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The Association Between Smoking Status and Breast Cancer Recurrence: A Systematic Review

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Conflict of Interest
The authors declare that they have no competing interests.

ABSTRACT

Purpose: To determine whether smoking status (active/passive) affects recurrence events after breast cancer (BC) diagnosis among women.
Methods: A comprehensive literature search of MEDLINE, Cochrane Central, EMBASE, and Web of Science databases on smoking status and BC outcomes retrieved 5,940 articles. After reviewing the inclusion and exclusion criteria, we selected 14 articles for a full review and synthesis.
Results: Five studies were cohort retrospective, 6 were case-control, 2 were prospective cohort studies, and 1 was a secondary analysis of a randomized control trial. Among the 8 articles that focused on active smoking, 6 showed an increased risk of BC recurrence, and 2 showed no evidence of such an association. Studies that examined former smokers found little evidence of an increased risk of BC recurrence. This association may be dose-dependent.
Conclusion: Given the current evidence, although limited, active smokers should quit smoking after BC diagnosis as trends indicate a positive association between active smoking and BC recurrence. More robust evidence is needed to assess such associations and examine the outcomes of quitting smoking in such patients.

Keywords: Breast Neoplasms; Recurrence; Smoking; Tobacco

INTRODUCTION

Breast cancer (BC) is the most common cancer among women globally, with 5-year survival rate of 87% in developed countries [1]. As a result, the number of BC survivors at risk of BC recurrence is increasing [2]. Therefore, reducing BC recurrence is important for BC survivors [3].

Smoking is a modifiable risk factor that a woman can change to improve her prognosis [3]. Surprisingly, recent literature on BC survivors found that a low number of patients with BC quit or reduce smoking after diagnosis [4]. Smoking is considered a risk factor for the initial diagnosis of BC [5]. However, current literature regarding the impact of tobacco smoking on BC recurrence is limited [4-6]. Evidence has shown that cigarette smoke and its constituents have been found to affect cell adhesiveness, stimulate angiogenesis by regulating diverse signaling pathways, and facilitate tumor growth [7,8]. According to the Canadian Expert

Author Contributions

Data curation: Alkhaifi M, Clayton A; Formal analysis: Alkhaifi M, Clayton A; Investigation: Alkhaifi M; Methodology: Alkhaifi M, Kishibe T; Supervision: Simpson J; Writing - original draft: Alkhaifi M, Clayton A; Writing - review & editing: Simpson J.

Panel, tobacco smoke contains several fat-soluble compounds that induce mammary tumors [9]. Further, the lifetime risk of smoking is also biologically plausible as there is evidence that tobacco carcinogens accumulate with exposure over time [9,10]. This persistence in risk may occur as a result of detoxification, DNA repair, cell cycle control, and the complex disequilibrium of genes controlling activation [7].

Numerous studies conducted in patients with lung, head, and neck cancer have shown that cigarette smoking is associated with recurrence after a primary diagnosis [4-6]. However, whether tobacco smoking is associated with BC recurrence remains controversial [4-6]. Some studies have reported an increased risk of BC recurrence in current smokers compared with never smokers [4-6]. Several studies have also reported a positive association between smoking and BC recurrence [4-6]. However, this risk is confined to heavy smokers, defined as former smokers with more than 20 pack-years of exposure [7]. On the contrary, there are several studies that showed no or weak association between smoking status and BC recurrence [4,11,12]. The most recent systematic review on this topic was published in 2020 [13]. This review was limited to patients with BC who underwent adjuvant radiation treatment and did not include the entire BC population [13]. Few studies have been sufficiently powered to accurately estimate this effect. Therefore, more robust evidence is required to examine the association between smoking status and BC recurrence in a more inclusive patient population.

This review aimed to investigate the impact of cigarette smoking status after the diagnosis of non-metastatic BC with recurrence events. Clarification about the impact of tobacco smoking and its effect on recurrence will provide healthcare providers with a clear message for their patients, which is lacking in the current literature. To the best of our knowledge, this is the first systematic review to evaluate this association.

METHODS

Data sources

A comprehensive literature search was conducted using 4 databases: MEDLINE, Cochrane Central, EMBASE, and Web of Science, with support from a research librarian. The search was performed on May 18th, 2021. The number of results per data base is presented in **Table 1**.

Subject headings and text word terms were used to search for articles on BC, smoking, and cancer outcomes (especially recurrence). Variations in these terms were used, depending on the database being searched. The search strategy for each database is shown in **Supplementary Data 1**. The search was limited by publication type (case reports, comments, editorials, and letters) and animal-only studies. No age groups were included in the search. All references were saved in the Mendeley library. Duplicate articles were excluded. We included only English journal articles and articles involving women with primary BC.

Table 1. Number of results per each database

Databases search	No. of results
All Ovid MEDLINE <1946–Present>	2,227
Evidence-Based Medicine reviews – Cochrane Central Register of Controlled Trials <April 2021>	267
EMBASE Classic + EMBASE <1947 to May 17, 2021>	3,209
Web of Science	3,009
Total	8,712
Total after deduplication	5,940

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Participants with metastatic (stage IV) BC (i.e., cancer no longer curable) at diagnosis will be excluded. This is because the study investigated the effect of smoking on the disease process itself, rather than its association with late presentation.

All original studies describing the association between smoking status and BC recurrence were included. Both current and former smokers were assessed in this study because the measurement of only current smoking would miss important cancer relationships that could lead to biased conclusions. Exclusion criteria were not explicitly commenting on BC recurrence or missing smoking demographics. Furthermore, we excluded articles that included men with a diagnosis of BC, exposure to second-hand smokers, or environmental smoking in the analysis. Studies that did not explicitly comment on the association between smoking status and BC recurrence using hazard ratios (HRs) or *p* value or were not available online were excluded.

Study selection

The preliminary search using MEDLINE for smoking status and BC recurrence was limited to 16 articles. Therefore, we decided to combine the terms smoking status and all BC outcomes to ensure that we captured all articles related to BC recurrence. Studies were identified using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (**Figure 1**). The initial search identified 5,940 unique references. Two independent reviewers performed a title and abstract screen, as well as a full-text review. Any disagreement over the eligibility of particular studies was resolved through discussion between them. The titles and abstracts were examined for relevance, and the studies underwent full-text and bibliography reviews. Of the full-text reviews, 14 articles met the inclusion criteria. A PRISMA chart of the study is shown in **Figure 1**. Two authors extracted data independently, and discrepancies were identified and resolved through discussion. The reasons for exclusion from the flow chart are presented in **Supplementary Table 1**.

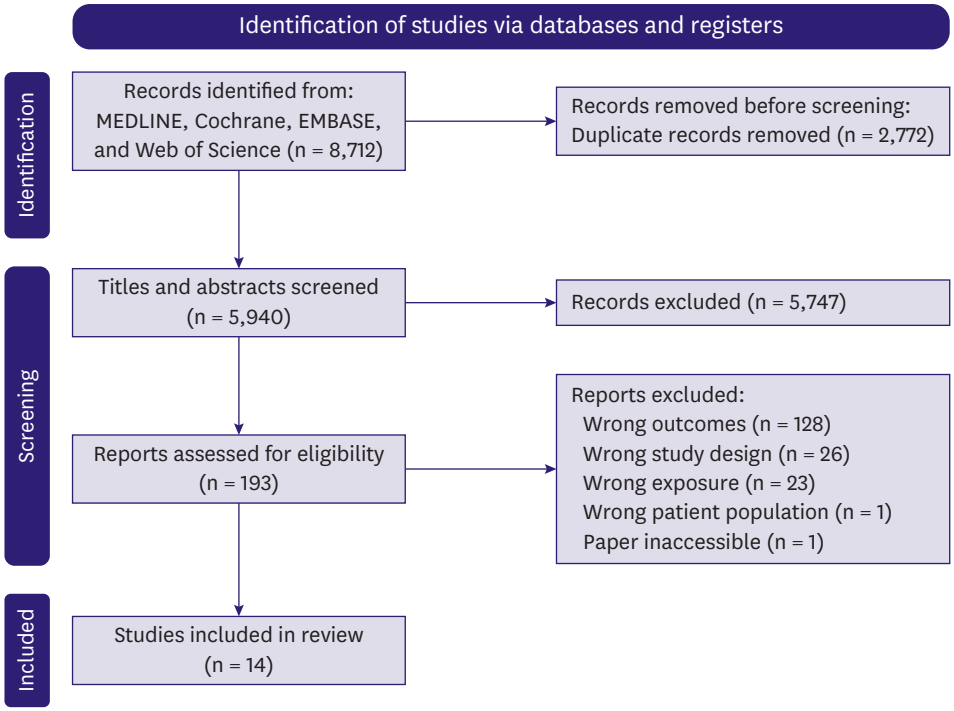

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) chart.

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Data collection and analysis

The following data were extracted from the studies: title, first author name, country of study, duration of study, year of publication, study design, population, mean age, sample size, BC definition and ascertainment, exposure assessment and ascertainment (smoking), follow-up time, and study design smoking (**Table 2**). The variables of interest were the risk of BC recurrence in active and passive smokers among women diagnosed with BC. We also extracted intervention details and control conditions, intensity of smoking (pack-years), adjustment for confounding factors, and outcomes (**Table 3**).

Table 2. Characteristics of included studies on smoking status and BC recurrence

Study	Study design	Setting	Sample	Age	Population	Assessment of smoking	BC recurrence definition and ascertainment	Follow-up time
Bishop et al. [5] (2014)	Retrospective chart analysis	US	624	Mean 60.4	Stage I–III BC patients who underwent partial mastectomy and radiation therapy	Medical records at the time of diagnosis (current and former smokers)	Medical records (local and distance)	Mean 45 mo
Pierce et al. [6] (2014)	Retrospective cohort	US	9,975	Mean 59.2	Stage I–III BC (3 US cohorts in the After Breast Cancer Project)	Questionnaires at diagnosis + 2-year follow-up (current and former smokers)	Medical report (recurrence and/or new primary breast cancer)	Median 11.1 yr
Abdel-Rahman et al. [7] (2018)	Secondary analysis of RCT	Canada	1,242	Mean 49.9	Early-stage BC patients, HER2-negative who received adjuvant chemotherapy	From the examined data set (never, former, and current smokers)	From the examined data set (local, regional distance)	Median 123 mo
Takada et al. [11] (2020)	Case-control	Japan	989	Median 60	Primary BC patients who underwent curative resection	Medical records	Medical records + pathology confirmation (local or distance)	Median 2,128 day
Lafourcade et al. [12] (2018)	Prospective cohort	France	4,926	Not reported	Stage I–III primary invasive BC patients	Medical records	Medical records (locoregional metastasis, second primary breast cancer)	Median 7.2 yr
Goldvaser et al. [14] (2017)	Retrospective cohort	Israel	622	Median 61	ER-positive and HER2-negative stage I–III BC patients	Medical records (active smoking at time of diagnosis)	Medical record + pathology confirmation + medical imaging (local-regional and distance)	Median 61.9 mo
Li et al. [15] (2009)	Case-control	US	Cases: 365 Controls: 726	Range 40–79	Stage I–III ER invasive BC with 2nd primary contralateral BC patients	Phone interviews + medical records	Medical records (second primary contralateral BC)	NA
Seibold et al. [16] (2014)	Prospective cohort	Germany	3,340	Mean 62.3	Stage I–III invasive BC patients	Pre-diagnostic smoking + self-reported interviews (current if > 100 cigarettes within a year, former if otherwise)	Medical records (ipsilateral, contralateral, regional, distant recurrence)	Median 6 yr
Schmidt et al. [17] (2020)	Retrospective chart analysis	Germany	197	Mean 57	Stage I–III triple-negative BC patients treated with chemotherapy	Medical records (current smokers)	Pathology confirmation (local, regional, distance)	Median 41.3 mo
Persson et al. [18] (2016)	Prospective cohort	Sweden	1,065	Median 61	Primary stage I–III BC patients	Medical records + questionnaires	Medical records (distance metastasis)	Median 5.1 yr
DiMarzio et al. [19] (2018)	Retrospective cohort	US	10,676	Median 57.5	Stage 0–III BC patients in those who underwent radiotherapy	Medical charts at time of diagnosis	Medical records + annual questionnaires	Median 6.7 yr
Knight et al. [20] (2017)	Case-control	US Canada Denmark	Cases: 1,521 Controls: 2,212	Median 46	Primary invasive BC patients (local, regional)	Phone interviews using structured questionnaire	Medical records + pathology confirmation + interviews	NA
Horn et al. [21] (1988)	Case-control	US	Cases: 292 Controls: 264	Mean 57	Cases: new contralateral BC Controls: previous primary BC but no second primary cancer	Medical records	Medical records + pathology confirmation	NA
Kato et al. [22] (1986)	Case-control	Japan	183	Mean 49	Primary BC patients and simultaneously or subsequently diagnosed with a second primary cancer	Medical records	Medical records	NA

US = United States; BC = breast cancer; RCT = randomized control trial; HER = human epidermal growth factor receptor; ER = estrogen receptor; NA = not available.

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Table 3. Summary of the association between smoking status and risk of recurrence the selected studies

Study	Classification	Results	Adjustment	Comment
Bishop et al. [5]	Never smokers Former smokers Current smokers	Reference HR, 1.43 (95% CI, 0.48–4.30) HR, 6.69 (95% CI, 2.00–22.42)	Race, age, tumor stage, histology, receptor status	Included only patients undergoing partial mastectomy and radiation therapy
Pierce et al. [6]	Never smokers < 20 pack-years 20–34.9 pack-years > 35 pack-years Current smokers	Reference HR, 0.98 (95% CI, 0.87–1.11) HR, 1.22 (95% CI, 1.01–1.48) HR, 1.37 (95% CI, 1.13–1.66) HR, 1.41 (95% CI, 1.16–1.96)	Tumor stage, grade, age, race/ethnicity, education, BMI	NA
Abdel-Rahman et al. [7]	Never smokers Ever smokers	Reference Locoregional p = 0.031 Distance p = 0.767	Age, BMI, T and N stages in surgical pathology, lymph node ratio, hormone receptor status, cancer grade, histological subcategory, type of surgery, number of adjuvant chemotherapy cycles, adjuvant radiotherapy	Result is only significant for locoregional recurrence
Takada et al. [11]	Never smokers Ever smokers	Reference p = 0.108	Not indicated	Concluded that smoking associated with a positive conversion HER2 in recurrence (p = 0.024)
Lafourcade et al. [12]	Never smokers Current smokers Former smokers	Reference HR, 1.55 (95% CI, 1.16–2.07) HR, 1.2 (95% CI, 1.00–1.44)	Age, BMI, receptor status, tumor grade, tumor size, axillary nodal involvement, history of benign breast disease, family history of cancer, alcohol consumption, education, menopausal status, use of HRT	Assessed smoking status at 1st visit
Goldvaser et al. [14]	Never smokers Current smokers < 30 pack-years ≥ 30 pack-years	Reference HR, 0.36 (95% CI, 0.09–1.48) HR, 0.73 (95% CI, 0.32–1.68) HR, 0.85 (95% CI, 0.26–2.80)	Age, menopausal status, ethnicity, tumor size, nodal involvement, grade	Population limited to subgroup (ER+, HER−)
Li et al. [15]	Never smokers Former smokers Current smokers	Reference OR, 1.2 (95% CI, 0.8–1.7) OR, 2.2 (95% CI, 1.2–4.0)	BMI, alcohol use, first-degree FH, HRT use, hormone therapy, chemotherapy	Only postmenopausal women were included
Seibold et al. [16]	Never smokers Current smokers < 10 pack-years 10–19 pack-years 20 pack-years	Reference HR, 1.19 (95% CI, 0.86–1.64) HR, 0.88 (95% CI, 0.46–1.69) HR, 0.99 (95% CI, 0.05–1.84) HR, 1.188 (95% CI, 0.71–1.94)	Tumor size, growth into chest wall, neoadjuvant chemotherapy, nodal status, metastasis status, histological grading, receptor status, BMI, alcohol use, radiotherapy, HRT use	Subgroup analysis showed risk of recurrence significantly increased for that current smoker women with HER2-positive tumor (HR, 3.6; 95% CI, 1.22–10.8)
Schmidt et al. [17]	Never smokers Ever smokers	Reference p = 0.604	Not indicated	NA
Persson et al. [18]	Never smokers Ever smokers	Reference HR, 1.45 (95% CI, 0.95–2.20) p = 0.14	Tumor size, muscle or skin involvement, axillary lymph node involvement, histological grade III, positive ER status, age, BMI, treatment with radiation therapy, chemotherapy or endocrine therapy (AI)	Subgroup analysis showed that only (AI)-treated patients > 50 years with ER+ tumors, smoking was associated with risk of BC events (adjusted HR, 2.97; 95% CI, 1.44–6.13), distant metastasis (adjusted HR, 4.19; 95% CI, 1.81–9.72)
DiMarzio et al. [19]	Never smokers Current smokers Former smokers	Reference HR, 1.18 (95% CI, 0.91–1.52) HR, 1.17 (95% CI, 0.99–1.38)	Age, race, family histology of cancer, tumor stage, chemotherapy, alcohol consumption	NA
Knight et al. [20]	Never smokers Current < 10 cigarettes/day Current ≥ 10 cigarettes/day	Reference p = 0.36 p = 0.03	Age, family history of cancer, BMI, age at menarche, number of full-term pregnancies, histology, tumor stage, receptor status, chemotherapy, radiation, HRT use, alcohol consumption	Limited contralateral BC
Horn et al. [21]	Never smokers 0.1–24.9 pack-years 25.0–39.9 pack-years ≥ 40.0. pack-years	Reference OR, 1.0 (95% CI, 0.5–2.2) OR, 2.9 (95% CI, 1.1–7.7) OR, 1.5 (95% CI, 0.7–3.2)	Age, nulliparity, menopausal status, HRT use, family history of cancer, benign breast disease, tumor histology, tumor stage, radiotherapy, chemotherapy	Receptor status of cases and controls unknown
Kato et al. [22]	< 10 cigarettes/day ≥ 10 cigarettes/day	Reference RR, 0.22 (p < 0.10)	Adjustments made but not reported which factors were adjusted for	Confidence intervals not provided

HR = hazard ratio; OR = odds ratio; RR = relative risk; HRT = hormone replacement therapy; AI = aromatase inhibitor; ER = estrogen receptor; HER = human epidermal growth factor receptor; BMI = body mass index; CI = confidence interval; BC = breast cancer.

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Table 4. Figure illustrating the total evaluation of risk of bias in our included articles

Reference	Bishop et al. [5]	Pierce et al. [6]	Abdel-Rahman et al. [7]	Takada et al. [11]	Lafourcade et al. [12]	Goldvaser et al. [14]	Li et al. [15]	Seibold et al. [16]	Schmidt et al. [17]	Persson et al. [18]	DiMarzio et al. [19]	Knight et al. [20]	Horn et al. [21]	Kato et al. [22]
Selection bias	+	+	+	o	+	+	+	+	+	+	+	+	+	+
Recall bias	+	+	+	o	+	+	o	+	+	–	+	+	+	+
Misclassification of the exposure	+	+	+	+	o	+	–	+	+	–	+	+	+	–
Assessment of the outcomes	+	+	o	+	+	+	+	+	+	+	+	+	+	+
Evaluation of the confounding factors	+	+	+	+	+	+	o	+	+	+	+	+	o	–
Follow-up time	–	o	+	+	+	+	–	+	+	+	+	+	o	–
Precision of the results	+	+	+	+	+	+	+	+	+	+	+	+	–	–

Risk of bias was categorized as either low risk of bias (+), intermediate risk of bias (o), or high risk of bias (–).

Risk of bias in individual studies

To determine the risk of bias in the individual studies, we evaluated the articles for the risk of selection bias, recall bias, outcome, follow-up time, and adjustments made (**Table 4**). Risk of bias in individual studies was assessed independently by 2 authors using the Critical Appraisal Skills Program to critically appraise the reviewed articles [23].

RESULTS

A summary of the association between smoking status and risk of BC recurrence is presented in **Table 2**. Owing to the heterogeneity of the studies included in the present review, no meta-analysis was conducted. The results were divided into 3 categories based on smoking status.

Association of current smoking and breast cancer recurrence

Among the studies that evaluated the risk of recurrence and current smoking status, 6 showed a significant positive association [5-7,12-15,20]. For example, Pierce et al. [6] found a significant increase in the risk of recurrent events in current smokers with stage I–III BC (HR, 1.41; 95% confidence interval [CI],1.14–1.96). Li et al. [15] found that compared to never or former smokers, current smokers had an elevated risk of contralateral BC in women with estrogen-positive BC (odds ratio, 2.2; 95% CI, 1.2–4.0). Similarly, Knight et al. [20] found that smoking an average of 10 cigarettes per day following a diagnosis of BC increased the risk of primary second BC compared with never smokers ($p = 0.03$).

In contrast, Goldvaser et al. [14] found no association between current smokers at the time of diagnosis and BC recurrence (population was limited to estrogen-positive and HER2-negative BC). Similarly, Seibold et al. [16] shows no association between active smoking and BC recurrence. However, the subgroup analysis showed risk of recurrence significantly increased in current smoker women with HER2-positive tumors (HR, 3.6; 95% CI, 1.22–10.8). Kato et al. [22] found a negative relationship between smoking and risk (relative risk, 0.22); however, no CIs were provided by the authors.

Association of former smoking and BC recurrence

Among the 7 studies that evaluated former smokers, 2 showed a positive association between former smoking and recurrence after the diagnosis of BC [5,6]. Pierce et al. [6] showed that compared to never smokers, former smokers with 20 to less than 34.9 pack-years of exposure had a 22% increase in BC recurrence (HR, 1.22; 95% CI, 1.01–1.48). For the former smokers with 35 or more pack-years, the probability of recurrence increased by 37% (HR, 1.37; 95% CI, 1.13–1.66) [6]. However, former smokers with less than 20 pack-years of exposure had no increased

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risk of BC recurrence [6]. Lafourcade et al. [12] showed that former smokers had a higher risk of recurrence (HR, 1.20; 95% CI, 1.0–1.44) than never smokers. In contrast, 5 studies showed no evidence of such an association [5,14-16]. For example, Goldvaser et al. [14] and Seibold et al. [16] found that smoking had no impact on BC recurrence regardless of the number of pack-years (0–29 or ≥ 30) and < 10 pack-years, 10–20 pack-years, and 20 pack-years, respectively.

Association between smoking status (ever vs. never smoking) and BC

Three studies compared ever smokers with never smokers [7,11,17]. One study showed a positive association, and 2 studies showed no association [7,11,17]. Of the 2 studies that showed no association, one involved only triple-negative BC [17].

DISCUSSION

To our knowledge, this is the first systematic review to examine the association between smoking status and BC recurrence. Despite the comprehensive search (5,940 articles from 4 databases) conducted, the articles that focused on this topic were limited (n = 14). Our analysis showed variation in the outcomes of the studies, making it difficult to draw a conclusion. However, the trends may indicate a positive association between active smoking and the risk of BC recurrence. Seven of the 14 articles showed an increase in BC recurrence. One of these studies with a large sample size (n = 9,975) showed a significant increase (44%) in the risk of recurrent events in current smokers (HR, 1.14; 95% CI, 1.44–1.96) [6]. The remaining articles that showed no association were likely to be affected by a smaller sample size. Additionally, Pierce et al. [6] included a large sample size and demonstrated a dose-response relationship in which increased smoking exposure (pack-years) increased the probability of recurrence. This effect was greatest in the 35 or more pack-years patients (HR, 1.37; 95% CI, 1.13–1.66) [6].

There are several potential reasons for the inconsistent results and variations among the reviewed studies. First, variations in the exposure classification, definition, and assessment were performed across the included studies. Three categories of smoking status (current, former, and ever smoker) in the included populations were determined using self-reported patient data (medical charts, questionnaires, and interviews). Previous studies have shown that patients' self-reported smoking status leads to uncertainty in the analysis of studies [23]. There is a possibility of patients falsely categorizing themselves as one or the other [24,25]. Furthermore, underreporting of smoking information (possibly because of its social stigma) can also exist, which might contribute to misclassification bias in these studies [24]. This can also be attributed to poor quality chart abstraction, which could have distorted the baseline characteristics of the study population. However, this was equally present in most of the included articles. Several studies have examined the degree of misclassification in smoking measurement and BC outcomes as measurement error may decrease causal effect estimates; it might be one of the reasons for the contradictory results [24,26-28].

Additionally, there was variation in smoking status definitions across the studies. Most of the included articles did not specify exactly what defines "smokers." Only one article specified this, with a cut-off point between "a smoker" and "non-smoker" for a total of > 100 cigarettes smoked [16]. Previous studies have shown a considerable measurement error in the definition of smoking [29,30]. In addition, there is no clear definition for participants who consider themselves occasional smokers. Further, for the majority of the studies, there was no clear

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definition of "former or current smoker"—if there are specific definitions, they vary from one study to another, which can make it difficult to draw a conclusion. Therefore, standard definitions and calcifications (cut-off points) are required when considering such studies. Many factors influence BC recurrence, including, but not limited to, therapies received after diagnosis, concurrent alcohol use, body mass index, and tumor characteristics [9,10]. When comparing these articles, it is important that they have adjusted for risk factors known to modify BC risk to reduce possible confounders. Six articles presented comprehensive lists of their adjustments [7,12,16,18,20,21], and 5 articles adjusted for a few covariates [5,6,14,15,19]. Schmidt et al. [17] and Takada et al. [11] did not report any statistical adjustments. None of the reviewed studies evaluated second-hand or environmental smoking exposure as a potential confounding factor. Some evidence suggests that secondhand smoke may be linked to an initial diagnosis of BC [30]. All the adjustments are shown in **Table 4**. Finally, with the emergence of electronic cigarettes and legalized marijuana in the future, there may be new risks for BC recurrence related to them. As an increasing number of patients turn to medical marijuana to manage the side effects associated with adjuvant treatments, medical professionals will rely on the medical literature to guide patients.

The greatest limitation pertains to the heterogeneity of the studies in this review, which makes it difficult to compare outcomes across studies, and a quantitative meta-analysis was not possible. Furthermore, we did not include unpublished articles, articles ahead of print, or articles not indexed at the time of the search. Articles that were not available online were excluded. Given the paucity of articles explicitly focused on smoking status and BC recurrence, we chose to include papers that described all BC outcomes, but only if they were indexed to BC recurrence in the database. In addition, the lack of follow-up information on patients would have allowed us to conclude beyond smoking status at the time of diagnosis.

In conclusion, there is a paucity of studies assessing the association between smoking status and BC recurrence. However, the trends may indicate a positive association between active smoking and the risk of BC recurrence. However, given the current evidence, although limited, active smokers can be counseled to quit smoking after a diagnosis of BC. Similarly, trends may indicate a positive association between smoking and the risk of BC recurrence. This association may depend on the intensity of smoking exposure. The current controversy may be due to differences in exposure classification between different studies, follow-up times, and confounding factors. More research is required to help physicians manage patients with BC to prioritize discussions regarding the benefits of smoking cessation when counseling their patients.

SUPPLEMENTARY MATERIALS

Supplementary Data 1

Search strategies

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Supplementary Table 1

Reasons of exclusion

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