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Decision Regret Regarding Treatments among Women with Early-Stage Breast Cancer:A Systematic Review Protocol

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Decision Regret Regarding Treatments among Women with Early-Stage Breast Cancer: A Systematic Review Protocol

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ABSTRACT

Introduction: Women with early-stage breast cancer are commonly required to make treatment decisions. Decision regret regarding treatments is an adverse outcome that negatively impacts women's psychological well-being and quality of life. A systematic review will be conducted to synthesize evidence about decision regret among patients regarding treatments for early-stage breast cancer. The study will focus on levels of decision regret, what is regretted, and the factors associated with decision regret.

Methods and analysis: A systematic review will be conducted following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 checklist. Electronic databases, including CINAHL Complete, Embase, PubMed, Medline, and Web of Science, will be searched for relevant articles published from 2000 to 2021. The reference lists of eligible studies will also be manually searched. All types of quantitative, qualitative, and mixed-method studies that report on decision regret regarding treatments among women with early-stage breast cancer will be included. The primary outcome of this review will be patients' levels of decision regret regarding breast cancer treatments, and the secondary outcomes will include the content of their regrets, and the factors contributing to decision regret. The methodological quality of the studies will be assessed using the Joanna Briggs Institute appraisal tools. Meta-analysis and thematic synthesis approaches will be used to synthesize quantitative and qualitative data, respectively. A convergent parallel approach will be used to integrate quantitative and qualitative findings.

Ethics and dissemination: Ethical approval is not required for this systematic review. Findings of this work will be disseminated at international conferences and peer-reviewed

journals. The findings of this systematic review will inform the development of decision interventions to improve the decision outcome of breast cancer treatments.

Registration: This protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 06 September 2021 (No. CRD42021260041).

Keywords: breast neoplasm, regret, systematic review, qualitative, meta-analysis, factors

ARTICLE SUMMARY

Strengths and Limitations of This Study

1. This systematic review will be the first of its kind to provide in-depth knowledge about decision regret related to treatments among women with early-stage breast cancer.
2. This review incorporated all types of studies which differed from other reviews that only include randomized control trials.
3. The findings of this review will be used to develop interventions which address decision regret among women with early-stage breast cancer.
4. This review only includes studies published in English; thus, eligible studies published in other languages may have been missed.

INTRODUCTION

Breast cancer is the most prevalent malignancy among women, contributing to 11.6% of new cancer cases in 2018 [1]. In many countries, the majority of the women with breast cancer were found to have early-stage breast cancer (ESBC) at the time of diagnosis [2 3].

Women with ESBC have a milder form of the disease, superior cure rates, and more treatment options than those with advanced and metastatic breast cancer (stages 3 and 4). Clinical trials suggest that survival rates after mastectomy and breast conservative surgery (BCS) for women with ESBC are equivalent [4 5], therefore, it is important to empower these women to make treatment decisions for themselves in order to achieve "shared decision-making" in breast cancer care [6]. However, choosing among multiple treatment options can be difficult. For example, a mastectomy surgery benefits women by a lower risk of recurrence but causes relatively larger body image impairment, whilst a BCS helps women maintain breast image but exposure women to a higher risk of local recurrence [5]. Therefore, when choosing between mastectomy and BCS, women must weigh the benefits and side effects of each option. Facing the difficult treatment choices, some women with ESBC may make a decision that they will regret in the future [7 8]. Thus, it is important to understand the decision-making behaviour of women with ESBC.

In the context of health care, *decision regret* refers to "distress or remorse after a health care decision" [9]. Decision regret is a significant indicator of treatment decision efficacy and may emerge when patients feel that they could have had a better outcome if they had chosen a different treatment [9 10].

In a study from the US, Advani et al. (2019) reported that 100 out of 421 (23.8%) women with breast cancer (>67 years) had experienced decision regret regarding some forms of local therapy (e.g., lumpectomy with radiotherapy, brachytherapy, or endocrine therapy or mastectomy). In this study, decision regret was associated with race, education level, and the extent of nodal dissection performed, but not the type of therapy [11]. In another survey among young women (<51 years), 42.5% of 449 women with breast cancer experienced decision regret five years after treatment. Of these women, 24.2% regretted having primary surgery and 21.5% regretted having chemotherapy or radiotherapy [12]. Qualitative explorations also reported women expressed regret about their surgery [12-14], and their regrets were mostly associated with not engaging in the decision-making process [13] and inadequate information about treatments [12 14].

The physical and psychosocial consequences associated with decision regret have been discussed in previous literature [10 12 15]. Regretting a treatment decision has been associated with a higher probability of undergoing a second round of treatment, which could result in delayed recovery and additional trauma. Regret regarding cancer treatments has also been associated with poor psychological well-being and quality of life [15 16]. Experiencing regret about a treatment decision may also increase patients' financial burden, especially for patients from economically disadvantaged backgrounds. Additionally, studies show that decision regret may damage the relationship between patients and their healthcare providers [17 18], such as blame of the doctor [17]. Thus, it is important for health care providers to support patients' decision making and minimise the occurrence of decision regret in clinical practice.

Previous reviews on decision regret related to breast reconstruction [19] and contralateral prophylactic surgery [20 21] could not provide a holistic understanding of decision regret

regarding ESBC treatments because other treatments, such as breast-conserving surgery, chemotherapy, and radiotherapy, are also common choices for ESBC. To date, there is a lack of literature synthesis regarding levels of decision regret, what patients regret, and factors associated with decision regret regarding breast cancer treatments among women with ESBC. Without such an understanding, it is difficult for healthcare workers to develop supportive interventions to help patients make treatment decisions.

Review Objectives

A systematic review will be conducted to assess studies dealing with decision regret regarding breast cancer treatment among patients with ESBC. The treatment approaches of interest will include unilateral mastectomy, breast-conserving surgery, chemotherapy, radiotherapy, endocrine therapy, and targeted therapy. The Participants, Interventions, Comparators and Outcomes (PICO) elements used for the systematic review are listed in Table 1.

The detailed objectives are:

1) To assess levels of decision regret among women with ESBC;
2) To identify what women regret;
3) To identify factors associated with decision regret.

Table 1. The PICO Elements Used as Selection Criteria in This Systematic Review.

Participants	• Women with early-stage breast cancer (stage 0/carcinoma in situ, stage 1 and stage 2).
Intervention/Exposure	• Experienced decision regret regarding their treatments.

Comparators	• No restriction. The comparator depends on the study design. • For example, the comparator could be a group of the normal population for a cohort comparative study; if the included study is a randomized control trial to assess the effectiveness of a decision aid, the comparator could be the group of the population who had not received the decisional intervention.
Outcomes	• Levels of decision regret; • Events/processes/things that women regret; • Factors associated with decision regret.
Settings	• No restriction

METHODS AND ANALYSIS

This protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42021260041). The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist is followed to report this protocol [22] (See supplemental material 1). This systematic review is anticipated to be performed during August 2021 and January 2022.

Study Selection

Information Sources

The authors will search electronic databases including CINAHL Complete, Embase, PubMed, Medline, and Web of Science. A manual search of the reference lists of eligible studies will be also performed. This systematic review will include primary studies published from January 2000 to June 2021 in order to provide the most recent evidence.

Selection Process

Two authors will independently conduct the literature search (JL and SH). Another researcher will validate the search process to ensure accuracy (SC). All studies will be exported using

Endnote X9 software for duplicate removal and further screening. Thereafter, two authors will independently review the titles, abstracts, and full texts of these papers to determine their eligibility (JL and SH). Disagreement about study eligibility will be resolved through discussions among all researchers (JL, SH, JMZ, RL, and SC). The selection process will be presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA flow diagram (see Figure 1).

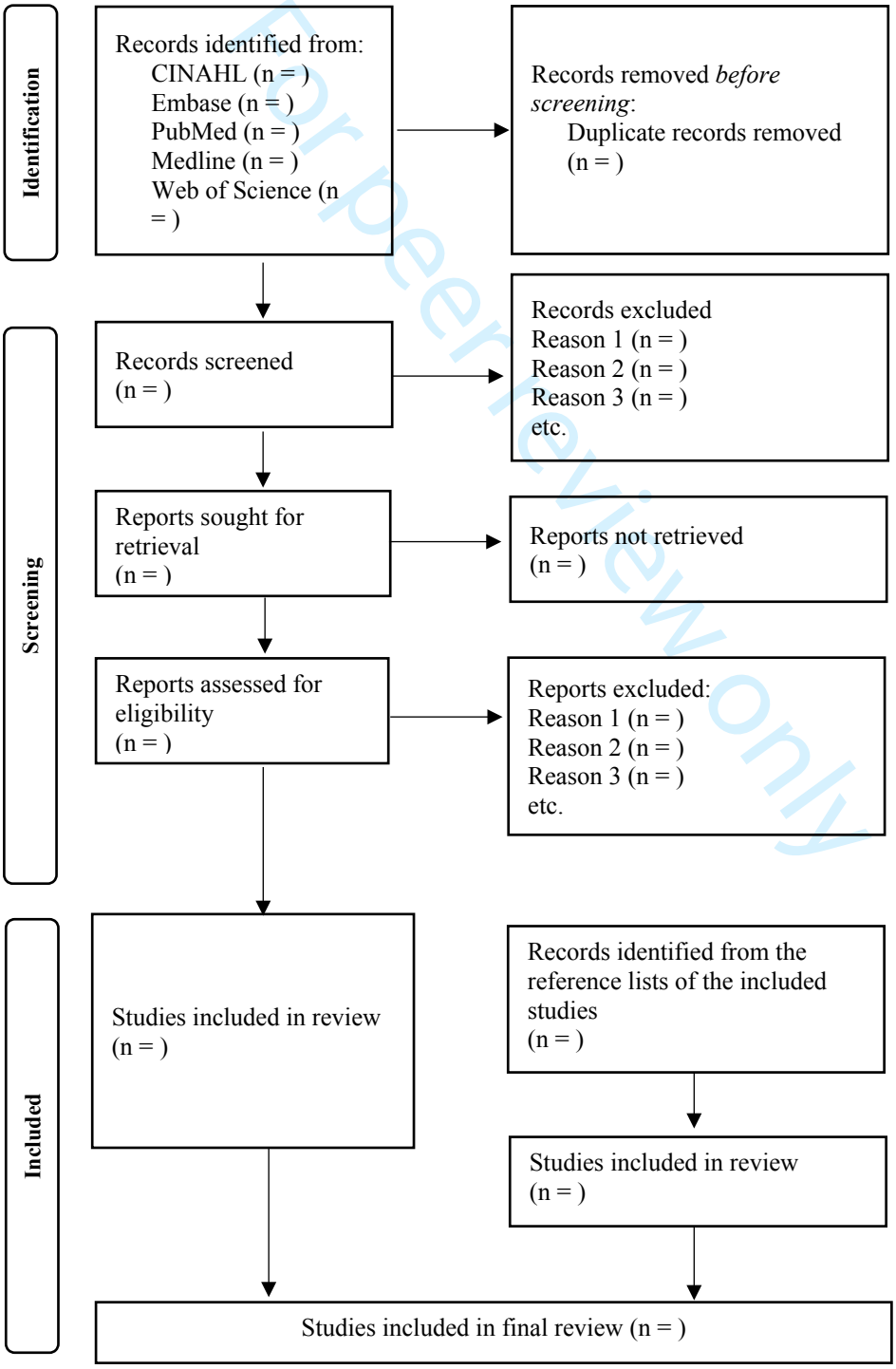

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram and Selection Process.

Search Terms

The keyword search terms are derived from the main concepts of the research topic. The key terms will include: “breast cancer,” “breast tumor,” “breast neoplasm,” “breast carcinoma,” “early-stage breast cancer,” “early breast cancer,” “regret,” “decision regret,” “treatment,” “intervention,” and “therapy.” An example of the search strategy is presented in Table 2.

Table 2. Search Strategy Used for CINAHL Complete Database

Main Concepts	**Search Terms**	**Outcomes**
Breast Cancer	1. Breast cancer or breast tumor or breast neoplasm or breast carcinoma or early-stage breast cancer or early breast cancer	109,841
Regret	2. Regret or decision regret	1,676
Treatment	3. Treatment or intervention or therapy	2,343,406
Combined: 1 and 2 and 3		61
Publication Year Limit from 2000 to 2021		58

Inclusion and Exclusion Criteria

All relevant quantitative, qualitative, and mixed-methods studies written in the English language will be included. There will be no restrictions regarding the design or setting of the study, as long as they are:

1) primary studies reporting decision regret regarding unilateral mastectomy, breast-conserving surgery, chemotherapy, radiotherapy, endocrine therapy, or targeted therapy;
2) among patients with ESBC; and
3) published in the English language.

Studies regarding risk-reducing treatment (e.g., contralateral prophylactic mastectomy) and reconstructive surgery will be excluded because there have been three published reviews specifically addressing these surgeries. Secondary studies and grey literature will also be excluded.

Analysis

Outcome Measures

The primary outcome of the systematic review will be patients' levels of decision regret regarding breast cancer treatment. The secondary outcomes will include what patients regret when they recall their decision-making process and the factors contributing to their decision regret.

Data Evaluation

Three researchers will conduct the data evaluation independently (JL, JMZ, and RL), and another author's (SC) advice will be sought if there is disagreement. The methodological quality of eligible studies will be evaluated using critical appraisal tools developed by the Joanna Briggs Institute. These tools were developed to assist in assessing the trustworthiness, relevance, and results of quantitative and qualitative studies. For qualitative studies, researchers are required to respond (*yes*, *no*, *unclear*, or *not applicable*) to ten questions to determine whether a study has addressed the possibility of bias in its design, conduct, or analysis [23]. Following these questions, researchers will decide if the study should be included or excluded, or if additional information should be sought [23]. Disagreements regarding study inclusion will be discussed by the entire group of researchers.

Data Extraction and Synthesis

Two researchers will analyze the data independently (JL and SH). Included studies will be first categorized into quantitative, qualitative, or mixed-methods studies according to their design. Information on the year of publication, author(s), setting, participant characteristics (e.g., age, number of participants, cancer stage, and treatment received), measures (e.g., instruments, time of measurement, and comparative groups), interventions (e.g., blinding and randomized methods), and findings of interest (e.g., level of decision regret, what patients regret, and factors associated with decision regret) will be extracted. The extracted data will be compiled into an Excel spreadsheet by each researcher before being compared by both researchers for completeness and accuracy. Any discrepancies will be resolved through discussion within the research group (JL, SH, JMZ, RL, and SC).

Quantitative results will be pooled into Review Manager Software (RevMan) Version 5 to conduct a meta-analysis where appropriate [24]. A forest plot will be created to present the pooled results. For example, if there are several interventional studies that have evaluated the effectiveness of decision aids in reducing patient-perceived regret, odds ratios (for dichotomous variables) or weighted mean differences (for continuous variables) and their 95% confidence intervals (CIs) will be calculated in order to precisely describe the impact of decision aids on decision regret. The I^2 statistic will be used to assess heterogeneity, and a value lower than 50% will be considered to indicate low heterogeneity. In case of low heterogeneity, the fixed-effects model will be applied to assess the pooled results. Otherwise, the pooled results will be assessed using the random-effects model. Sensitivity analysis will be conducted if the pooled results have substantial heterogeneity, and the results will be carefully interpreted. A subgroup analysis on the interventions and types of received treatment (e.g., chemotherapy or radiotherapy) will be performed where applicable. The

publication bias will be indicated by the asymmetry of the funnel plot [25]. The findings will be described in narrative form where meta-analysis is impossible. For example, if there is only one cross-sectional survey reporting regret after chemotherapy, results concerning the level of regret, what women regret, and related factors will be narratively described.

Qualitative evidence will be analyzed using the thematic synthesis approach proposed by Thomas and Harden [26]. Qualitative studies will be read and reread by two researchers (JL and SH), and findings associated with the three review questions will be identified and coded line-by-line. These initial codes will be compared and consolidated until a number of descriptive subthemes emerge. All researchers will discuss the subthemes until a consensus is reached regarding whether the subthemes comply with the meaning of the original study. Thereafter, similar subthemes will be further grouped based on their similarity in order to produce several analytical themes that are pertinent to the review questions. A coding sheet will be developed by the author to facilitate the data synthesis. The other three researchers (JMZ, RL, and SC) will comment on the synthesis by reviewing the coding sheet until a final consensus is reached.

A third integrative analysis using a convergent parallel approach will be conducted to incorporate the quantitative and qualitative findings [27]. Quantitative outcomes and qualitative themes will be combined to provide rich insights into the three review questions. It is anticipated the quantitative outcomes will quantify the qualitative findings, and the qualitative themes will help explain the quantitative outcomes; thus, the review findings will be convergent and complimentary [28].

Quality of Evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines will be followed to evaluate the certainty of reviewed evidence [29], and a GRADE evidence profile will be included when reporting the review findings.

Patient and Public Involvement

Patients and/or the public are not involved in the design, or conduct, or reporting or dissemination plans of this research.

Ethics and Dissemination

Ethical approval is not required for this systematic review because no human participants will be involved. The findings of this study will be disseminated in international peer-reviewed journals and at nursing conferences. This review will also be disseminated as part of Jing Liu's PhD thesis.

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Authors Contributions

All authors contributed to the design of this review. JL drafted the initial manuscript of this protocol. SH and SC provided important comments to the manuscript. JL and SH will search and select the studies, and conduct the data analysis. JL, RL, and JMZ will appraise the quality of included studies. SC will validate the study selection, study evaluation, and data synthesis process. All authors (JL, SH, SC, RL and JMZ) will involve in resolving disagreement and drafting publications of the systematic review. All authors have approved the publication of this protocol.

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Competing Interests Statement

The authors declare that they have no competing interests.

Availability of Data and Materials

Not applicable for this protocol.

Consent for Publication

Not applicable.

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Reporting checklist for protocol of a systematic review and meta-analysis.

Based on the PRISMA-P guidelines.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	NA, It is a protocol for a new systematic review.
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	17
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA, It is a protocol for a new systematic review.
Support			
Sources	#5a	Indicate sources of financial or other support for the review	17
Sponsor	#5b	Provide name for the review funder and / or sponsor	17
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	17
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	5-7

Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7-8
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7-8, 10-11
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8-9
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11-12
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11-12
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	12
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	12-13
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	12-13

Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	12-13
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	13
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12-13
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13-14

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Keywords: breast neoplasm, regret, systematic review, qualitative, meta-analysis, factors

ARTICLE SUMMARY

Strengths and Limitations of This Study

- This review will include all types of studies which differed from other reviews that only include randomized control trials.
- Meta-analysis and narrative description will be used to analyze quantitative data, and a thematic synthesis approach will be used to synthesize qualitative data, producing robust evidence about decision regret about breast cancer treatments.
- A third integrative analysis using a convergent parallel approach will be conducted to incorporate the quantitative and qualitative findings; thus, the review findings will be convergent and complementary.
- This review only includes studies published in English; thus, eligible studies published in other languages may be missed.

INTRODUCTION

Breast cancer is the most prevalent malignancy among women, contributing to 11.7% of new cancer cases in 2020 [1]. In many countries, the majority of the women with breast cancer were found to have early-stage breast cancer (EBC) at the time of diagnosis [2 3].

Women with EBC have a milder form of the disease, superior cure rates, and more treatment options than those with advanced and metastatic breast cancer (stages 3 and 4). Clinical trials suggest that survival rates after mastectomy and breast conservative surgery (BCS) for women with EBC are equivalent [4 5]; therefore, it is important to empower these women to make treatment decisions for themselves to achieve "shared decision-making" in breast cancer care [6 7]. However, choosing among multiple treatment options can be difficult. For example, a mastectomy surgery benefits women by a lower risk of recurrence but causes relatively larger body image impairment, whilst a BCS helps women maintain breast image but exposure women to a higher risk of local recurrence [5]. Therefore, when choosing between mastectomy and BCS, women must weigh the benefits and side effects of each option. Negative emotions, such as fear, can further complicate the decision-making about breast cancer treatments [8 9]. Facing the difficult treatment choices, some women with EBC may make a decision that they will regret in the future [10 11]. Thus, it is important to understand the decision-making behaviour of women with EBC.

In the context of health care, *decision regret* refers to "remorse or distress over a decision" [12]. Decision regret is a significant indicator of treatment decision efficacy and may emerge when patients feel that they could have had a better outcome if they had chosen a different treatment [12 13]. In a study from the US, Advani et al. (2019) reported that 100 out of 421 (23.8%) older women with breast cancer (>67 years) had experienced decision regret

regarding some forms of local therapy (e.g., lumpectomy with radiotherapy, brachytherapy, or endocrine therapy or mastectomy). In this study, decision regret was associated with race, education level, and the extent of nodal dissection performed, but not the type of therapy [14]. In another survey among young women (<51 years), 42.5% of 449 women with breast cancer experienced decision regret five years after treatment. Of these women, 24.2% regretted having primary surgery and 21.5% regretted having chemotherapy or radiotherapy [15]. Qualitative explorations also reported women expressed regret about their treatment decisions [15-17], and their regrets were mostly associated with not engaging in the decision-making process [16] and inadequate information [15 17].

The physical and psychosocial consequences associated with decision regret have been discussed in previous literature [13 15 17 18]. Regretting a treatment decision has been associated with a higher probability of undergoing a second round of treatment, which could result in delayed recovery and additional trauma. Regret regarding cancer treatments has also been associated with poor psychological well-being and quality of life [18 19]. Experiencing regret about a treatment decision may also increase patients' financial burden, especially for patients from economically disadvantaged backgrounds. Additionally, studies show that decision regret may damage the relationship between patients and their healthcare providers [20 21]. Thus, it is important for health care providers to support patients' decision-making and minimise the occurrence of decision regret in clinical practice.

Reviews summarizing evidence about patients' decision-making about breast cancer treatments have been published [22 23], However, they have not specifically addressed the issue of regret about treatment decisions, and were not able to generalize to the whole population because these reviews only included older women [22] and women who had a mastectomy [23].

Previous reviews on decision regret related to breast reconstruction [24] and risk-reducing treatment [25 26] also could not provide a holistic understanding of decision regret regarding EBC treatments because other treatments, such as breast-conserving surgery, chemotherapy, and radiotherapy, are also common choices for EBC. To date, there is a lack of literature synthesis regarding levels of decision regret, what patients regret, and factors associated with decision regret regarding breast cancer treatments among women with EBC. Without such an understanding, it is difficult for healthcare professionals to develop supportive interventions to help patients make treatment decisions.

Review Objectives

A systematic review will be conducted to assess studies dealing with decision regret regarding breast cancer treatment among patients with EBC. The treatment approaches of interest will include unilateral mastectomy, breast-conserving surgery, chemotherapy, radiotherapy, endocrine therapy, and targeted therapy. The Participants, Interventions, Comparators and Outcomes (PICO) elements used for the systematic review are listed in Table 1. The detailed objectives are:

1) To assess levels of decision regret about treatments among women with EBC;
2) To identify what women regret;
3) To identify factors associated with decision regret.

Table 1. The PICO Elements Used as Selection Criteria in This Systematic Review.

Participants	• Women with early-stage breast cancer (stage 0/carcinoma in situ, stage 1 and stage 2).
Intervention/Exposure	• Experienced decision regret regarding their treatments.

Comparators	• No restriction. The comparator depends on the study design. • For example, the comparator could be a group of the normal population for a cohort comparative study; if the included study is a randomized control trial to assess the effectiveness of a decision aid, the comparator could be the group of the population who had not received the decisional intervention.
Outcomes	• Levels of decision regret; • Events/processes/things that women regret; • Factors associated with decision regret.
Settings	• No restriction

METHODS AND ANALYSIS

This protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42021260041). The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist is followed to report this protocol [27] (See Supplemental Material 1). This systematic review is anticipated to be performed during August 2021 and January 2022.

Study Selection

Information Sources

The authors will search electronic databases including CINAHL Complete, Embase, PubMed, Medline, and Web of Science. A manual search of the reference lists of eligible studies will be also performed. This systematic review will include primary studies published from January 2000 to June 2021 in order to provide the most recent evidence.

Selection Process

Two authors will independently conduct the literature search (JL and SH). Another researcher will validate the search process to ensure accuracy (SC). All studies will be exported using

Endnote X9 software for duplicate removal and further screening. Thereafter, two authors will independently review the titles, abstracts, and full texts of these papers to determine their eligibility (JL and SH). Disagreement about study eligibility will be resolved through discussions among all researchers (JL, SH, JMZ, RL, and SC). The selection process will be presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis PRISMA flow diagram (see Figure 1).

Search Terms

The keyword search terms are derived from the main concepts of the research topic. The key terms will include "breast cancer," "breast tumor," "breast neoplasm," "breast carcinoma," "early-stage breast cancer," "early breast cancer," "regret," "decision regret," "treatment," "intervention," and "therapy." Search strategies for all databases are presented in Supplementary Material 2.

Inclusion and Exclusion Criteria

All relevant quantitative, qualitative, and mixed-methods studies written in the English language will be included. There will be no restrictions regarding the design or setting of the study, as long as they are:

1) primary studies reporting decision regret regarding unilateral mastectomy, breast-conserving surgery, chemotherapy, radiotherapy, endocrine therapy, or targeted therapy;
2) among patients with EBC; and
3) published in the English language.

Studies regarding risk-reducing treatment (e.g., contralateral prophylactic mastectomy) and reconstructive surgery will be excluded because there have been three published reviews

specifically addressing these surgeries [19 25 26]. Secondary studies and grey literature will also be excluded.

Analysis

Outcome Measures

The primary outcome of the systematic review will be patients' levels of decision regret regarding breast cancer treatments. Levels of decision regret was measured using different methods across the studies. For example, decision regret was measured using the validated 5-item, 5-point Likert Decision Regret Scale in Advani et al.'s (2019) study. Researchers in this study considered scores 1, 2 and 3 as feeling regret, while 4 and 5 indicated no regret [14]. Martinez et al. (2013) revised the items of the Decision Regret Scale. In this study, the ratings of each item were summed up as total scores ranging from 0 to 20, where higher scores indicated higher levels of regret [28]. Regret was also measured by a single-item dichotomous choice question in Yamauchi et al.'s (2019) study, in which women were asked to indicate "having no regret" or "having some regret" about breast cancer treatments [29].

The secondary outcomes will include what patients regret when they recall their decision-making process and the factors contributing to their decision regret.

Data Evaluation

Three researchers will conduct the data evaluation independently (JL, JMZ, and RL), and another author's (SC) advice will be sought if there is disagreement. The methodological quality of eligible studies will be evaluated using critical appraisal tools developed by the Joanna Briggs Institute. These tools were developed to assist in assessing the trustworthiness, relevance, and results of quantitative and qualitative studies. For qualitative studies,

researchers are required to respond (*yes*, *no*, *unclear*, or *not applicable*) to ten questions to determine whether a study has addressed the possibility of bias in its design, conduct, or analysis [30]. Following these questions, researchers will decide if the study should be included or excluded, or if additional information should be sought [30]. Disagreements regarding study inclusion will be discussed by the entire group of researchers.

Data Extraction and Synthesis

Two researchers will analyze the data independently (JL and SH). Included studies will be first categorized into quantitative, qualitative, or mixed-methods studies according to their design. Information on the year of publication, author(s), setting, participant characteristics (e.g., age, number of participants, cancer stage, and treatment received), measures (e.g., instruments, time of measurement, and comparative groups), interventions (e.g., blinding and randomized methods), and findings of interest (e.g., level of decision regret, what patients regret, and factors associated with decision regret) will be extracted. The extracted data will be compiled into an Excel spreadsheet by each researcher before being compared by both researchers for completeness and accuracy. Any discrepancies will be resolved through discussion within the research group (JL, SH, JMZ, RL, and SC).

Quantitative results will be pooled into Review Manager Software (RevMan) Version 5 to conduct a meta-analysis where appropriate [31]. A forest plot will be created to present the pooled results. For example, if there are several interventional studies that have evaluated the effectiveness of decision aids in reducing patient-perceived regret, odds ratios (for dichotomous variables) or weighted mean differences (for continuous variables) and their 95% confidence intervals (CIs) will be calculated in order to precisely describe the impact of decision aids on decision regret. The I^2 statistic will be used to assess heterogeneity, and a

value lower than 50% will be considered to indicate low heterogeneity. In case of low heterogeneity, the fixed-effects model will be applied to assess the pooled results. Otherwise, the pooled results will be assessed using the random-effects model. Sensitivity analysis will be conducted if the pooled results have substantial heterogeneity, and the results will be carefully interpreted. A subgroup analysis on the interventions and types of received treatment (e.g., chemotherapy or radiotherapy) will be performed where applicable. The publication bias will be indicated by the asymmetry of the funnel plot [32]. The findings will be described in narrative form where meta-analysis is impossible. For example, if there is only one cross-sectional survey reporting regret after chemotherapy, results concerning the level of regret, what women regret, and related factors will be narratively described.

Qualitative evidence will be analyzed using the thematic synthesis approach proposed by Thomas and Harden [33]. Qualitative studies will be read and reread by two researchers (JL and SH), and findings associated with the three review questions will be identified and coded line-by-line. These initial codes will be compared and consolidated until a number of descriptive subthemes emerge. All researchers will discuss the subthemes until a consensus is reached regarding whether the subthemes comply with the meaning of the original study. Thereafter, similar subthemes will be further grouped based on their similarity in order to produce several analytical themes that are pertinent to the review questions. A coding sheet will be developed by the author to facilitate the data synthesis. The other three researchers (JMZ, RL, and SC) will comment on the synthesis by reviewing the coding sheet until a final consensus is reached.

A third integrative analysis using a convergent parallel approach will be conducted to incorporate the quantitative and qualitative findings [34]. Quantitative outcomes and qualitative

themes will be combined to provide rich insights into the three review questions. It is anticipated the quantitative outcomes will quantify the qualitative findings, and the qualitative themes will help explain the quantitative outcomes; thus, the review findings will be convergent and complementary [35].

Quality of Evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines will be followed to evaluate the certainty of reviewed evidence [36], and a GRADE evidence profile will be included when reporting the review findings.

Patient and Public Involvement

Patients and/or the public are not involved in the design, or conduct, or reporting or dissemination plans of this research.

Ethics and Dissemination

Ethical approval is not required for this systematic review because no human participants will be involved. The findings of this study will be disseminated in international peer-reviewed journals and at nursing conferences. This review will also be disseminated as part of Jing Liu's PhD thesis.

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Flow Diagram and Selection Process.

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Authors Contributions

All authors contributed to the design of this review. JL drafted the initial manuscript of this protocol. SH and SC provided important comments to the manuscript. JL and SH will search and select the studies, and conduct the data analysis. JL, RL, and JMZ will appraise the quality of included studies. SC will validate the study selection, study evaluation, and data synthesis process. All authors (JL, SH, SC, RL and JMZ) will involve in resolving disagreement and drafting publications of the systematic review. All authors have approved the publication of this protocol.

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Competing Interests Statement

The authors declare that they have no competing interests.

Availability of Data and Materials

Not applicable for this protocol.

Consent for Publication

Not applicable.

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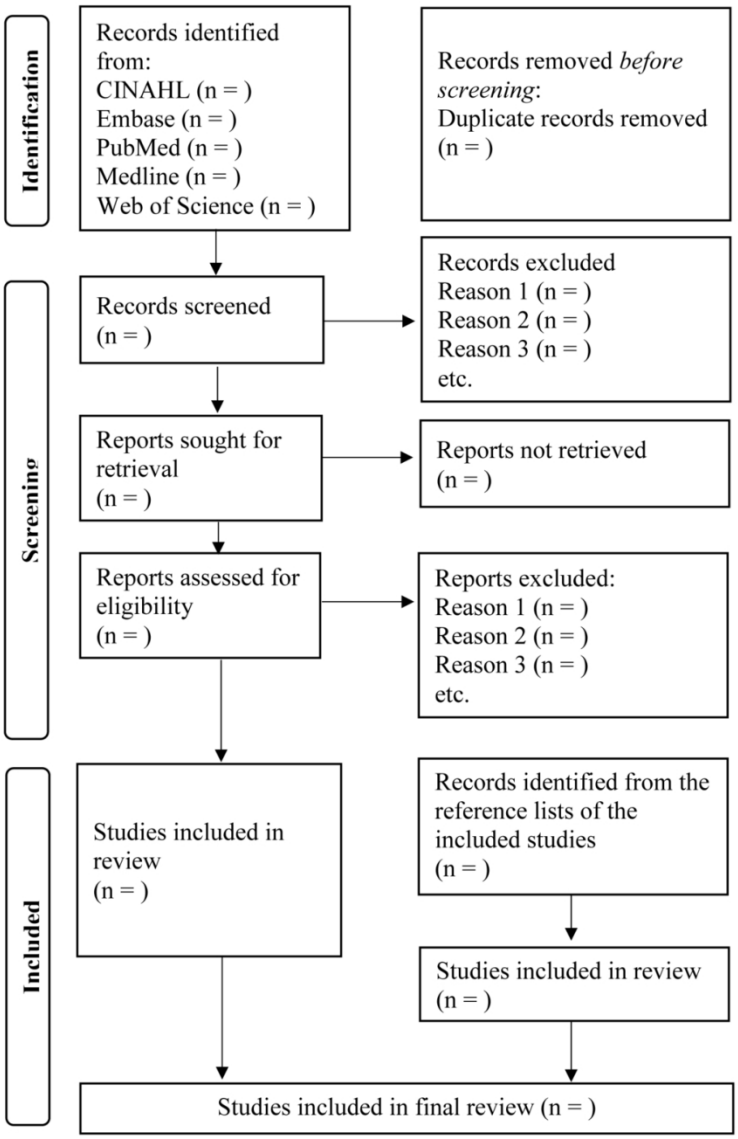

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Flow Diagram and Selection Process.

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Supplementary Material 1: Reporting Checklist for Protocol of A Systematic Review and Meta-Analysis.

		Reporting Item	Page Number in Manuscript
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	NA, It is a protocol for a new systematic review.
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	18
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA, It is a protocol for a new systematic review.
Support			
Sources	#5a	Indicate sources of financial or other support for the review	18
Sponsor	#5b	Provide name for the review funder and / or sponsor	18
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	18
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	5-7
Objectives	#7	Provide an explicit statement of the question(s) the review will address with	7-8

		reference to participants, interventions, comparators, and outcomes (PICO)	
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7-10
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	9 and Supplementary Material 2
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10-11
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11-12
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	11-12
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	11-12
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies,	11-12

		including any planned exploration of consistency (such as I2, Kendall's τ)	
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11-12
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13

Supplementary Material 2: Full Search Strategies for All Databases.

Database	Search Strategy
CINAHL Complete	TX (breast cancer or breast tumor or breast neoplasm or breast carcinoma or early-stage breast cancer or early breast cancer) AND TX (regret or decision regret) AND TX (treatment or intervention or therapy) Filters: publication time from 2000-2021
Embase	1. (breast cancer or breast tumor or breast neoplasm or breast carcinoma or early-stage breast cancer or early breast cancer).mp. 2. Limit 1 to (full text and yr="2000 - 2021") 3. (regret or decision regret).mp. 4. Limit 3 to (full text and yr="2000 - 2021") 5. (treatment or intervention or therapy).mp 6. Limit 5 to (full text and yr="2000 - 2021") 7. 1 and 2 and 3 and 4 and 5 and 6
PubMed	((((("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields]) AND ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "tumor"[All Fields]) OR "breast tumor"[All Fields])) OR ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "neoplasm"[All Fields]) OR "breast neoplasm"[All Fields]) OR ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "carcinoma"[All Fields]) OR "breast carcinoma"[All Fields]) OR ("early"[All Fields] AND ("stage"[All Fields] OR "staged"[All Fields] OR "stages"[All Fields] OR "staging"[All Fields] OR "stagings"[All Fields]) AND ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields])) OR ("early"[All Fields] AND ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields]))) AND ("emotions"[MeSH Terms] OR "emotions"[All Fields] OR "regret"[All Fields] OR "regrets"[All Fields] OR "regretful"[All Fields] OR "regretted"[All Fields] OR "regretting"[All Fields] OR (("decision"[All Fields] OR "decision s"[All Fields] OR "decisions"[All Fields] OR "decisive"[All Fields] OR "decisively"[All Fields]) AND ("emotions"[MeSH Terms] OR "emotions"[All Fields] OR "regret"[All Fields] OR "regrets"[All Fields] OR "regretful"[All Fields] OR

	"regretted"[All Fields] OR "regretting"[All Fields])) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields] OR ("intervention s"[All Fields] OR "interventions"[All Fields] OR "interventive"[All Fields] OR "methods"[MeSH Terms] OR "methods"[All Fields] OR "intervention"[All Fields] OR "interventional"[All Fields]) OR ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields])) AND (2000:2021[pdat]))
Medline	1. (breast cancer or breast tumor or breast neoplasm or breast carcinoma or early-stage breast cancer or early breast cancer).mp. 2. Limit 1 to (full text and yr="2000 - 2021") 3. (regret or decision regret).mp. 4. Limit 3 to (full text and yr="2000 - 2021") 5. (treatment or intervention or therapy).mp. 6. Limit 5 to (full text and yr="2000 - 2021") 7. 1 and 2 and 3 and 4 and 5 and 6
Web of Science	((ALL=(breast cancer or breast tumor or breast neoplasm or breast carcinoma or early-stage breast cancer or early breast cancer)) AND ALL=(regret or decision regret)) AND ALL=(treatment or intervention or therapy) Filters: publication time from 2000.01.01-2021.06.30