META-ANALYSIS

Meta-analysis on Asymptomatic Endometrial Thickening and Its Association with Endometrial Cancer Risk in Women Over 50 Years of Age

Jie Cai, MM; Yanni Huang, MM; Qiaoyun Li, BM

ABSTRACT

Purpose • This study systematically assesses the correlation between asymptomatic endometrial thickening after the age of 50 and the risk of endometrial cancer (EC).

Methods • A comprehensive search was conducted using the Cochrane Library, Web of Science, PubMed, ProQuest, and Chinese biomedical literature databases Wanfang, Weipu, and CNG until August 2022. The included literature was analyzed using RevMan 5.3 software to explore heterogeneity in each study.

Results • Five studies were finally included. The assessment of odds ratio (OR) heterogeneity between women with endometrial thickening and the risk of EC showed $P = .18$, I^2=95%, indicating significant heterogeneity. A random-effects model was applied for meta-analysis, revealing a result of 0.96, 95% CI (0.92, 1.02), $P = .18$, indicating no statistical significance between the two groups ($P > .05$). The funnel plot demonstrated asymmetry, suggesting evident publication bias.

Conclusion • There is no consistent correlation between asymptomatic endometrial thickening and the occurrence of EC in individuals over 50 years of age. (*Altern Ther Health Med.* 2024;30(10):174-178).

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INTRODUCTION

Endometrial carcinoma (EC) is one of the most prevalent gynecological cancers in developed countries and the second most common malignancy among females, after breast cancer.[1] The rising incidence of endometrial cancer is primarily attributed to shifts in human lifestyle factors, such as the obesity and diabetes epidemic, along with the impact of aging and socioeconomically driven reproductive factors.[2]

According to epidemiological data, EC primarily affects middle-aged and older women, with the majority presenting symptoms such as abnormal postmenopausal vaginal bleeding and fluid flow. Additionally, some patients may experience symptoms like lower abdominal pain.[3] However, a subset of patients exhibits subtle or no obvious symptoms in the early stages of the disease, resulting in delayed hospital visits and diagnosis at an advanced stage. This delayed diagnosis contributes to an increasing annual mortality rate of EC. Timely intervention in the early stages could significantly enhance the survival rate of the disease.[4]

Menopause is a crucial stage for women, constituting about one-third of their lives. The pathogenesis of postmenopausal endometrial thickening is complex, and abnormal thickening of the endometrium may arise from changes in the uterine cavity's microenvironment due to various factors.[5] Roughly 90-95% of patients with EC experience irregular vaginal bleeding.[6] Most guidelines designate a standard endometrial layer thickness of 5 mm, with the likelihood of developing EC in patients having less than 5 mm being less than 1%.[5,6]

Moreover, there is a growing occurrence of asymptomatic endometrial thickening. This rise is attributed to the increasing number of women who, despite not having a history of vaginal bleeding, undergo ultrasound for various reasons.[7,8] Hence, there is a need to enhance clinical screening for endometrial thickness in women to lower the incidence of EC.

In recent years, numerous researchers have explored the correlation between endometrial thickening and the risk of EC development in menopausal women around the age of 50. However, due to variations in interventions across studies, differing evaluation methods, and limited sample sizes in all current published relevant studies, there exists a deficiency in validity, range, and systematic exploration.[9-11] Therefore, in this study, we conducted a comprehensive literature review

on the association between endometrial thickening and the risk of developing EC in menopausal women both domestically and internationally. Our analysis aims to establish a correlation and provide evidence-based medical data regarding the risk of developing EC and the influencing factors in individuals with endometrial thickening.

DATA AND METHODS

Search Strategy

The library's online resources were utilized to access relevant literature and comprehend the advancements in China and other countries' research. The databases employed include the Cochrane Library, Web of Science, PubMed, ProQuest, and Chinese biomedical literature databases Wanfang, Wipu, and China Knowledge Network. The search strategy involved a combination of subject terms and free words, supplemented by manual searches to identify relevant references as needed.

The search period covered from the establishment of the databases to December 2022. The English search terms included "Endometrial thickening," "Endometrial cancer," "Postmenopausal," and "Asymptomatic,". For the Chinese searches, terms such as endometrial thickening, endometrial cancer, postmenopausal, and asymptomatic, were employed.

Literature Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) Study Type: Epidemiological study of a single-arm study, cohort study, or case-control study, with the primary aim of investigating the association between asymptomatic endometrial thickening and the risk of developing EC; (2) Language: Chinese or English literature; (3) Study Population: Pathological examinations meeting the diagnostic criteria for EC,[12] with the study incorporating asymptomatic endometrial thickening among the observations; (4) The text must clearly state the Odds ratio (OR), or a 95% confidence interval (CI) was reported; (5) Original data of the study subjects must not be incomplete or left unprovided in the text; (6) The mean age of investigators in the included literature was 50 years or older.

Exclusion criteria were as follows: (1) Incomplete study content; (2) Literature types including reviews, conference proceedings, empirical summaries, and other non-cohort studies; (3) Insufficient rigor in study design; (4) Duplicate publications; (5) Literature in languages other than Chinese and English.

Literature Screening and Data Extraction

The literature meeting the study objectives and predefined criteria underwent screening. Materials not aligning with the current analysis were excluded after reviewing their titles and abstracts. The full text was then examined further to eliminate literature with unreasonable study design, poor quality, and lack of usable data. Data extraction from the literature was carried out using Microsoft Excel software, focusing on extracting information such as the first author, time of publication, cohort size, RR or OR, and 95% CI for each trial.

The screening process involved two investigators, both trained in comprehensive systematic evaluation, working independently. Any disagreements were resolved through negotiation, determining the screening basis, and, if necessary, seeking consultation with a third-party expert possessing expertise in the field.

Literature Quality Evaluation

The included literature underwent independent assessment by two researchers using the Newcastle-Ottawa Scale for quality evaluation (NOS).[13] The score was based on 4 items: "quality of selection," "comparability," "exposure assessment," and "outcome assessment," with a maximum possible score of 9. If the literature scored ≥6, it was considered to be of high quality, and any literature scoring <6 was excluded.

Statistical Analysis

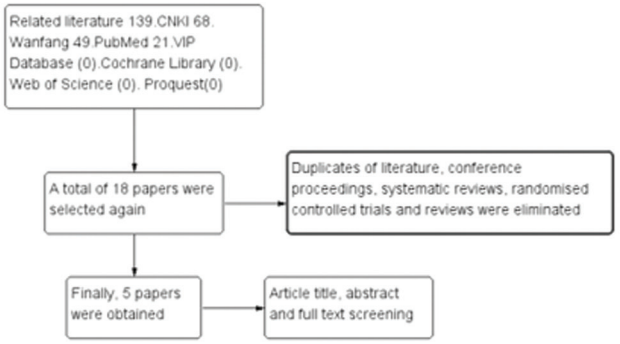
Statistical analysis was conducted through Meta-analysis using RevMan 5.3. In this analysis, an Odds Ratio (OR) > 1 indicated a positive correlation, OR < 1 indicated a negative correlation, and OR = 1 signified irrelevance. Additionally, a 95% Confidence Interval (CI) crossing 1 was considered nonsignificant. The degree of heterogeneity was primarily assessed using I^2. When I^2 was less than 50% and $P > .1$, indicating low or no heterogeneity among studies, the fixed-effects model was employed for Meta-analysis. Conversely, when I^2 was 50% or greater and P was .1 or less, signifying high heterogeneity, the random-effects model was applied. Finally, a funnel plot was utilized for bias evaluation.

RESULT

Literature Search Results

A total of 139 articles were initially retrieved by searching each database using the specified keywords. After removing duplicates, conference proceedings, systematic reviews, randomized controlled trials, and reviews, the remaining pool yielded 18 articles. Further refinement through screening titles, abstracts, and full-text articles based on predefined criteria resulted in a final selection of 5 articles. The detailed search process is outlined in Figure 1.

Figure 1. Flow Chart of Literature Search



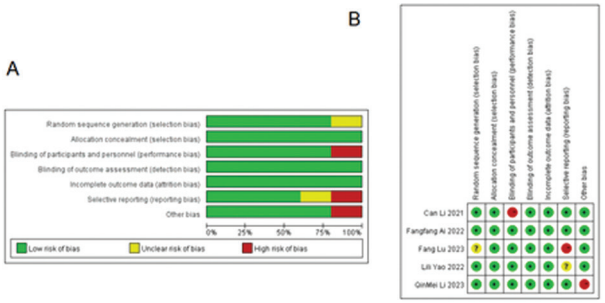
Note: The figure illustrates the systematic process of literature search, depicting the stages of identification, screening, eligibility, and inclusion of studies based on predefined criteria. This flow chart provides a visual representation of the systematic approach employed to select relevant literature for the meta-analysis.

Table 1. Basic Characteristics of the Included Literature

First Author	Published (Year)	Sample Size (Control Group/ Experimental Group)	Type of Research	Research Period	Research Projects	NOS Score
Li Qinmei[14]	2013	374/159	Cohort Comparison	2016~2020	① Age ② Time of menopause ③ Pregnancy ④ Birth ⑤ BMI ⑥ Hypertension ⑦ Diabetes ⑧ Tamoxifen ⑨ Endometrial thickness	7
Li Chan[15]	2021	121/124	Cohort studies	2016~2018	① Age ② Endometrial thickness ③ Hypertension ④ Full-term delivery ⑤ Miscarriage	6
Lu Fang[16]	2022	354/43	Cohort studies	2019~2022	① Age ② Endometrial thickness ③ Age at menarche ④ Age at menopause ⑤ Age at menarche ⑥ Year of menopause ⑦ History of infertility ⑧ History of hypertension ⑨ BMI ⑩ History of diabetes mellitus, family history of malignancy	7
Lili Yao[17]	2013	150/50	Case-control	2018~2021	① older ② thicker endometrium ③ previous menstrual irregularities ④ postmenopausal bleeding ⑤ polypoid mass-like lesions	8
Fangfang Ai[18]	2012	300/85	Case-control	2016~2020	① Age ② Thicker endometrium ③ High blood pressure ④ Time of full-term delivery ⑤ Time of miscarriage	6

Abbreviation: NOS, Score represents the Newcastle-Ottawa Scale score used for quality assessment.

Figure 2. Risk of Bias Table



Note: This figure presents a comprehensive Risk of Bias Table, providing an overview of the critical assessments made during the quality evaluation of the included literature. The table encompasses various domains, evaluating the methodological rigor and potential biases in each study. This visual representation enhances transparency in assessing the overall quality and reliability of the literature included in the meta-analysis.

Basic Characteristics and Methodological Quality Evaluation of the Nano Study

The five included studies encompassed a total of 461 subjects in the experimental group and 1299 subjects in the control group, comprising 3 cohort-controlled experiments and 2 case-control experiments. An independent evaluation of these studies was conducted using the NOS. The characteristics of the included literature are presented in Table 1. The results of the quality evaluation, assessed using the Cochrane risk of bias assessment tool, are detailed in Figure 2.

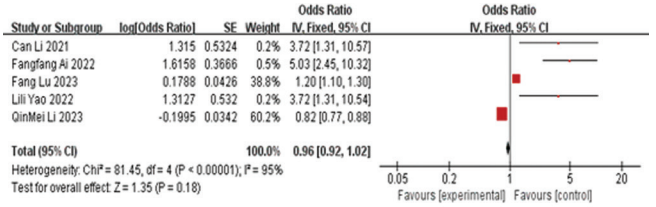
Meta-Analysis Results

Five studies were included in the meta-analysis. Heterogeneity detection for the OR assessment of endometrial thickening and the risk of EC in women revealed a significant heterogeneity, with P = .18 and I^2=95%. Subsequently, a random-effects model was employed for the meta-analysis. The results indicated an OR of 0.96 with a 95% CI of (0.92, 1.02), and a P-value of 0.18, signifying no statistical significance between the two groups (P > .05), refer to Figure 3.

Publication Bias Evaluation

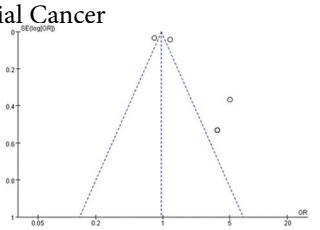
The funnel plot analysis of the study indicates asymmetry, deviating from the expected funnel shape. This observation suggests a notable publication bias. Refer to Figure 4 for details.

Figure 3. Meta-analysis Results of the Correlation Between Endometrial Thickening and Endometrial Cancer (EC)



Note: Figure 3 describes the outcomes of the meta-analysis assessing the correlation between endometrial thickening and the occurrence of endometrial cancer (EC). Each horizontal line represents a study included in the meta-analysis, with the point estimate and confidence interval indicating the effect size and precision of each study.

Figure 4. The Correlation Between Endometrial Thickening And Endometrial Cancer



Note: Figure 4 displays a Funnel Plot, a graphical representation used to assess potential publication bias in studies investigating the correlation between endometrial thickening and endometrial cancer. The asymmetry or shape of the funnel helps evaluate the presence of bias, with a symmetrical funnel suggesting fewer biases. This plot aids in visually examining the distribution of study results and publication bias, contributing to a comprehensive understanding of the reliability and potential limitations in the meta-analysis of the correlation between endometrial thickening and endometrial cancer.

DISCUSSION

In China, EC ranks as the second most prevalent malignant tumor in the female reproductive tract, following cervical cancer. Its occurrence is predominantly observed in postmenopausal women, significantly affecting women's well-being. Analyzing the associated causative factors can assist clinicians in making timely and accurate diagnoses.[14] Recent clinical studies[15,16] have demonstrated that metabolic syndrome and dietary intake are independent risk factors for EC in women.

Furthermore, after the age of 50, women typically enter the menopausal phase. Due to diminished ovarian function

during this period, the cervix and endometrium undergo a desiccated and shrunken transformation, rendering them more vulnerable to the invasion of external microorganisms. This susceptibility can induce alterations in the local microenvironment and facilitate the production of relevant pathogenic factors.[17] Additionally, estrogen and progesterone receptors are widely recognized to maintain consistently high expression levels with advancing age and years since menopause, without exhibiting antagonistic effects over time.[18]

Estrogen plays a crucial role in sustaining the healthy and normal growth of the endometrium. As ovarian function declines, estrogen levels in a woman's body undergo a significant decrease. Consequently, the decline in estrogen levels post-menopause may result in abnormal endometrial hyperplasia or other pathological changes, such as inappropriate endometrial hyperplasia. These changes elevate the risk of developing endometrial cancer.

Typically, a postmenopausal woman experiences the cessation of egg production by her ovaries, leading to a decline in estrogen levels and the cessation of the menstrual cycle. Consequently, postmenopausal women are not expected to have vaginal bleeding. The presence of irregular, intermittent, or excessive vaginal bleeding may signal an underlying issue, such as endometrial thickening, uterine polyps, cervical erosion, and other conditions. In some cases, it could even indicate malignant lesions like endometrial cancer.[15-18]

Therefore, most postmenopausal endometrial cancer patients manifest with noticeable vaginal bleeding. For individuals experiencing vaginal bleeding during menopause, it is imperative to undergo ultrasound scanning to assess the endometrial thickness. This evaluation aids in determining whether a diagnostic curettage or a hysteroscopy is warranted.[19]

As vaginal ultrasound becomes increasingly accurate and screening becomes more widespread, there is a gradual rise in the incidence of inadvertently detected endometrial thickening (5 mm or more) during physical examinations of postmenopausal women. Therefore, many physicians adopt the same treatment plan for both postmenopausal women with and without symptomatic endometrial thickening. This approach leads to unnecessary uterine operations, thus increasing the psychological burden on the patient.[20,21]

In the postmenopausal period, endometrial thickening typically lacks significant symptoms, but when symptoms do manifest, vaginal bleeding is the most common presentation.[22] Studies on EC patients indicate that approximately 8-10% of women experiencing vaginal bleeding after menopause are diagnosed with endometrial malignancy.[23] The correlation between asymptomatic endometrial thickening and EC remains a topic of controversy in clinical research results. This study conducts a meta-analysis to explore the association between endometrial thickening and EC, aiming to establish a medical foundation for clinical practice.

The results of the current meta-analysis indicate no significant correlation between endometrial thickening and EC. Findings from Zhang Can's study suggest that benign and malignant lesions in the asymptomatic endometrial thickening group only differ in the thickness of the endometrium and are not independent risk factors for EC (OR 3.724, 95% CI 1.312 ~ 10.574).

Lili et al.[24] study illustrated that endometrial thickening in postmenopausal asymptomatic women was predominantly benign. The incidence of EC and precancerous lesions was higher in postmenopausal women with endometrial thickening and vaginal bleeding than in asymptomatic women (95% CI 0.707 - 0.960). Li et al.[25] study results suggest that the development of EC can be predicted by endometrial thickening, but the threshold for malignant lesions differs between patients with bleeding symptoms and asymptomatic endometrial thickening (95% CI 0.661 ~ 0.771).

Lu et al.[26] study suggests that late menopausal patients with endometrial thickening, exhibiting an increased uterine volume, smaller mean platelet volume, and elevated D-dimer levels, may serve as independent risk factors for EC or endometrial atypical hyperplasia (95% CI 1.000 ~ 1.299).

Notably, there was significant heterogeneity in the meta-analysis of the five included studies, which may be attributed to (1) variations in pharmacological interventions received by patients across different studies, influencing the progression of the disease in individuals with endometrial thickening.[29] Several studies indicate that asymptomatic postmenopausal women, after the age of 50, have a higher risk of endometrial thickening.

Furthermore, (2) several studies have shown that asymptomatic postmenopausal women with endometrial thickening after the age of 50 are less likely to develop malignancy. Researchers have been actively investigating in recent years to establish the thickness threshold for the conversion to EC in patients with asymptomatic endometrial thickening. However, specific threshold criteria have not yet been determined because the criteria used by investigators to categorize subjects with different endometrial thicknesses may vary.[30]

(3) Despite the inclusion of thousands of women with endometrial data in the literature, data entry in each study remains imprecise. Endometrial thickness measurements cannot be made with sufficient sensitivity during clinical examination due to variations in machines and physicians. Bias can also arise from differences in the quality of the included studies.[31] (4) Different studies may employ varied methods to measure endometrial thickening, such as ultrasound and tissue biopsy. The accuracy and reliability of these methods may differ, contributing to the heterogeneity of measurement results.

(5) Variations in the selection of research samples, including differences in age, region, and population characteristics, as well as variances in baseline risk among different populations, can impact the results. Heterogeneity resulting from these differences may lead to inconsistencies in study results, making it challenging to arrive at a uniform conclusion. Different studies may yield contrasting OR values, leading to varying interpretations of the relationship between endometrial thickening and the risk of EC.

(6) Due to the presence of heterogeneity, the conclusions may lack stability and reliability, making it challenging to

conduct a comprehensive analysis and interpretation of the research results. This situation presents difficulties in clinical practice and fails to provide clear guidance. To address these challenges, this study conducted a meta-analysis of asymptomatic endometrial thickening and the risk of endometrial cancer after the age of 50 to more accurately assess the association between endometrial thickening and endometrial cancer. The findings suggest that endometrial thickening is a significant risk factor. Therefore, screening in this age group may be beneficial for the early detection and treatment of endometrial cancer.

To develop personalized prevention strategies, such as hormone replacement therapy, and lifestyle changes, relevant professional organizations or guidelines committees may need to reassess and update relevant diagnostic and treatment guidelines for improved guidance in clinical practice. Therefore, for women with asymptomatic endometrial thickening after the age of 50, regular follow-up and monitoring are crucial. It involves scheduling periodic reviews of endometrial thickness, conducting ultrasound examinations, and inquiring about any new symptoms or abnormalities. These measures contribute to the early detection and intervention of potential problems.

Study Limitations

It is essential to acknowledge certain limitations in this study. Firstly, the presence of heterogeneity across various studies could impact the stability and reliability of the conclusions drawn. Additionally, inconsistencies in data entry, imprecise measurements due to different machines and physicians, and variations in the methods used for measuring endometrial thickening contribute to potential bias. Furthermore, differences in the selection of research samples, such as age, region, and population characteristics, may influence the study results. Finally, the lack of a universally defined threshold for endometrial thickness and variations in diagnostic criteria may introduce challenges in synthesizing and interpreting the findings. These limitations highlight the need for cautious interpretation and emphasize areas for improvement in future research.

CONCLUSION

In conclusion, the findings from this meta-analysis of the five included papers reveal no consistent association between asymptomatic endometrial thickening and the occurrence of EC in patients over 50 years of age. It is crucial to note that the small sample size of the included literature in this study, the inability to control for other confounding factors in the original studies, differences in study design, and variations in observed risk factors could introduce complexity to the interpretation of the results. Therefore, there is a need for more controlled trials and comprehensive meta-analyses to further investigate and validate these associations.

DATA AVAILABILITY

The experimental data used to support the findings of this study are available from the corresponding author upon request.

CONFLICTS OF INTEREST

The authors declared that they have no conflicts of interest regarding this work.

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AUTHOR CONTRIBUTIONS

Jie Cai and Yanni Huang are co-first authors.

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