a].

Modifiable factors	Non-modifiable factors
Smoking	**Family history of breast cancer**[a]
Alcohol consumption	Ethnicity
Physical activity	Height
Weight/BMI[a]	Age at menarche
Diet/fat intake	**Menopausal status**[a]
Use of hormonal contraception	**Breast density**[a]
Breast feeding	
Hormone Replacement Therapy (HRT)	
Gravidity and parity	
Age at birth of first child	

[a] Statistically significant associations found in this systematic review are in bold.

2.3. Methodological quality assessment

An adjusted Newcastle-Ottawa scale was used to assess methodological quality and potential bias in the included articles [44]. The Newcastle-Ottawa scale assessment is based on study

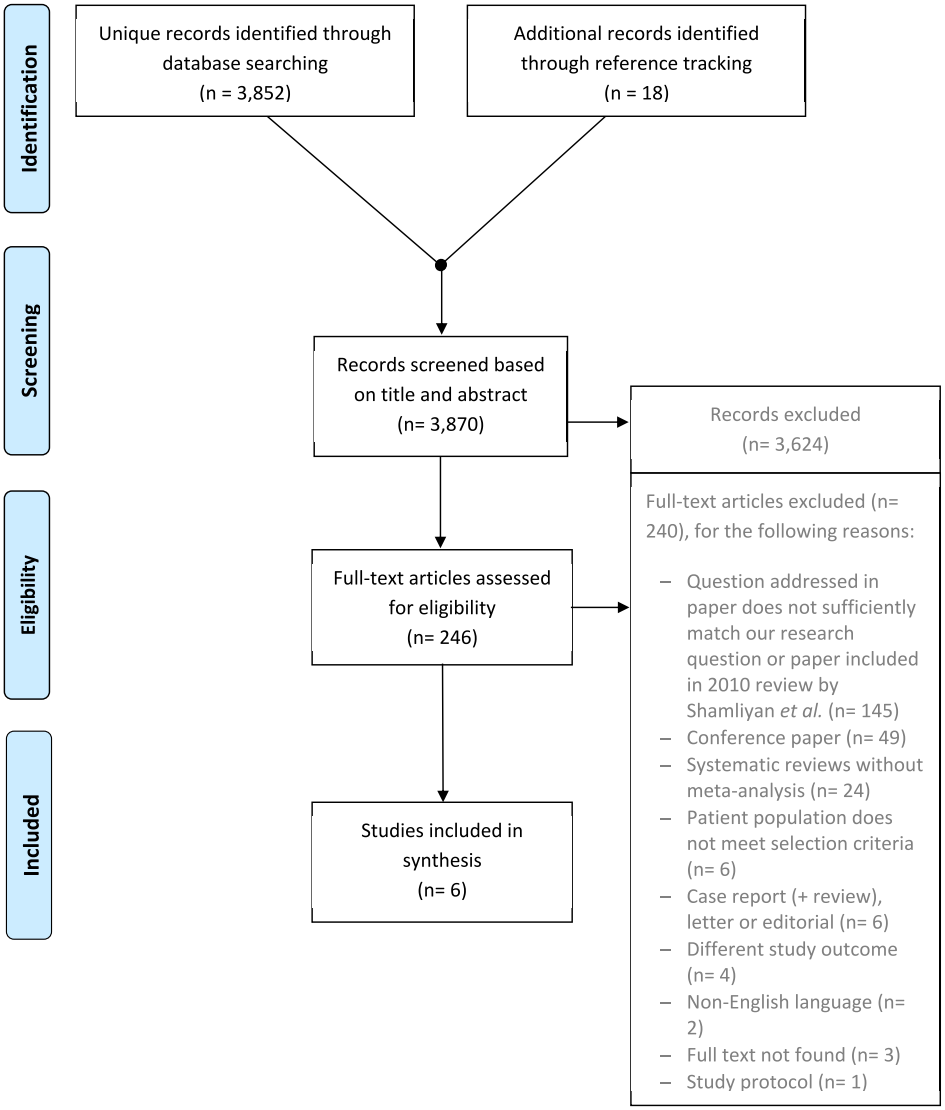


Fig. 1. PRISMA flow diagram.

population selection, assessment of confounders, and quality of outcome measurement (see Appendix B for the adapted version used in this study).

3. Results

3.1. Study & patients characteristics

Six articles were included (Fig. 1). These studies reported data from 4950 women of European descent (sample sizes ranging between 50 and 1533 patients per study) with primary DCIS. A total of 640 (range: 13–239) breast events ($IBC_{ipsilateral}$, iDCISr, locoregional, and/or distant metastasis) were observed and the median follow-up varied between 4.4 and 9.0 years. Most patients underwent breast conserving surgery often followed by radiotherapy and also sometimes by endocrine therapy or mastectomy (see Table 2 for the characteristics of included studies).

The studies included in this review lacked data on smoking, alcohol consumption, physical activity, diet/fat intake, use of hormonal contraception, breast feeding, hormone replacement therapy, gravidity/parity/age at birth of first child, ethnicity, height, and age at menarche. For four factors significant associations were reported (Table 1).

3.1.1. Family history

Of the three studies [45–47] reporting on family history, one reported a statistically significant association [47]. Baglia et al. found that women with more than two first degree relatives with breast cancer gives a two-fold risk increase for a subsequent breast event after a primary DCIS ($OR_{(multivariate)}$ 1.78 (95%-CI: 1.02–3.10)) compared to women with no first degree family members with breast cancer. Also, having an affected first degree relative younger than 50 years, increased the risk for a subsequent breast event, ($OR_{(multivariate)}$ 1.56 (95%-CI: 1.05–2.33)) compared to having an affected first degree family member aged 50 years or older.

3.1.2. BMI

One study reported on BMI [46] documenting a 52% risk reduction for a subsequent breast event in women with a BMI lower than 25 compared to women with a BMI of 25 or higher ($HR_{(multivariate)}$ 0.48 (95%-CI: 0.26–0.90)).

3.1.3. Menopausal status

Three studies [45,46,48] described statistically significant associations between menopausal status and the risk of developing a subsequent breast event. De Lorenzi et al. [46] stated that the risk for a subsequent breast event was higher in women who were pre- or peri-menopausal ($HR_{(multivariate)}$ 1.89 (95%-CI: 1.09–3.29)) compared to post-menopausal women. Shurell et al. [45] reported a lower risk of experiencing a subsequent breast event in post-menopausal compared to pre-menopausal women ($HR_{(multivariate)}$ 0.54 (95%-CI: 0.37–0.77)). Similarly, Hathout et al. [48], reported that post-menopausal women have a decreased risk of developing a subsequent breast event compared to pre-menopausal women ($OR_{(multivariate)}$ 0.13 (95%-CI: 0.04–0.43)).

Table 2
Description of included studies and populations.

Articles	$N_{population}$	N_{events}	Cohort Source Country	Recruitment period	Median follow-up (years)	Age at diagnosis	Treatment received for primary DCIS	
							Surgery	Adjuvant treatment
De Lorenzi et al. 2018	419	34 iDCISr 37 $IBC_{ipsilateral}$ 1 Distant metastasis 3 Regional metastasis	**Cohort:** Women with primary DCIS **Source:** Single hospital-based **Country:** Italy	2000–2008	7.7	<50 years: n = 152 50–69 years: n = 130 ≥60 years: n = 137	Oncoplastic Surgery n = 44 BCS n = 375	RT n = 419 ET n = 189
Baglia et al. 2018	1533 Cases: 539 Controls: 994	239 $IBC_{ipsilateral}$ 296 contralateral breast cancers 4 bilateral breast cancers	**Cohort:** Women with primary DCIS **Source:** Population-based **Country:** United States	1995–2013	NR	<50 years: n = 531 50–69 years: n = 530 60–69 years: n = 317 70–79 years: n = 155	BCS n = 1239 MST n = 294	RT n = 721
Shurell et al. 2018	1323	71 iDCISr 55 $IBC_{ipsilateral}$	**Cohort:** Women with primary DCIS **Source:** Single hospital-based **Country:** United States	1980–2010	6.6	Median: 56 (range 27–86)	BCS n = 1323	RT n = 1323
Hathout et al. 2013	440	8 iDCISr 5 $IBC_{ipsilateral}$	**Cohort:** Women with primary DCIS **Source:** Multi-Centre **Country:** Canada	2003–2010	4.4	Median: 58 (range NR)	BCS n = 440	RT n = 440
Shah et al. 2013	300	13 Unspecified recurrences 1 Distant metastases	**cohort:** Women with primary DCIS **Source:** Multi-Centre **Country:** United States	1993–2010	4.7	Median: 66 (range 41–88)	BCS n = 300	RT n = 300
Habel et al. 2010	935	164 Unspecified recurrences 5 regional/distant metastasis[a]	**Cohort:** Women with primary DCIS **Source:** Multi-Centre **Country:** United States	1990–1997	8.6	Median: NA (range NR)	BCS n = 935	RT: n = 446 ET: n = 44

*WBRT: Whole Breast Radiation Therapy, BCS: Breast Conserving Surgery, MST: Mastectomy, RT: Radiotherapy, ET: Endocrine Treatment, IBC: Invasive Breast Cancer, NR: Not Reported.

[a] Regional or distant metastases (without ipsilateral breast involvement).

3.1.4. Breast density

Breast density assessment, was variously considered: assessment of parenchymal patterns, area of density (quintiles), percentage of density, and BI-RADS (Breast Imaging Reporting and Data System) classification. Habel et al. reported the strongest association between a subsequent breast event after DCIS and parenchymal patterns ($HR_{(univariate)}$ 2.0 (1.0–3.7)). For area of density in quintiles, the second ($HR_{(univariate)}$ 1.6 (1.0–2.8)) and fifth ($HR_{(univariate)}$ 1.9 (1.2–3.20)) quintile were associated with a statistically significant increase in the risk of developing a subsequent breast event after DCIS compared to the first quintile [49].

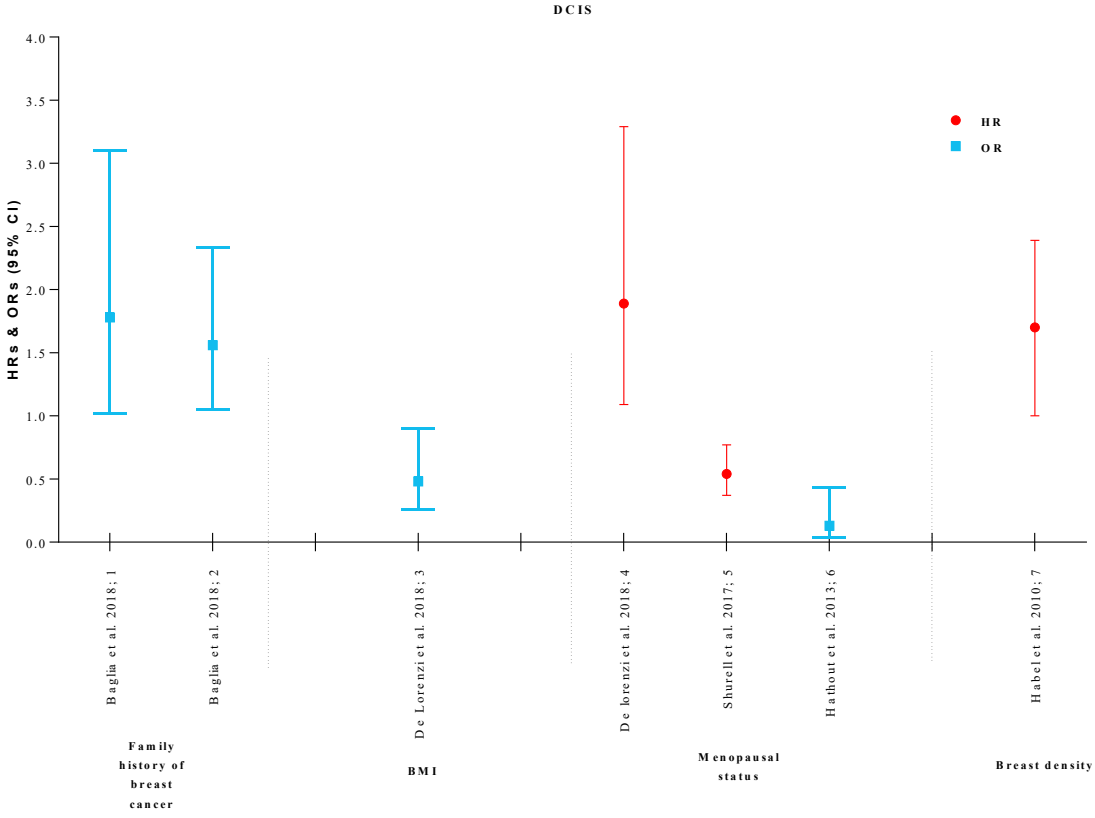
In Fig. 2 the multivariable adjusted estimates of all statistically significant associations reported by the included studies are shown. A complete overview of all estimates reported by the included studies is provided in Appendix C.

3.1.5. Study quality assessment

Out of a maximum of nine points that could be achieved on the adjusted Newcastle-Ottawa scale, quality scores ranged from four to eight points. Only one study [50] reported adequately about the loss to follow-up, and in three of the six studies [47,48,50] the length of follow-up was less than five years or the length of follow-up was not reported. Table 3 provides more details regarding the findings of the quality assessment.

4. Discussion

This systematic review was performed to evaluate the impact of established modifiable and non-modifiable breast cancer risk factors on the risk of developing further in situ or invasive disease after treatment of primary DCIS. We concluded that the available studies and evidence on the association between established modifiable and non-modifiable breast cancer risk factors and progression to invasive disease after a primary DCIS remains limited, particularly regarding modifiable factors. Also, all of the studies we identified used cohorts of women of European-descent. Thus, it is unclear whether the associations reported apply to women of non-European descent, for example in the United States or Asia. DCIS is a low-event rate disease, which requires large cohorts with long-term follow-up to identify potential risk factors for subsequent invasive breast cancer. Most studies we identified were retrospective in nature and data on particularly lifestyle and reproductive factors are not routinely collected (e.g., in cancer registries or trials that do not focus on lifestyle). Based on this and a prior review [39],



Please note these are not pooled estimates but point estimates from individual included studies

1: No. of first-degree relatives with breast cancer (two or more affected family members)
2: Age at diagnosis of first-degree family member (affected family member younger than 50 years)
3: Body Mass Index greater than 25 Kg/m^2
4: Premenopausal vs postmenopausal
5: Postmenopausal vs premenopausal
6: Highest quintile of area of breast density
HR: hazard ratio; OR: odds ratio; bars represent the 95% confidence intervals (CI)

Fig. 2. Overview of significant multivariable Hazard Ratios (HR) and odd Ratios (OR) for the risk of a subsequent breast event after primary DCIS.

Table 3
Assessment of the methodological quality of included studies.

COHORT STUDIES									
Study	Selection				Comparability	Outcome			Overall quality assessment[a]
	Representativeness of exposed cohort	*Selection of non-exposed cohort*	*Ascertainment of exposure*	*Demonstration outcome not present at start study*		*Assessment of outcome*	*Adequate length follow-up*	*Adequacy of follow-up of cohorts*	
De Lorenzi et al. 2018	★	★	★	★	Unclear	★	★	No statement	Poor
Shurell et al. 2018	★	★	★	★	★	★	★	No statement	Good
Hathout et al. 2013	★	★	★	Unclear	★	★	Not sufficient	Unclear	Poor
Shah et al. 2013	★	★	★	★	Unclear	★	★	High drop-out rate (49.7%)	Poor
Habel et al. 2010	★	★	★	★	★	★	Unclear	★	Good

CASE CONTROL STUDY									
Study	**Selection**				**Comparability**	**Exposure**			**Overall quality assessment**
	Adequate case definition	*Representativeness of cases*	*Selection of controls*	*Definition of controls*		*Ascertain-ment of exposure*	*Ascertain-ment cases and controls the same*	*Non-response rate*	
Baglia et al. 2018	Record linkage	★	★	★	★	★	★	High non-response rate	Good

[a] Thresholds for converting the Newcastle-Ottawa scales to the United States Agency for Healthcare Research and Quality (AHRQ; https://www.ahrq.gov/) standards (good, fair, or poor quality): Good quality: 3 or 4 stars in selection 0domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

there is moderate evidence for an increased risk of developing a subsequent breast event after a primary DCIS in women with a family history of breast cancer, those being premenopausal at diagnosis, or in women with high breast density. The results for BMI were conflicting. We did not perform a meta-analysis because the level of the studies included in the article by Shamliyan et al. and our own review are of insufficient quality to yield meaningful pooled estimates.

A family history of breast cancer is associated with the development of primary breast cancer and DCIS [15,51,52]. Compared to women with no history of breast cancer in their family, women with one first degree family member have an approximately two-fold risk to develop invasive disease, and women with more than one affected first-degree family member have a three to four-fold increased risk [5,15,52,53]. Few studies have investigated whether the risk for subsequent breast events in women with primary DCIS is associated with having a positive family history. In this systematic review, one study addressed family history and the risk for subsequent breast event [47] confirming the previous review [39]. Shamliyan et al. identified four studies that considered family history and the risk for a subsequent breast event, with one showing a three-fold statistically significant increased risk for a subsequent breast event [54]. Notably, the study included in this systematic review did not report on breast cancer specific mutations in their included population [47].

In contrast to the published literature [55–57], de Lorenzi et al. [46] found that a high BMI was associated with a risk reduction of 52% [46], whereas the literature consistently shows high BMI to be a risk factor for invasive disease in post-menopausal women [54–57]. The majority of patients included by de Lorenzi et al. were post-menopausal at diagnosis (62%), indicating that their findings are in contrast to published literature. Two of the studies included by Shamliyan et al. showed that women in the highest decile of BMI had approximately twice the risk for developing a recurrence after DCIS compared to women in the four lowest deciles, with the associations remaining the same when analyses were stratified for menopausal status [55,56]. Considering that the increase in risk for breast cancer attributable to BMI differs by menopausal status [57], it is essential for studies investigating the role of BMI in patients with DCIS, to take menopausal status into account (30–32). More studies are needed to clarify whether BMI is associated with the development of a subsequent breast event after DCIS, the direction of the association and potential underlying mechanisms.

Three studies [45,46,48] assessed whether menopausal status was associated with the risk for experiencing a subsequent breast event after DCIS. All three studies concluded that pre- or peri-menopausal status is correlated with a higher risk of subsequent breast event compared to post-menopausal status [45,46,48], concordant with the findings in Shamliyan et al. The association between menopausal status and breast cancer incidence has been extensively described in the literature and cannot be disconnected from BMI [45,46,48,57,59]. The results regarding BMI and menopausal status suggest that the risk for experiencing a breast event after DCIS has a potential underlying mechanism involving body weight, menopausal status, and age. Such mechanisms could be driven by hormonal pathways, fat compositions, micro-environmental reactions, however, these underlying mechanisms are as of yet poorly understood. The correlation between pre-menopausal status and increased risk of developing subsequent breast events is also in line with the evidence showing that younger age is a prognostic factor for invasive disease in patients with DCIS [4,5,39,48,50,60–62].

Though, given the mandatory reporting of breast density at least in some US states conducting breast screening, this review

retrieved only one study [49] assessing the relationship between breast density and the risk of developing a subsequent breast event in women with DCIS. High breast density has been reported to be an independent risk factor for breast cancer due to two reasons [63–65]. First a potentially cancerous lesion can be more difficult to detect in dense breasts, thereby negatively impacting the sensitivity of mammography [66–68]. Second, characteristics involving biological processes associated with dense breast tissue and breast density may increase the likelihood of the transformation of normal epithelium to malignant cells [69]. This potential biological mechanism could also play a role in malignant transformation of DCIS. Indeed the literature suggests that breast density might also play a role in the progression of DCIS to IBC [39,49,70].

Our study has strengths and limitations. A strength of this review was the comprehensive search strategy, rigorously developed in collaboration with an experienced information specialist. Furthermore, we adhered to the PRISMA method to ensure a complete and transparent reporting of studies. A limitation of this systematic review is that the inconsistent terminology used in the literature to define DCIS between studies (e.g. Breast Carcinoma In Situ, Non infiltrating Breast Cancer, Intraductal Carcinoma) made it difficult to identify relevant papers. However, with reference tracking we expect to have limited the impact of this potential bias. This challenge to recover relevant studies highlights the need for more consistent use of terminology. Another limitation is the different types of subsequent breast events were not always considered separately in the analyses. For example, we had to exclude one relevant publication since the analyses did not discriminate between ipsilateral and contralateral events [71]. In addition, the majority of the included studies in this systematic review did not discriminate between ipsilateral invasive disease and re-occurrence of DCIS in their analyses.

This work was carried out in the broader context of the current randomised controlled active surveillance trials (The COMET, LORIS and LORD-trial) [40–42] evaluating the safety of active surveillance for the management of low-risk DCIS. If these trials are positive, half of all women diagnosed with low-risk DCIS may be eligible for active surveillance [40–42]. Therefore, there is an urgent need for insight into factors involved in progression from DCIS to invasive disease in these women as well as about potential targets for interventions (e.g., weight loss) to further reduce these risks [4,72] In conclusion, our findings highlight the knowledge gap about the association between known risk factors for developing IBC and subsequent breast events after a primary DCIS.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Declaration of competing interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.breast.2020.02.006.

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