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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 ageing 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 summarise 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 24 August 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 summarise the findings of the included systematic reviews through quantitative or narrative syntheses and present the summarised 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.

PROSPERO registration number CRD42022356085.

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 major primary cancers include breast, thyroid, colon, rectal, lung and stomach cancers.[3] The 5-year survival rate of Korean patients with cancer 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 ageing population, its incidence may increase significantly.[7]

Among women, 3 out of the 10 most common cancer types are gynaecological cancers. Breast cancer is the most common, cervical cancer is the 4th most common and ovarian cancer is the 10th most common cancer among women worldwide, and the incidence and mortality rates of gynaecological cancers have continued to increase.[8] The incidence of breast and ovarian cancers

is expected to increase in Korea.[6] Among the fertilisable reproductive factors, a higher number of births are 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 longer breastfeeding duration prevented thyroid cancer.[16] Thyroid, breast and lung cancers are also associated with childbirth.[17–20]

Korea has a rapidly ageing 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 summarise 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 female Korean 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 breast feeding; and (4) studies presenting the effect estimates (relative ratio (RR), OR or HR for cancer incidence or mortality and corresponding 95% 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 caesarean 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 and HIV 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 24 August 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. Online supplemental 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 of eligible studies for duplicates. 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 breast feeding), 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 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 categorised 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, randomised controlled trials begin with evidence of high certainty, whereas observational studies begin with evidence of low certainty. The final certainty of evidence will be categorised 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 Preferred Reporting Items for Systematic Reviews and Meta-Analyses 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 breast feeding 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 breast feeding 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 CIs 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 V.5.3 (Cochrane, London, UK) and R (the R Foundation, Vienna, Austria).

Patient and public involvement

No patients or members of 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 breast feeding) might prevent direct comparison or synthesis of the study results.

Contributors MAH conceptualised and designed the study. S-HK drafted the study protocol. Both authors reviewed the study plan and manuscript, and offered comments and edits. Both authors approved the final manuscript.

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Competing interests None declared.

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

Patient consent for publication Not required.

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