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The impact of modifiable reproductive factors on cancer incidence and mortality in Korea: A systematic review protocol

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Abstract

Introduction: Cancer is a leading cause of death worldwide. In Korea, it is also a major public health problem. Cancer burden may increase significantly due to aging population and changes in lifestyle. The features of reproductive factors have changed, which include decreased age at first childbirth and decreased breastfeeding duration. This study aims to systematically summarize the association between modifiable reproductive factors and cancer incidence and mortality to provide evidence for planning strategies aimed at reducing cancer incidence and mortality in women.

Methods and Analysis: A literature search will be performed using the EMBASE, MEDLINE, Cochrane Library, and Korean databases such as the Korean Studies Information Service System, Research Information Sharing Service, KoreaMED, Korean Medical Database, National Assembly Library, and Korea Institute from their inception to date. We will include cohort studies addressing the associations between at least one of the reproductive factors and the incidence and mortality of all or specific cancers among Korean women. Two reviewers will screen the references, extract the data, and assess the risk of bias independently and in duplicates. Discrepancies will be resolved through discussion or consultation with a third-party reviewer. We will use the Grading of Recommendations Assessment, Development, and Evaluation approach to evaluate the certainty of evidence. We will summarize the findings of the included systematic reviews through quantitative or narrative syntheses and present the summarized findings in tables.

Ethics and dissemination: Ethical approval is not required, since we will use only the published data. We will disseminate the study findings in peer-reviewed publications.

Registration: Submitted to PROSPERO

Keywords: Childbirth, Female, Korea, Neoplasms, Reproductive factors, Systematic review

Strengths and limitations of this study

- This review will provide an up-to-date, comprehensive assessment of the effects of modifiable reproductive factors on cancer.
- Reference screening, data extraction, and assessment of the certainty of evidence will be performed independently by two reviewers to reduce bias.
- Heterogeneity due to differences in the classification of reproductive factors among studies might prevent a direct comparison or synthesis of the study results.

INTRODUCTION

Cancer is a leading cause of death worldwide.[1] In Korea, it has also been a major public health problem since 1983.[2] In 2019, lung cancer overtook gastric cancer and was ranked first in terms of incidence rate for the first time, excluding thyroid cancer. Since 1999, the incidence of gastric, colon, liver, and cervical cancers has been decreasing, while the incidence of prostate and breast cancers has been increasing.[3] Korea's current cancer burden has predicted 274,488 new cancer cases and 81,277 cancer-related deaths by 2022.[4]

Lung, colon, rectal, pancreatic, breast, and liver cancers are the most common causes of death. Among women, the five major primary cancers include breast, thyroid, colon, rectal, lung, and stomach cancers.[3] The 5-year survival rate of Korean cancer patients has improved significantly from 41.2% in 1993–1995 to 70.6% in 2012–2016. Since 2016, the number of cancer survivors has exceeded 1.74 million and the survival rate for more than 5 years is highest among the 32 countries belonging to the Organization for Economic Cooperation and Development.[5] Nevertheless, the cancer mortality rate is predicted to increase by 2032.[6] As cancer enters the social and economic development and aging population, its incidence may increase significantly.[7]

Among women, three out of the ten most common cancer types are gynecological cancers. Breast cancer is the most common, cervical cancer is the fourth most common, and ovarian cancer is the tenth most common cancer among women worldwide and the incidence and mortality rates of gynecological cancers have continued to increase.[8] The incidence of breast and ovarian cancers is expected to increase in Korea.[6] Among the fertilizable reproductive factors, a higher number of births is associated with a higher incidence of cancer.[9] Moreover, older age at first childbirth is associated with a higher risk of adenocarcinoma.[10] It was also related to a higher risk of bladder cancer in women who did not give birth.[11]

Reproductive factors have evolved worldwide in recent years. These changes include older age at childbirth and shorter breastfeeding duration, which may have influenced the health outcomes among women.[12-14] According to a systematic review and meta-analysis, menopause and older age at childbirth were associated with an increased risk of thyroid cancer and a longer breastfeeding duration prevented thyroid cancer.[15] Thyroid, breast, and lung cancers are also associated with childbirth.[16-19]

Korea has a rapidly aging population. Moreover, changes in the reproductive factors such as advanced age at first childbirth and no or short breastfeeding duration are expected to increase the risk of cancer.[20] Therefore, we aim to summarize the effects of modifiable reproductive factors on cancer incidence and mortality in Korean women. We will conduct a systematic review adhering to the methodological standards in this region and report our study plan to promote transparency.

METHODS

We will follow the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols checklist for reporting the protocol[21] and submit the protocol to PROSPERO.

Eligibility criteria

We will include studies meeting the following criteria: (1) cohort studies focusing on Korean female population aged ≥18 years without cancer history at baseline; (2) studies reporting the association between reproductive factors and the incidence or mortality of all or specific cancers; (3) studies considering at least one of the following modifiable reproductive factors as an exposure: childbirth, age at first childbirth, age at last childbirth, number of childbirths, breastfeeding experience, and duration of breastfeeding; and (4) studies presenting the effect estimates (relative ratio [RR], odds ratio [OR], or hazard ratio [HR]) for cancer incidence or mortality and corresponding 95% confidence intervals (CIs).

We will consider reproductive factors as modifiable if women could choose their own status or duration of these factors. Therefore, delivery methods such as cesarean section and hormone replacement therapy would not be considered exposures of interest in this study, since these factors are influenced mainly by the physician's recommendations.

Studies will be excluded if they involve women with specific health conditions (such as inflammatory bowel disease, human immunodeficiency virus infection). We will also exclude reviews, conference summaries, editorials, commentaries, critiques, letters to editors, and publications without primary data.

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We will conduct a literature search in the EMBASE, MEDLINE, Cochrane Library, and Korean databases such as the Korean Studies Information Service System, Research Information Sharing Service, KoreaMED, Korean Medical Database, National Assembly Library, and Korea Institute from their inception to date. We will develop a search strategy using controlled vocabulary as well as free-text words related to reproductive factors and cancers, in collaboration with an experienced librarian.

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For all studies identified by searching the electronic databases, two reviewers will independently screen the titles and/or abstracts for eligibility in duplicate. Subsequently, the reviewers will screen the full texts for potentially eligible studies independently and in duplicate. Discrepancies between the reviewers will be resolved through discussion or consultation with a third reviewer if needed. Calibration exercises will be conducted at each stage to ensure reliability and accuracy between the reviewers.

Data abstraction

We will collect the following information from each study:

1. Study information: First author, year of publication, name of cohort, number of participants, age at baseline, year, and mean age

2. Modifiable reproductive factors: Type of reproductive factors (childbirth, age at first childbirth, age at last childbirth, number of births, breastfeeding experience, duration of breastfeeding), categories of reproductive factors, and exposure assessment method

3. Cancer incidence and mortality: Cancer type, outcome measurement method, follow-up period, the most fully adjusted risk estimate (RR, OR, or HR), and corresponding 95% CIs.

We will conduct calibration exercises to ensure consistency between the reviewers. Two reviewers will

independently extract the data. Discrepancies will be resolved through discussion or consultation with a third-party reviewer.

Risk of bias

We will evaluate the risk of bias in the included studies using the Clinical Advances through Research and Information Translation tool for cohort studies, which includes with the following seven domains[22]: (1) "Was the selection of exposed and non-exposed cohorts drawn from the same population?," (2) "Can we be confident in the assessment of exposure?," (3) "Can we be confident that the outcome of interest was not present at the start of the study?," (4) "Did the study match exposed and non-exposed cohorts for all variables?," (5) "Can we be confident in the assessment of the presence or absence of prognostic factors?," (6) "Can we be confident in the assessment of the outcomes?," and (7) "Was the follow-up of the cohorts adequate?" Answers for Each domain will be categorized as definitely yes, probably yes, probably no, and definitely no. A study found to have a high risk of bias in more than two of the seven domains will be considered to have a high overall risk of bias. Two reviewers will independently assess the risk of bias. In case of disagreement, inconsistencies will be resolved through consensus or discussion with a third reviewer.

Certainty of evidence

We will assess the certainty of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. This approach to assess the certainty of evidence starts with the study design and considers five factors (risk of bias, inconsistency, indirection, imprecision, and publication bias) to rate down the certainty of the evidence and three factors (large effect sizes, dose-response relationships, etc.) to rate up the certainty. While assessing causality in the GRADE approach, randomized controlled trials begin with evidence of high certainty, whereas observational studies begin with evidence of low certainty. The final certainty of evidence will be categorized into one of the following four levels: high, moderate, low, and very low.[23]

Analysis and tables presenting the summary of findings

We will perform a meta-analysis to present the pooled relative effect estimates of reproductive factors for cancer. We will conduct two types of meta-analyses if possible. Initially, we will conduct categorical meta-analyses to calculate the pooled relative effect estimates (such as analysis to assess the effect of highest vs. lowest duration of breastfeeding on cancer). Subsequently, if a study reports the exposure in at least three categories or continuous types, we will conduct dose-response meta-analyses (such as analysis to assess the effect of duration of breastfeeding on cancer). For each meta-analysis, summary estimates and their corresponding 95% CIs will be calculated using a random effects model.

Heterogeneity will be assessed using visual inspection of effect estimates, overlapping of confidence intervals in forest plots, and I^2 and Q statistics. Publication bias will be explored by visual inspection of the funnel plots and Egger's test. We will conduct subgroup analysis according to low and high risk of bias in the studies. We will calculate the absolute effect of reproductive factors on cancer by multiplying the pooled relative effects from the meta-analyses with the baseline risk of cancer incidence and mortality. All statistical analyses will be performed using RevMan 5.3 (Cochrane, London, UK) and R (the R foundation, Austria, Vienna).

Patients and public involvement

No patients or the public will be involved.

DISCUSSION

This systematic review aims to identify, evaluate, and consolidate evidence of the effects of reproductive factors on cancer in the Korean population. We expect that our research results will help prevent cancer and aid in future research on reproductive factors among Koreans.

The advantages of this review include the use of a systematic and transparent process with stringent research criteria including a comprehensive search of eligible studies, explicit eligibility criteria, independent and duplicate screening, data abstraction, and risk of bias assessment.

Heterogeneity due to differences in the classification of reproductive factors among studies (such as that due to differences in age at first childbirth and duration of breastfeeding) might prevent direct comparison or synthesis of the study results.

Ethics and dissemination

This systematic review does not require approval from the institutional review board. We will disseminate the findings of this systematic review in peer-reviewed publications.

Contributors: MAH conceptualized and designed the study. SHK drafted the study protocol. All authors reviewed the study plan and manuscript and offered comments and edits. All authors approved the final manuscript.

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Competing interests: None declared.

Patients consent for publication: Not required.

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PRISMA-P checklist

Section and topic	Item No	Checklist item	Page #
ADMINISTRATIVE INFORMATION			
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
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	7
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
Support:			
Sources	5a	Indicate sources of financial or other support for the review	7
Sponsor	5b	Provide name for the review funder and/or sponsor	7
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	7
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
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	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial	5

		registers or other grey literature sources) with planned dates of coverage	
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	5
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
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)	5
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	5
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	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
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	6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6
	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 I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

NA, not applicable.

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Registration: PROSPERO (CRD42022356085)

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Reproductive factors have evolved worldwide in recent years. These changes include older age at childbirth and shorter breastfeeding duration, which may have influenced the health outcomes among women.[13-15] According to a systematic review and meta-analysis, menopause and older age at childbirth were associated with an increased risk of thyroid cancer and a longer breastfeeding duration prevented thyroid cancer.[16] Thyroid, breast, and lung cancers are also associated with childbirth.[17-20]

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2. Modifiable reproductive factors: Type of reproductive factors (childbirth history, age at first childbirth, age at last childbirth, number of births, breastfeeding experience, duration of breastfeeding), categories of reproductive factors, and exposure assessment method

3. Cancer incidence and mortality: Cancer type, outcome measurement method, follow-up period, the most fully adjusted risk estimate (RR, OR, or HR), and corresponding 95% CIs.

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We will evaluate the risk of bias in the included studies using the Clinical Advances through Research and Information Translation tool for cohort studies, which includes with the following seven domains[23]: (1) "Was the selection of exposed and non-exposed cohorts drawn from the same population?," (2) "Can we be confident in the assessment of exposure?," (3) "Can we be confident that the outcome of interest was not present at the start of the study?," (4) "Did the study match exposed and non-exposed cohorts for all variables?," (5) "Can we be confident in the assessment of the presence or absence of prognostic factors?," (6) "Can we be confident in the assessment of the outcomes?," and (7) "Was the follow-up of the cohorts adequate?" Answers for Each domain will be categorized as definitely yes, probably yes, probably no, and definitely no. A study found to have a high risk of bias in more than two of the seven domains will be considered to have a high overall risk of bias. Two reviewers will independently assess the risk of bias. In case of disagreement, inconsistencies will be resolved through consensus or discussion with a third reviewer.

Certainty of evidence

We will assess the certainty of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. This approach to assess the certainty of evidence starts with the study design and considers five factors (risk of bias, inconsistency, indirection, imprecision, and publication bias) to rate down the certainty of the evidence and three factors (large effect sizes, dose-response relationships, etc.) to rate up the certainty. While assessing causality in the GRADE approach, randomized controlled trials begin with evidence of high certainty, whereas observational studies begin with evidence of low certainty. The final certainty of evidence will be categorized into one of the following four levels: high, moderate, low, and very low.[24]

Analysis and tables presenting the summary of findings

We will use a PRISMA flow diagram to illustrate the study selection process. We will perform a meta-analysis to present the pooled relative effect estimates of reproductive factors for cancer. We will conduct two types of meta-analyses if possible. Initially, we will conduct categorical meta-analyses to calculate the pooled relative effect estimates (such as analysis to assess the effect of highest vs. lowest duration of breastfeeding on cancer). Subsequently, if a study reports the exposure in at least three categories or continuous types, we will conduct dose-response meta-analyses (such as analysis to assess the effect of duration of breastfeeding on cancer). For each meta-analysis, summary estimates and their corresponding 95% CIs will be calculated using a random effects model.

Heterogeneity will be assessed using visual inspection of effect estimates, overlapping of confidence intervals in forest plots, and I^2 and Q statistics. Publication bias will be explored by visual inspection of the funnel plots and Egger's test. We will conduct subgroup analysis according to low and high risk of bias in the studies. We will calculate the absolute effect of reproductive factors on cancer by multiplying the pooled relative effects from the meta-analyses with the baseline risk of cancer incidence and mortality. All statistical analyses will be performed using RevMan 5.3 (Cochrane, London, UK) and R (the R foundation, Austria, Vienna).

Patients and public involvement

No patients or the public will be involved.

DISCUSSION

This systematic review aims to identify, evaluate, and consolidate evidence of the effects of reproductive factors on cancer in the Korean population. We expect that our research results will help prevent cancer and aid in future research on reproductive factors among Koreans.

The advantages of this review include the use of a systematic and transparent process with stringent research criteria including a comprehensive search of eligible studies, explicit eligibility criteria, independent and duplicate screening, data abstraction, and risk of bias assessment.

Heterogeneity due to differences in the classification of reproductive factors among studies (such as that due to differences in age at first childbirth and duration of breastfeeding) might prevent direct comparison or synthesis of the study results.

Ethics and dissemination

This systematic review does not require approval from the institutional review board. We will disseminate the findings of this systematic review in peer-reviewed publications.

Contributors: MAH conceptualized and designed the study. SHK drafted the study protocol. All authors reviewed the study plan and manuscript and offered comments and edits. All authors approved the final manuscript.

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Supplementary appendix

Appendix 1. Search strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to July Week 2 2021

#	Searches
1	(reproductive adj (factor* or characteristic* or histor*)).tw,kf.
2	Milk, Human/ or Breast Feeding/ or (breast adj (feed* or milk)).tw,kf.
3	Maternal Age/ or (age* adj (birth* or childbirth* or deliver* or parity or childbearing* or maternal or pregnanc* or mother* or first birth* or last birth* or first childbirth* or last childbirth*)).tw,kf.
4	Parity/ or Delivery, Obstetric/ or Pregnancy, Multiple/ or (((parity or pregnan* or child* or birth*) adj (histor* or number* or frequenc* or order*)) or nullipar* or multiparous or multiparit*).tw,kf.
5	1 or 2 or 3 or 4
6	exp Neoplasms/ or (cancer* or neoplas* or tumo?r* or malignan*).tw,kf.
7	exp cohort studies/ or ((cohort adj (study or studies)) or cohort analy*).tw,kf.
8	(follow up adj (study or studies)).tw,kf.
9	(longitudinal or prospective or retrospective).tw,kf.
10	7 or 8 or 9
11	korea*.mp.
12	5 and 6 and 10 and 11

EMBASE

#	Searches
#1	(reproductive NEXT/1 (factor* OR characteristic* OR histor*)):ti,ab,kw
#2	'breast milk'/exp OR 'breast feeding'/exp OR ((breast NEXT/1 (feed* OR milk)):ti,ab,kw)
#3	'maternal age'/exp OR ((age* NEXT/1 (birth* OR childbirth* OR deliver* OR parity OR childbearing* OR maternal OR pregnanc* OR mother* OR 'first birth*' OR 'last birth*' OR 'first childbirth*' OR 'last childbirth*')):ti,ab,kw)
#4	'parity'/exp OR 'obstetric delivery'/de OR 'multiple pregnancy'/de OR (((parity OR pregnan* OR child* OR birth*) NEXT/1 (histor* OR number* OR frequenc* OR order*)):ti,ab,kw) OR nullipar*:ti,ab,kw OR multiparous:ti,ab,kw OR multiparit*:ti,ab,kw
#5	#1 OR #2 OR #3 OR #4
#6	'neoplasm'/exp OR cancer*:ti,ab,kw OR neoplas*:ti,ab,kw OR tumor*:ti,ab,kw OR tumour*:ti,ab,kw OR malignan*:ti,ab,kw
#7	'cohort analysis'/exp OR ((cohort NEXT/1 (study OR studies)):ti,ab,kw) OR 'cohort analy*':ti,ab,kw
#8	('follow up' NEXT/1 (study OR studies)):ti,ab,kw
#9	longitudinal:ti,ab,kw OR prospective:ti,ab,kw OR retrospective:ti,ab,kw
#10	#7 OR #8 OR #9
#11	korea:ti,ab,kw
#12	#5 AND #10 AND #11

Cochrane Library

#	Searches
#1	(reproductive next/1 (factor* or characteristic* or histor*)):ti,ab,kw
#2	[mh ^"Milk, Human"] or [mh ^"Breast Feeding"] or (breast next/1 (feed* or milk)):ti,ab,kw
#3	[mh ^"Maternal Age"] or (age* next/1 (birth* or childbirth* or deliver* or parity or childbearing* or maternal or pregnanc* or mother* or "first birth*" or "last birth*" or "first childbirth*" or "last childbirth*")):ti,ab,kw
#4	[mh ^"Parity"] or [mh ^"Delivery, Obstetric"] or [mh ^"Pregnancy, Multiple"] or (((parity or pregnan* or child* or birth*) next/1 (histor* or number* or frequenc* or order*)) or nullipar* or multiparous or multiparit*):ti,ab,kw

#5	#1 or #2 or #3 or #4
#6	[mh "Neoplasms"] or (cancer* or neoplas* or tumo?r* or malignan*):ti,ab,kw
#7	[mh "cohort studies"] or ((cohort next/1 (study or studies)) or "cohort analy*"):ti,ab,kw
#8	(follow up next/1 (study or studies)):ti,ab,kw
#9	(longitudinal or prospective or retrospective):ti,ab,kw
#10	#7 or #8 or #9
#11	korea*:ti,ab,kw
#12	#5 and #6 and #10 and #11

KoreaMED

#	Searches
1	"reproductive factor"[TIAB] OR "reproductive characteristic"[TIAB] OR "reproductive history"[TIAB] OR breastfeeding[TIAB] OR "breast feeding"[TIAB] OR parity[TIAB] OR delivery[TIAB] OR pregnant[TIAB] OR pregnancy[TIAB] OR pregnancies[TIAB] OR "age at menarche"[TIAB] OR "age at first birth"[TIAB] OR "age at last birth"[TIAB] OR "age at first birth"[TIAB] OR "age at last childbirth"[TIAB] OR "number of births"[TIAB] OR "number of childbirth"[TIAB]
2	cancer[TIAB] OR cancers[TIAB] OR tumor[TIAB] OR tumors[TIAB] OR tumour[TIAB] OR tumours[TIAB] OR neoplasm[TIAB] OR neoplasms[TIAB] OR neoplasia[TIAB] OR neoplasias[TIAB] OR malignant[TIAB] OR malignancy[TIAB] OR malignancies[TIAB]
3	cohort[TIAB] OR "follow up"[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB]
4	1 AND 2 AND 3

Korean Medical Database (KMBASE)

#	Searches
1	((((((((([ALL=reproductive] OR [ALL=breastfeeding]) OR [ALL=breast feeding]) OR [ALL=birth*]) OR [ALL=생식]) OR [ALL=모유]) OR [ALL=수유]) OR [ALL=출산]) AND ((([ALL=cancer*] OR [ALL=tumor*]) OR [ALL=암]) OR [ALL=종양])) AND ((((([ALL=cohort] OR [ALL=Follow up]) OR [ALL=longitudinal]) OR [ALL=prospective]) OR [ALL=retrospective]) OR [ALL=코호트]))

Research Information Sharing Service (RISS)

#	Searches
1	논문명 : "reproductive factor" | "reproductive characteristic" | "reproductive history" | "생식요인" | "생식인자" | "생식특성" | breastfeeding | "breast feeding" | 모유 | 수유 | parity | delivery | pregnancy | "age at menarche" | "age at first birth" | "age at last birth" | "age at first birth" | "age at last childbirth" | "number of births" | "number of childbirth" | 출산 | 초산 | "출생아수" <AND> 논문명 : cancer | tumor | tumour | neoplasm | malignancy | 암 | 종양 <AND> 논문명 : cohort | "Follow up" | longitudinal | prospective | retrospective | 코호트 | 추적 | 전향적 | 후향적 | 종단
2	초록 : "reproductive factor" | "reproductive characteristic" | "reproductive history" | "생식요인" | "생식인자" | "생식특성" | breastfeeding | "breast feeding" | 모유 | 수유 | parity | delivery | pregnancy | "age at menarche" | "age at first birth" | "age at last birth" | "age at first birth" | "age at last childbirth" | "number of births" | "number of childbirth" | 출산 | 초산 | "출생아수" <AND> 초록 : cancer | tumor | tumour | neoplasm | malignancy | 암 | 종양 <AND> 초록 : cohort |

	"Follow up" | longitudinal | prospective | retrospective | 코호트 | 추적 | 전향적 | 후향적 | 종단
3	1 OR 2

Korean Studies Information Service System (KISS)

#	Searches
1	reproductive | 생식 | breast feeding | 모유 | 수유 | parity | delivery | pregnancy | menarche | birth | childbirth | 출산 | 초산 | 출생아수
2	cancer | tumor | tumour | neoplasm | malignancy | 암 | 종양
3	cohort | Follow up | longitudinal | prospective | retrospective | 코호트 | 추적조사 | 전향적 | 후향적 | 종단
4	1 AND 2 AND 3

Korea Institute of Science and Technology Information (KISTI)

#	Searches
1	논문명="reproductive factor" | "reproductive characteristic" | "reproductive history" | 생식요인 | 생식인자 | 생식특성 | breastfeeding | "breast feeding" | 모유 | 수유 | parity | delivery | pregnancy | "age at menarche" | "age at first birth" | "age at last birth" | "age at first birth" | "age at last childbirth" | "number of births" | "number of childbirth" | 출산 | 초산 | 출생아수 AND 논문명=cancer* | tumor* | tumour* | neoplasm* | malignan* | 암 | 종양 AND 논문명=cohort | "Follow up" | longitudinal | prospective | retrospective | 코호트 | 추적 | 전향적 | 후향적 | 종단
2	초록="reproductive factor" | "reproductive characteristic" | "reproductive history" | 생식요인 | 생식인자 | 생식특성 | breastfeeding | "breast feeding" | 모유 | 수유 | parity | delivery | pregnancy | "age at menarche" | "age at first birth" | "age at last birth" | "age at first birth" | "age at last childbirth" | "number of births" | "number of childbirth" | 출산 | 초산 | 출생아수 AND 초록=cancer* | tumor* | tumour* | neoplasm* | malignan* | 암 | 종양 AND 초록=cohort | "Follow up" | longitudinal | prospective | retrospective | 코호트 | 추적 | 전향적 | 후향적 | 종단
3	1 OR 2

National Assembly Library

#	Searches
1	"reproductive | "생식요인" | "생식인자" | "생식특성" | breastfeeding | "breast feeding" | 모유 | 수유 | parity | delivery | pregnancy | "age at menarche" | "age at first birth" | "age at last birth" | "age at first birth" | "age at last childbirth" | "number of births" | "number of childbirth" | 출산 | 초산 | "출생아수"
2	cancer* | tumor* | tumour* | neoplasm* | malignan* | 암 | 종양
3	1 AND 2

PRISMA-P checklist

Section and topic	Item No	Checklist item	Page #
ADMINISTRATIVE INFORMATION			
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
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	7
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
Support:			
Sources	5a	Indicate sources of financial or other support for the review	7
Sponsor	5b	Provide name for the review funder and/or sponsor	7
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	7
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
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	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial	5

		registers or other grey literature sources) with planned dates of coverage	
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	5
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
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)	5
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	5
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	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
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	6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6
	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 I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

NA, not applicable.

BMJ Open

The impact of modifiable reproductive factors on cancer incidence and mortality in Korea: A systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-067826.R2
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Secondary Subject Heading:	Oncology
Keywords:	Reproductive medicine < GYNAECOLOGY, PREVENTIVE MEDICINE, PUBLIC HEALTH, ONCOLOGY

The impact of modifiable reproductive factors on cancer incidence and mortality in Korea: A systematic review protocol

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Word count:
Abstract: 253 words
Main Text: 1666 words

Abstract

Introduction: Cancer is a leading cause of death worldwide. In Korea, it is also a major public health problem. Cancer burden may increase significantly due to aging population and changes in lifestyle. The features of reproductive factors have changed, which include increased age at first childbirth and decreased breastfeeding duration. This study aims to systematically summarize the association between modifiable reproductive factors and cancer incidence and mortality to provide evidence for planning strategies aimed at reducing cancer incidence and mortality in women.

Methods and Analysis: A literature search was performed using the EMBASE, MEDLINE, Cochrane Library, and Korean databases such as the Korean Studies Information Service System, Research Information Sharing Service, KoreaMED, Korean Medical Database, National Assembly Library, and Korea Institute from their inception to August 24, 2022. We will include cohort studies addressing the associations between at least one of the reproductive factors and the incidence and mortality of all or specific cancers among Korean women. Two reviewers will screen the references, extract the data, and assess the risk of bias independently and in duplicates. Discrepancies will be resolved through discussion or consultation with a third-party reviewer. We will use the Grading of Recommendations Assessment, Development, and Evaluation approach to evaluate the certainty of evidence. We will summarize the findings of the included systematic reviews through quantitative or narrative syntheses and present the summarized findings in tables.

Ethics and dissemination: Ethical approval is not required, since we will use only the published data. We will disseminate the study findings in peer-reviewed publications.

Registration: PROSPERO (CRD42022356085)

Keywords: Childbirth, Female, Korea, Neoplasms, Reproductive factors, Systematic review

Strengths and limitations of this study

- This review will provide an up-to-date, comprehensive assessment of the effects of modifiable reproductive factors on cancer.
- Reference screening, data extraction, and assessment of the certainty of evidence will be performed independently by two reviewers to reduce bias.
- Heterogeneity due to differences in the classification of reproductive factors among studies might prevent a direct comparison or synthesis of the study results.

INTRODUCTION

Cancer is a leading cause of death worldwide.[1] In Korea, it has also been a major public health problem since 1983.[2] In 2019, lung cancer overtook gastric cancer and was ranked first in terms of incidence rate for the first time, excluding thyroid cancer. Since 1999, the incidence of gastric, colon, liver, and cervical cancers has been decreasing, while the incidence of prostate and breast cancers has been increasing.[3] Korea's current cancer burden has predicted 274,488 new cancer cases and 81,277 cancer-related deaths by 2022.[4]

Lung, colon, rectal, pancreatic, breast, and liver cancers are the most common causes of death. Among women, the five major primary cancers include breast, thyroid, colon, rectal, lung, and stomach cancers.[3] The 5-year survival rate of Korean cancer patients has improved significantly from 41.2% in 1993–1995 to 70.6% in 2012–2016. Since 2016, the number of cancer survivors has exceeded 1.74 million and the survival rate for more than 5 years is highest among the 32 countries belonging to the Organization for Economic Cooperation and Development.[5] Nevertheless, the cancer mortality rate is predicted to increase by 2032.[6] As cancer enters the social and economic development and aging population, its incidence may increase significantly.[7]

Among women, three out of the ten most common cancer types are gynecological cancers. Breast cancer is the most common, cervical cancer is the fourth most common, and ovarian cancer is the tenth most common cancer among women worldwide and the incidence and mortality rates of gynecological cancers have continued to increase.[8] The incidence of breast and ovarian cancers is expected to increase in Korea.[6] Among the fertilizable reproductive factors, a higher number of births is associated with a higher incidence of cancer.[9] Moreover, older age at first childbirth is associated with a higher risk of adenocarcinoma.[10] It was also related to a higher risk of bladder cancer in women who did not give birth.[11] However, different associations have been observed for different types of cancer, such as a higher risk of breast cancer with increasing age at first birth.[12]

Reproductive factors have evolved worldwide in recent years. These changes include older age at childbirth and shorter breastfeeding duration, which may have influenced the health outcomes among women.[13-15] According to a systematic review and meta-analysis, menopause and older age at childbirth were associated with an increased risk of thyroid cancer and a longer breastfeeding duration prevented thyroid cancer.[16] Thyroid, breast, and lung cancers are also associated with childbirth.[17-20]

Korea has a rapidly aging population. Moreover, changes in the reproductive factors such as advanced age at first childbirth and no or short breastfeeding duration are expected to increase the risk of cancer.[21] Therefore, we aim to summarize the effects of modifiable reproductive factors on cancer incidence and mortality in Korean women. We will conduct a systematic review adhering to the methodological standards in this region and report our study plan to promote transparency.

METHODS

We will follow the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols checklist for reporting the protocol[22] and registered the protocol to PROSPERO (CRD42022356085).

Eligibility criteria

We will include studies meeting the following criteria: (1) cohort studies focusing on Korean female population aged ≥18 years without cancer history at baseline; (2) studies reporting the association between reproductive factors and the incidence or mortality of all or specific cancers; (3) studies considering at least one of the following modifiable reproductive factors as an exposure: childbirth history (nulliparous or parous), age at first childbirth, age at last childbirth, number of childbirths, breastfeeding experience, and duration of breastfeeding; and (4) studies presenting the effect estimates (relative ratio [RR], odds ratio [OR], or hazard ratio [HR]) for cancer incidence or mortality and corresponding 95% confidence intervals (CIs).

We will consider reproductive factors as modifiable if women could choose their own status or duration of these factors. Therefore, delivery methods such as cesarean section and hormone replacement therapy would not be considered exposures of interest in this study, since these factors are influenced mainly by the physician's recommendations.

Studies will be excluded if they involve women with specific health conditions (such as inflammatory bowel disease, human immunodeficiency virus infection). We will also exclude reviews, conference summaries, editorials, commentaries, critiques, letters to editors, and publications without primary data.

Literature search

We conducted a literature search in the EMBASE, MEDLINE, Cochrane Library, and Korean databases such as the Korean Studies Information Service System, Research Information Sharing Service, KoreaMED, Korean Medical Database, National Assembly Library, and Korea Institute from their inception to August 24, 2022. We developed a search strategy using controlled vocabulary as well as free-text words related to reproductive factors and cancers, in collaboration with an experienced librarian. We will include publications in Korean and English, and manually search the reference lists of included studies. Supplementary Appendix Table 1 shows the search strategy.

Study selection

For all studies identified by searching the electronic databases, two reviewers will independently screen the titles and/or abstracts for eligibility in duplicate. Subsequently, the reviewers will screen the full texts for potentially eligible studies independently and in duplicate. Discrepancies between the reviewers will be resolved through discussion or consultation with a third reviewer if needed. Calibration exercises will be conducted at each stage to ensure reliability and accuracy between the reviewers.

Data abstraction

We will collect the following information from each study:

1. Study information: First author, year of publication, name of cohort, number of participants, age at baseline, year, and mean age

2. Modifiable reproductive factors: Type of reproductive factors (childbirth history, age at first childbirth, age at last childbirth, number of births, breastfeeding experience, duration of breastfeeding), categories of reproductive factors, and exposure assessment method

3. Cancer incidence and mortality: Cancer type, outcome measurement method, follow-up period, the most fully adjusted risk estimate (RR, OR, or HR), and corresponding 95% CIs.

We will conduct calibration exercises to ensure consistency between the reviewers. Two reviewers will independently extract the data. Discrepancies will be resolved through discussion or consultation with a third-party reviewer.

Risk of bias

We will evaluate the risk of bias in the included studies using the Clinical Advances through Research and Information Translation tool for cohort studies, which includes with the following seven domains[23]: (1) "Was the selection of exposed and non-exposed cohorts drawn from the same population?," (2) "Can we be confident in the assessment of exposure?," (3) "Can we be confident that the outcome of interest was not present at the start of the study?," (4) "Did the study match exposed and non-exposed cohorts for all variables?," (5) "Can we be confident in the assessment of the presence or absence of prognostic factors?," (6) "Can we be confident in the assessment of the outcomes?," and (7) "Was the follow-up of the cohorts adequate?" Answers for Each domain will be categorized as definitely yes, probably yes, probably no, and definitely no. A study found to have a high risk of bias in more than two of the seven domains will be considered to have a high overall risk of bias. Two reviewers will independently assess the risk of bias. In case of disagreement, inconsistencies will be resolved through consensus or discussion with a third reviewer.

Certainty of evidence

We will assess the certainty of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. This approach to assess the certainty of evidence starts with the study design and considers five factors (risk of bias, inconsistency, indirection, imprecision, and publication bias) to rate down the certainty of the evidence and three factors (large effect sizes, dose-response relationships, etc.) to rate up the certainty. While assessing causality in the GRADE approach, randomized controlled trials begin with evidence of high certainty, whereas observational studies begin with evidence of low certainty. The final certainty of evidence will be categorized into one of the following four levels: high, moderate, low, and very low.[24]

Analysis and tables presenting the summary of findings

We will use a PRISMA flow diagram to illustrate the study selection process. We will perform a meta-analysis to present the pooled relative effect estimates of reproductive factors for cancer. We will conduct two types of meta-analyses if possible. Initially, we will conduct categorical meta-analyses to calculate the pooled relative effect estimates (such as analysis to assess the effect of highest vs. lowest duration of breastfeeding on cancer). Subsequently, if a study reports the exposure in at least three categories or continuous types, we will conduct dose-response meta-analyses (such as analysis to assess the effect of duration of breastfeeding on cancer). For each meta-analysis, summary estimates and their corresponding 95% CIs will be calculated using a random effects model.

Heterogeneity will be assessed using visual inspection of effect estimates, overlapping of confidence intervals in forest plots, and I^2 and Q statistics. Publication bias will be explored by visual inspection of the funnel plots and Egger's test. We will conduct subgroup analysis according to low and high risk of bias in the studies. We will calculate the absolute effect of reproductive factors on cancer by multiplying the pooled relative effects from the meta-analyses with the baseline risk of cancer incidence and mortality. All statistical analyses will be performed using RevMan 5.3 (Cochrane, London, UK) and R (the R foundation, Austria, Vienna).

Patients and public involvement

No patients or the public will be involved.

DISCUSSION

This systematic review aims to identify, evaluate, and consolidate evidence of the effects of reproductive factors on cancer in the Korean population. We expect that our research results will help prevent cancer and aid in future research on reproductive factors among Koreans.

The advantages of this review include the use of a systematic and transparent process with stringent research criteria including a comprehensive search of eligible studies, explicit eligibility criteria, independent and duplicate screening, data abstraction, and risk of bias assessment.

Heterogeneity due to differences in the classification of reproductive factors among studies (such as that due to differences in age at first childbirth and duration of breastfeeding) might prevent direct comparison or synthesis of the study results.

Ethics and dissemination

This systematic review does not require approval from the institutional review board. We will disseminate the findings of this systematic review in peer-reviewed publications.

Contributors: MAH conceptualized and designed the study. SHK drafted the study protocol. All authors reviewed the study plan and manuscript and offered comments and edits. All authors approved the final manuscript.

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Competing interests: None declared.

Patients consent for publication: Not required.

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Supplementary appendix

Appendix 1. Search strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to July Week 2 2021

#	Searches
1	(reproductive adj (factor* or characteristic* or histor*)).tw,kf.
2	Milk, Human/ or Breast Feeding/ or (breast adj (feed* or milk)).tw,kf.
3	Maternal Age/ or (age* adj (birth* or childbirth* or deliver* or parity or childbearing* or maternal or pregnanc* or mother* or first birth* or last birth* or first childbirth* or last childbirth*)).tw,kf.
4	Parity/ or Delivery, Obstetric/ or Pregnancy, Multiple/ or (((parity or pregnan* or child* or birth*) adj (histor* or number* or frequenc* or order*)) or nullipar* or multiparous or multiparit*).tw,kf.
5	1 or 2 or 3 or 4
6	exp Neoplasms/ or (cancer* or neoplas* or tumo?r* or malignan*).tw,kf.
7	exp cohort studies/ or ((cohort adj (study or studies)) or cohort analy*).tw,kf.
8	(follow up adj (study or studies)).tw,kf.
9	(longitudinal or prospective or retrospective).tw,kf.
10	7 or 8 or 9
11	korea*.mp.
12	5 and 6 and 10 and 11

EMBASE

#	Searches
#1	(reproductive NEXT/1 (factor* OR characteristic* OR histor*)):ti,ab,kw
#2	'breast milk'/exp OR 'breast feeding'/exp OR ((breast NEXT/1 (feed* OR milk)):ti,ab,kw)
#3	'maternal age'/exp OR ((age* NEXT/1 (birth* OR childbirth* OR deliver* OR parity OR childbearing* OR maternal OR pregnanc* OR mother* OR 'first birth*' OR 'last birth*' OR 'first childbirth*' OR 'last childbirth*')):ti,ab,kw)
#4	'parity'/exp OR 'obstetric delivery'/de OR 'multiple pregnancy'/de OR (((parity OR pregnan* OR child* OR birth*) NEXT/1 (histor* OR number* OR frequenc* OR order*)):ti,ab,kw) OR nullipar*:ti,ab,kw OR multiparous:ti,ab,kw OR multiparit*:ti,ab,kw
#5	#1 OR #2 OR #3 OR #4
#6	'neoplasm'/exp OR cancer*:ti,ab,kw OR neoplas*:ti,ab,kw OR tumor*:ti,ab,kw OR tumour*:ti,ab,kw OR malignan*:ti,ab,kw
#7	'cohort analysis'/exp OR ((cohort NEXT/1 (study OR studies)):ti,ab,kw) OR 'cohort analy*':ti,ab,kw
#8	('follow up' NEXT/1 (study OR studies)):ti,ab,kw
#9	longitudinal:ti,ab,kw OR prospective:ti,ab,kw OR retrospective:ti,ab,kw
#10	#7 OR #8 OR #9
#11	korea:ti,ab,kw
#12	#5 AND #10 AND #11

Cochrane Library

#	Searches
#1	(reproductive next/1 (factor* or characteristic* or histor*)):ti,ab,kw
#2	[mh ^"Milk, Human"] or [mh ^"Breast Feeding"] or (breast next/1 (feed* or milk)):ti,ab,kw
#3	[mh ^"Maternal Age"] or (age* next/1 (birth* or childbirth* or deliver* or parity or childbearing* or maternal or pregnanc* or mother* or "first birth*" or "last birth*" or "first childbirth*" or "last childbirth*")):ti,ab,kw
#4	[mh ^"Parity"] or [mh ^"Delivery, Obstetric"] or [mh ^"Pregnancy, Multiple"] or (((parity or pregnan* or child* or birth*) next/1 (histor* or number* or frequenc* or order*)) or nullipar* or multiparous or multiparit*):ti,ab,kw

#5	#1 or #2 or #3 or #4
#6	[mh "Neoplasms"] or (cancer* or neoplas* or tumo?r* or malignan*):ti,ab,kw
#7	[mh "cohort studies"] or ((cohort next/1 (study or studies)) or "cohort analy*"):ti,ab,kw
#8	(follow up next/1 (study or studies)):ti,ab,kw
#9	(longitudinal or prospective or retrospective):ti,ab,kw
#10	#7 or #8 or #9
#11	korea*:ti,ab,kw
#12	#5 and #6 and #10 and #11

KoreaMED

#	Searches
1	"reproductive factor"[TIAB] OR "reproductive characteristic"[TIAB] OR "reproductive history"[TIAB] OR breastfeeding[TIAB] OR "breast feeding"[TIAB] OR parity[TIAB] OR delivery[TIAB] OR pregnant[TIAB] OR pregnancy[TIAB] OR pregnancies[TIAB] OR "age at menarche"[TIAB] OR "age at first birth"[TIAB] OR "age at last birth"[TIAB] OR "age at first birth"[TIAB] OR "age at last childbirth"[TIAB] OR "number of births"[TIAB] OR "number of childbirth"[TIAB]
2	cancer[TIAB] OR cancers[TIAB] OR tumor[TIAB] OR tumors[TIAB] OR tumour[TIAB] OR tumours[TIAB] OR neoplasm[TIAB] OR neoplasms[TIAB] OR neoplasia[TIAB] OR neoplasias[TIAB] OR malignant[TIAB] OR malignancy[TIAB] OR malignancies[TIAB]
3	cohort[TIAB] OR "follow up"[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB]
4	1 AND 2 AND 3

Korean Medical Database (KMBASE)

#	Searches
1	((((((((([ALL=reproductive] OR [ALL=breastfeeding]) OR [ALL=breast feeding]) OR [ALL=birth*]) OR [ALL=생식]) OR [ALL=모유]) OR [ALL=수유]) OR [ALL=출산]) AND ((([ALL=cancer*] OR [ALL=tumor*]) OR [ALL=암]) OR [ALL=종양])) AND ((((([ALL=cohort] OR [ALL=Follow up]) OR [ALL=longitudinal]) OR [ALL=prospective]) OR [ALL=retrospective]) OR [ALL=코호트]))

Research Information Sharing Service (RISS)

#	Searches
1	논문명 : "reproductive factor" | "reproductive characteristic" | "reproductive history" | "생식요인" | "생식인자" | "생식특성" | breastfeeding | "breast feeding" | 모유 | 수유 | parity | delivery | pregnancy | "age at menarche" | "age at first birth" | "age at last birth" | "age at first birth" | "age at last childbirth" | "number of births" | "number of childbirth" | 출산 | 초산 | "출생아수" <AND> 논문명 : cancer | tumor | tumour | neoplasm | malignancy | 암 | 종양 <AND> 논문명 : cohort | "Follow up" | longitudinal | prospective | retrospective | 코호트 | 추적 | 전향적 | 후향적 | 종단
2	초록 : "reproductive factor" | "reproductive characteristic" | "reproductive history" | "생식요인" | "생식인자" | "생식특성" | breastfeeding | "breast feeding" | 모유 | 수유 | parity | delivery | pregnancy | "age at menarche" | "age at first birth" | "age at last birth" | "age at first birth" | "age at last childbirth" | "number of births" | "number of childbirth" | 출산 | 초산 | "출생아수" <AND> 초록 : cancer | tumor | tumour | neoplasm | malignancy | 암 | 종양 <AND> 초록 : cohort |

	"Follow up" | longitudinal | prospective | retrospective | 코호트 | 추적 | 전향적 | 후향적 | 종단
3	1 OR 2

Korean Studies Information Service System (KISS)

#	Searches
1	reproductive | 생식 | breast feeding | 모유 | 수유 | parity | delivery | pregnancy | menarche | birth | childbirth | 출산 | 초산 | 출생아수
2	cancer | tumor | tumour | neoplasm | malignancy | 암 | 종양
3	cohort | Follow up | longitudinal | prospective | retrospective | 코호트 | 추적조사 | 전향적 | 후향적 | 종단
4	1 AND 2 AND 3

Korea Institute of Science and Technology Information (KISTI)

#	Searches
1	논문명="reproductive factor" | "reproductive characteristic" | "reproductive history" | 생식요인 | 생식인자 | 생식특성 | breastfeeding | "breast feeding" | 모유 | 수유 | parity | delivery | pregnancy | "age at menarche" | "age at first birth" | "age at last birth" | "age at first birth" | "age at last childbirth" | "number of births" | "number of childbirth" | 출산 | 초산 | 출생아수 AND 논문명=cancer* | tumor* | tumour* | neoplasm* | malignan* | 암 | 종양 AND 논문명=cohort | "Follow up" | longitudinal | prospective | retrospective | 코호트 | 추적 | 전향적 | 후향적 | 종단
2	초록="reproductive factor" | "reproductive characteristic" | "reproductive history" | 생식요인 | 생식인자 | 생식특성 | breastfeeding | "breast feeding" | 모유 | 수유 | parity | delivery | pregnancy | "age at menarche" | "age at first birth" | "age at last birth" | "age at first birth" | "age at last childbirth" | "number of births" | "number of childbirth" | 출산 | 초산 | 출생아수 AND 초록=cancer* | tumor* | tumour* | neoplasm* | malignan* | 암 | 종양 AND 초록=cohort | "Follow up" | longitudinal | prospective | retrospective | 코호트 | 추적 | 전향적 | 후향적 | 종단
3	1 OR 2

National Assembly Library

#	Searches
1	"reproductive | "생식요인" | "생식인자" | "생식특성" | breastfeeding | "breast feeding" | 모유 | 수유 | parity | delivery | pregnancy | "age at menarche" | "age at first birth" | "age at last birth" | "age at first birth" | "age at last childbirth" | "number of births" | "number of childbirth" | 출산 | 초산 | "출생아수"
2	cancer* | tumor* | tumour* | neoplasm* | malignan* | 암 | 종양
3	1 AND 2

PRISMA-P checklist

Section and topic	Item No	Checklist item	Page #
ADMINISTRATIVE INFORMATION			
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
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	7
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
Support:			
Sources	5a	Indicate sources of financial or other support for the review	7
Sponsor	5b	Provide name for the review funder and/or sponsor	7
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	7
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
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	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial	5

		registers or other grey literature sources) with planned dates of coverage	
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	5
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
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)	5
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	5
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	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
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	6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6
	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 I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

NA, not applicable.