Original Article

# Risks of Malignancy among 11,204 Patients with Endometrial Polyp: A Systematic Review and Meta-analysis

**Sarah Al-Rayes[1,2], Mariam Mohamed[3], Eva Suarthana[1,2], Hormoz Nassiri Kigloo[2,4], Jason Raina[5], Togas Tulandi[1,2]***

[1]Faculty of Medicine and Health Sciences, McGill University, [2]Department of Obstetrics and Gynecology, McGill University, [3]Faculty of Medicine, University of Montreal, Montreal, [4]Faculty of Medicine, University of Laval, Quebec, [5]Department of Family Medicine, University of Manitoba, Manitoba, Winnipeg, Canada

## Abstract

**Objectives:** To evaluate factors associated with malignancy in patients with endometrial polyps.

**Materials and Methods:** We conducted electronic database research on PubMed, MEDLINE, EMBASE, COCHRANE, and Google Scholar from inception for all studies on endometrial polyp. After removing duplicates, and title and abstract screening, we had a total of 121 articles and 151 others from screening the reference list. Inclusion criteria included peri and postmenopausal women > 45 years diagnosed histopathologically with endometrial polyp(s). We excluded women with a history of endometrial cancer or hysterectomy.

**Results:** Twenty studies were analyzed. Of 11204 patients with endometrial polyp, 287 had malignant polyps (2.75%), 182 (1.8%) had concomitant endometrial hyperplasia with atypia, and 520 (5.2%) had hyperplasia without atypia within the polyp. Menopausal women had a higher risk of pre-malignancy/malignancy than non-menopausal women (OR 5.63 (95CI 3.87, 8.20, $I^2 = 0\%$, $P < 0.001$). Endometrial thickness on ultrasound in pre-malignancy/malignancy cases was significantly thicker than in the benign polyp (mean difference 4.2 mm, 95% CI 0.8 to 7.6 mm, $I^2 = 18\%$, $P = 0.02$). Women who used tamoxifen or hormone replacement therapy (HRT) had a lower likelihood of endometrial pre-malignancy/malignancy, while women with abnormal uterine bleeding (AUB) had a higher probability of pre-malignancy/malignancy. The odd ratio of having pre-malignancy/malignancy among those who used tamoxifen was 0.50 (95% CI 0.26-0.94: $I^2$ 12%, $p = 0.03$).

**Conclusion:** In women with endometrial polyp, menopausal age and thickened endometrium might increase the probability while tamoxifen or HRT use might lower the likelihood of endometrial pre-malignancy/malignancy; and the presence of AUB might signal endometrial pre-malignancy/malignancy.

**Keywords:** Abnormal uterine bleeding, endometrial cancer, endometrial hyperplasia, endometrial intraepithelial neoplasia, perimenopause, polyp

## Introduction

Endometrial polyp is a common uterine lesion in women.[1] Although most polyps are benign, some are hyperplastic and could progress to malignancy within the polyp itself or in the endometrium.[1] A meta-analysis of eight retrospective studies including 127 patients with the initial diagnosis of atypical endometrial polyp (atypia within an endometrial polyp) showed a 5.6% risk estimate for concurrent endometrial cancer.[2]

Several authors have evaluated factors that contribute to the development of malignancy associated with endometrial polyp. Although polyp size was considered a risk factor, the results of the studies were mixed. In a retrospective study of 472 postmenopausal women, the authors reported premalignant and malignant lesions in 11 (2.33%) cases; endometrial carcinoma in 4 cases (0.84%), and atypical endometrial hyperplasia in 7 others (1.49%). They could not determine any relationship between various polyp sizes (10, 15, 20 mm) and malignancy.[3]

*Article History:*
**Submitted:** 22-Nov-2024
**Revised:** 26-Nov-2024
**Accepted:** 03-Dec-2024
**Published:** 27-Feb-2025

**Supplementary material available online**

**Access this article online**

Quick Response Code:

**Website:** https://journals.lww.com/gmit

**DOI:** 10.4103/gmit.GMIT-D-24-00056

**Address for correspondence:** Prof. Togas Tulandi, Department of Obstetrics and Gynecology, McGill University, 1001 Decarie Boulevard, Montréal, Québec H4A 3J1, Canada.
E-mail: togas.tulandi@mcgill.ca



**How to cite this article:** Al-Rayes S, Mohamed M, Suarthana E, Kigloo HN, Raina J, Tulandi T. Risks of malignancy among 11,204 patients with endometrial polyp: A systematic review and meta-analysis. Gynecol Minim Invasive Ther 2025;14:40-50.

However, a retrospective study from Brazil with 1139 patients showed that endometrial polyps measuring more than 15 mm were significantly associated with hyperplasia (14.8%) compared to 7.7% in the group with smaller polyps.[4]

Advanced age has consistently emerged as a significant risk factor.[5] Compared to premenopausal women, postmenopausal women have a higher risk.[6] In addition, those with abnormal uterine bleeding (AUB) are at increased risk to harboring concealed cancer within the polyps than asymptomatic women.[7] Orvieto *et al*. reported that the use of hormone replacement therapy (HRT) was the only significant contributing factor predisposing women with endometrial polyp to abnormal histopathological changes.[8]

The purpose of our study was to provide a systematic review of the malignancy potential and the risk factors associated with endometrial malignancy in women with endometrial polyp. Specifically, we evaluated the use of tamoxifen, use of HRT, AUB, menopausal status, polyp size, and endometrial thickness as risk factors.

## Materials and Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [Figure 1]. The protocol was registered in PROSPERO (CRD42022361378). Formal institutional review board approval was not required.

### Eligibility criteria, information sources, search strategy

We conducted an electronic database search on PubMed, Medline, Embase, Cochrane, and Google Scholar from inception to August 2022 for all studies on endometrial polyp and peri- and postmenopausal women. The following medical search terms and their combinations were used: Endometrial polyp* AND (Perimenopause* OR Postmenopausal* Women) AND (Endometrial Cancer OR [Premalignancy OR Premalignant Feature*]). We included studies in English or French language. Identified studies were exported into Rayyan, a web-based platform for systematic reviews.[9] In addition, we manually verified systematic reviews and meta-analyses on similar topics to identify additional studies. We removed duplicates before title and abstract screening.

We included studies assessing the risk of endometrial cancer in patients with endometrial polyp. Review articles, case reports, case series ($n$ <10), meeting abstracts, posters, letters, opinion articles, abstracts without full text, and non-English or non-French language were excluded. Our inclusion criteria were perimenopausal women over 45 years of age with endometrial polyp(s) who had undergone polypectomy or hysterectomy. We included women from any region or country. Exclusion criteria included women younger than 45 years, previous history of endometrial cancer, women who had had hysterectomy, and pregnant women.

### Study selection

Two authors independently screened articles based on titles and abstract (JR and MM). The final list of full texts was reviewed and selected based on inclusion criteria. A third author (SA) resolved any discrepancy. Figure 1 shows the PRISMA selection flow chart.

### Data extraction

Once consensus was reached regarding studies to be included in the final analysis, both authors (SA, ES) independently extracted data from selected studies and compiled them into an Excel spreadsheet. We extracted data on study characteristics, including study design, population size, number of participants, diagnostic methods, duration of follow-up, and outcomes including the prevalence of endometrial hyperplasia, associated risk factors (use of tamoxifen, use of HRT, AUB, menopausal status, polyp size, and endometrial thickness), as well as patient characteristics.

### Assessment of risk of bias

Quality assessment was performed using the National Heart, Lung and Blood Institute Study Quality Assessment Tool for case reports, case series, or chart reviews [Supplementary Table 1].

### Data synthesis

The pooled prevalence was calculated for endometrial carcinoma, hyperplasia with atypia, and hyperplasia without atypia within the polyp and/or the endometrium. The presence of hyperplasia with or without atypia within endometrial polyp or endometrium was considered as premalignancy, while endometrial carcinoma was considered as malignancy. To quantify the associations between various risk factors and endometrial premalignancy/malignancy, we conducted meta-analyses and calculated the odds ratios (ORs) with their 95% confidence intervals (CIs). Individual and pooled estimates with their 95% CI were presented in forest plots. We assessed the heterogeneity in the effect estimates study by calculating $I^2$, as well as by inspecting the forest plots. A random-effects model (DerSimonian and Laird) was used when there was substantial heterogeneity, defined as $I^2 >$ 50. Sensitivity analyses was done to investigate the possible source of heterogeneity and to assess the robustness of the results. A two-sided $P \leq 0.05$ was considered statistically significant. Meta-analyses were performed with RevMan web software.

## Results

### Study selection and study characteristics

We screened 1,660 publications that evaluated the risk of uterine malignancy in patients with endometrial polyp. The

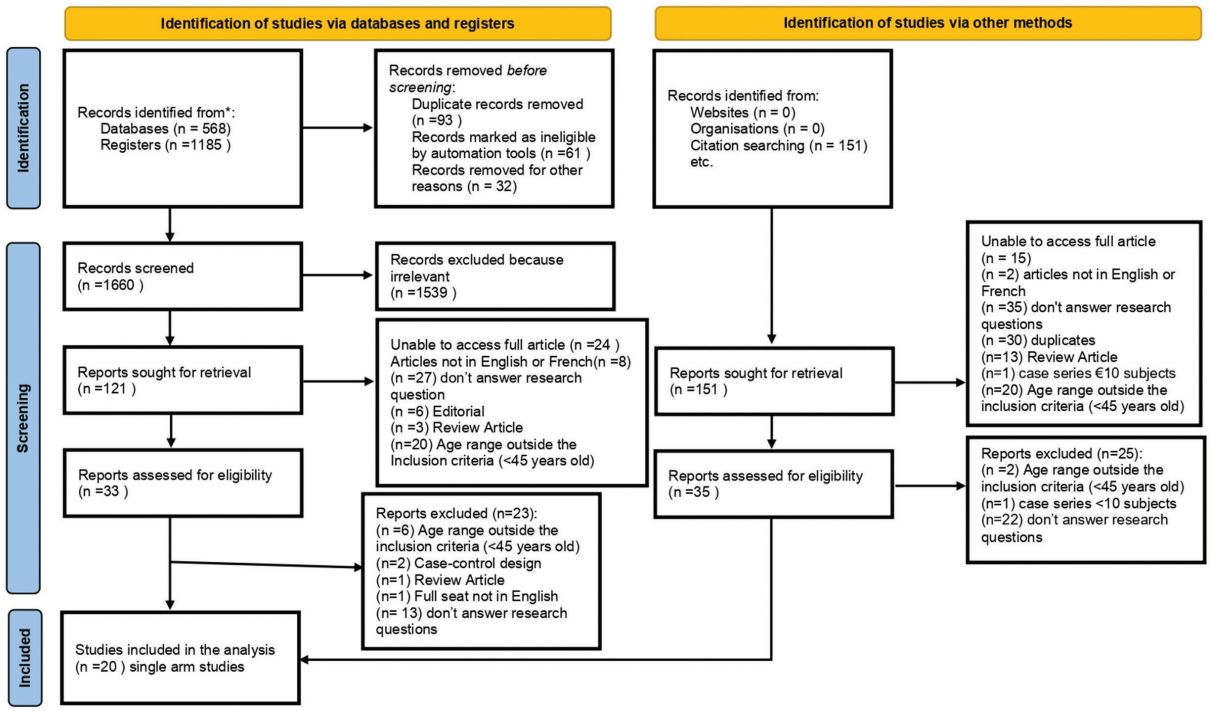


**Figure 1:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 flow diagram for systematic review of studies on endometrial polyp

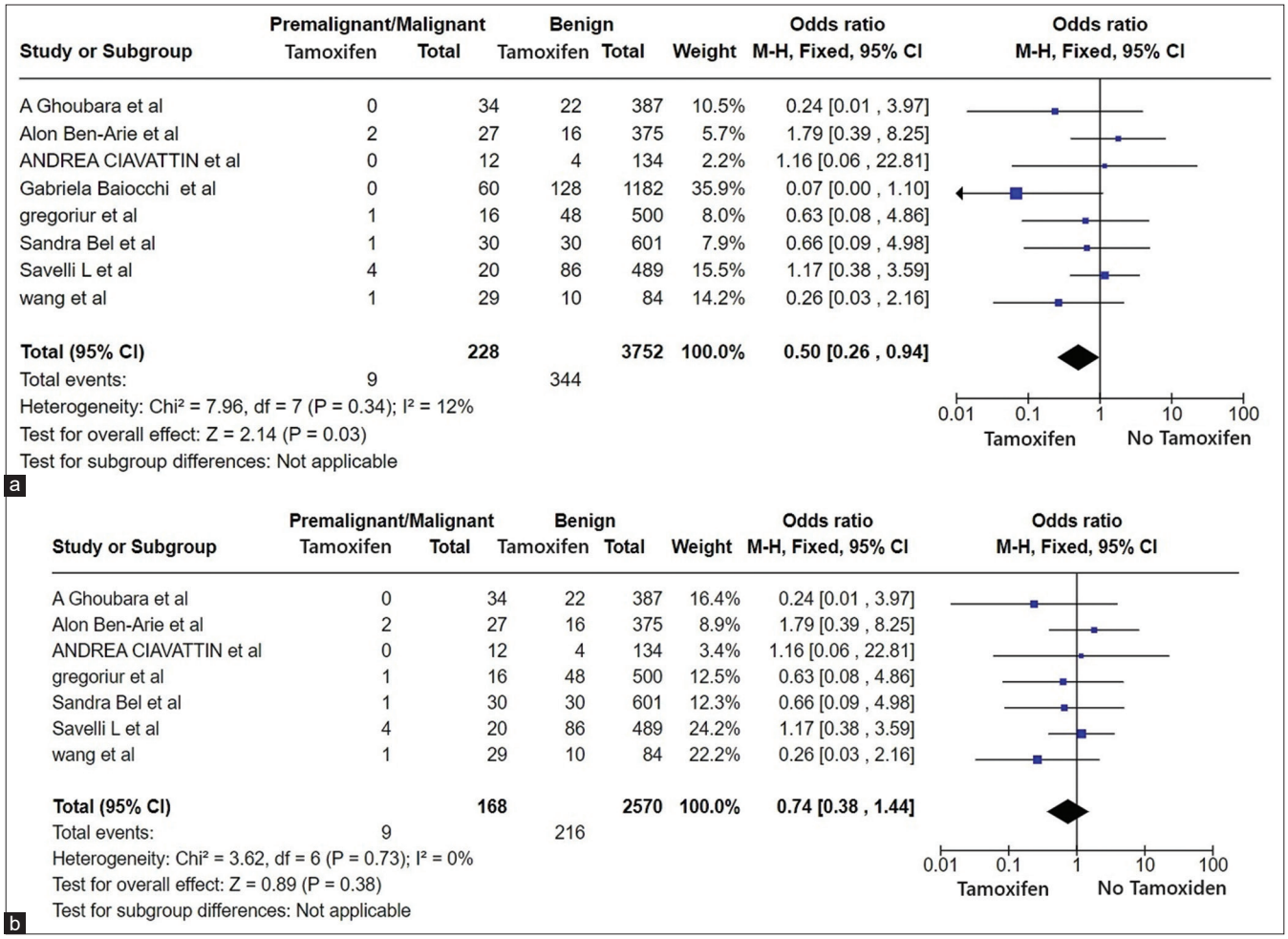


**Figure 2:** Forest plots for tamoxifen (a); Forest plots for tamoxifen after excluding a study by Baiocchi *et al.* (b)

**Table 1: Characteristics of included studies of patients with endometrial polyp**

| Author, Year of Publication | Country | Study Design | Study Period | No. patients | Population | Aim |
|---|---|---|---|---|---|---|
| Akış *et al*. 2022[18] | Turkey | Retrospective cross-sectional | March 2011-March 2016 | 229 | Patients who underwent hysteroscopy after a pre-diagnosis endometrial polyp. | Evaluating polyp size as measured by sonohysterography in predicting premalignant/malignant lesions. |
| Antunes *et al*. 2007[12] | Brazil | Retrospective observational Study | January 1998-December 2005 | 475 | Women who underwent hysteroscopy polypectomy. | Evaluate the prevalence of premalignant and malignant polyps, menopausal status, hormone therapy and clinical characteristics in perimenopausal and postmenopausal women |
| Arslan *et al*. 2003[21] | Turkey | Retrospective cross-sectional | March 2001-December 2001 | 181 | Postmenopausal women with endometrial polyp. | Characterize postmenopausal women with endometrial polyp and to evaluate their significance. |
| Baiocchi *et al*. 2009[13] | Italy | Cohort | January 1995-December 2006 | 1242 | Patients with endometrial polyps and/or endometrial thickness of (≥5 mm) and/ or abnormal uterine bleeding who underwent hysteroscopy. | Evaluate the risk of premalignant and malignant changes in endometrial polyps and to investigate whether clinical parameters could predict the histopathological features of some lesions |
| Bel *et al*. 2017[23] | France | Retrospective cross-sectional | October 2007- December 2014 | 631 | Patients who underwent hysteroscopy for suspected polyp. | Estimate the prevalence of lesions in menopausal patients with a pre-operative diagnosis of endometrial polyp and evaluate the risk factors for malignancy. |
| Ben-Arie *et al*. 2004[19] | Israel | Retrospective observational Study | January 1996 to July 2001. | 420 | Women where endometrial polyp was suspected by diagnostic hysteroscopy | Determine the pre-malignant and malignant potential of endometrial polyps and to assess whether different clinical parameters are associated with malignancy in the polyps |
| Ciavattini *et al*. 2015[22] | Italy | Cohort | January 2010-May 2013 | 146 | Women who underwent transvaginal ultrasound then and hysteroscopy. | Evaluating preperitoneal fat thickness and the risk of premalignant and malignant changes of endometrial polyp in overweight and obese women. |
| Domingues *et al*. 2009[20] | Portugal | Retrospective cross-sectional | 2004-2007 | 481 | Women who underwent a diagnostic hysteroscopy | Evaluate the risk of malignancy of endometrial poly in postmenopausal women. |
| Ferrazzi *et al*. 2009[14] | Italy | Cohort | January 2005-December 2006 | 1152 | Patients treated for endometrial polyps | Evaluate the prevalence of cancer and premalignant lesions in polyps on atrophic endometrium in asymptomatic postmenopausal women |
| Fernandez-Parra *et al*. 2006[11] | Spain | Retrospective observational study | May 2002-July 2004 | 637 | Women who underwent hysteroscopy. | Establish the validity of hysteroscopy for predicting cancer in endometrial polyp based on the number, size and hysteroscopic appearance |
| Ghoubara, *et al*. 2018[24] | United Kingdom | Retrospective cross-sectional | January 2011-December 2015 | 431 | Women with postmenopausal bleeding | Quantify the prevalence and identify the predictors of hyperplasia and cancer in polyps. |
| Gregoriou *et al*. 2009[16] | Greece | Retrospective observational Study | January 2002-December 2006 | 425 | Women who underwent hysteroscopic polypectomy. | Investigate the association of clinical parameters with the histological diagnosis and the prevalence of premalignant and malignant endometrial polyp. |
| Hileeto *et al*. 2005[6] | USA | Retrospective cross-sectional | 1986-1995 | 513 | Cases with endometrial polyp were retrieved from the pathology database | Investigate the age-group of cases with endometrial polyp and those with malignancy, as well as histological subtype. |
| Karakaya *et al*. 2018[25] | Turkey | Retrospective cross-sectional | 2007-2016 | 133 | Women aged>65 years with endometrial polyp. | Prevalence of malignant endometrial polyp in a population of geriatric women. |
| Lasmar *et al*. 2013[5] | Brazil | Retrospective cross-sectional | January 1, 1999-December 31, 2012 | 1136 | Patients who underwent outpatient hysteroscopy . | Assess the correlation between the size of the polyp and histopathologic diagnosis of hyperplasia or cancer. |

*Contd...*

**Tables 1: Contd...**

| | | | | | | |
|---|---|---|---|---|---|---|
| Orvieto *et al.* 1999[8] | Israel | Retrospective cross-sectional | January 1996- December 1997 | 146 | All postmenopausal women referred to the ambulatory gynecological unit. | Characterize endometrial polyp in postmenopausal women and to determine risk factors for concomitant endometrial pathology. |
| Savelli *et al.* 2003[10] | Italy | Retrospective cross-sectional | January 1998 -December 2001 | 509 | Patients who consecutively underwent hysteroscopic polypectomy | Determine the rate of benign, hyperplastic, and malignant endometrial polyp and whether clinical data can predict histopathologic outcome |
| Shushan *et al.* 2004[17] | Israel | Retrospective observational Study | January 1998-May 2003 | 300 | Women who underwent hysteroscopic polypectomy. | Investigate the frequency of malignant endometrial polyps, and to characterize the hysteroscopic image of these polyps. |
| Uglietti *et al.* 2014[27] | Italy | Cohort | 1 January 2007-31 December 2010 | 481 | Patients who underwent outpatient hysteroscopy . | Assess frequency of malignancy of malignancy within polyps and identify risk factors for thus condition |
| Wang al. 2010[15] | China | Retrospective observational Study | January 2000 to February 2006 | 766 | Patients who underwent hysteroscopic polypectomy. | Estimate the prevalence and risk factors of benign, premalignant, and malignancy . |

**Table 2: Prevalence of endometrial precarcinoma (hyperplasia with and without atypia) and carcinoma among women with endometrial polyp**

| | Sample size | *n* (%) |
|---|---|---|
| All | | |
| Endometrial precarcinoma* | 11,204 | 809 (7.2) |
| EMP with hyperplasia without atypia** | 9922 | 520 (5.2) |
| EMP with atypical hyperplasia** | 9922 | 182 (1.8) |
| Endometrial carcinoma | 11,204 | 287 (2.6) |
| 1999–2010 | | |
| Endometrial precarcinoma* | 8017 | 555 (6.9) |
| EMP with hyperplasia without atypia | 8017 | 426 (5.3) |
| EMP with atypical hyperplasia | 8017 | 129 (1.6) |
| Endometrial carcinoma | 8017 | 207 (2.6) |
| 2011–2022 | | |
| Endometrial precarcinoma* | 3187 | 254 (8.0) |
| EMP with hyperplasia without atypia** | 1905 | 94 (4.9) |
| EMP with atypical hyperplasia** | 1905 | 53 (2.8) |
| Endometrial carcinoma | 3187 | 80 (2.5) |

*Combined atypical and nonatypical hyperplasia, **Excluding studies by Lasmar *et al.*[5] and Ciavattini *et al.*[22] EMP: Endometrial polyp

study flow of these publications is shown in Figure 1. Of the 1,660 studies originally identified, 1,539 were excluded as they did not include the risk factors of malignancy, and the indication of polyp removal based on the size [Supplementary Table 2]. Of the 68 studies initially considered, we excluded 48 studies that did not fulfill the inclusion criteria. Twenty chart reviews (cross-sectional studies) were ultimately included in the analysis, encompassing 10 studies from the original database research, and 10 others[5-8,10-25] from Lee *et al.*'s systematic review[26] Characteristics of the included studies are shown in Table 1. The list of excluded studies with the reason of exclusion is presented in Supplementary Table 2.

## Synthesis of results

In those included 20 chart-review studies, all 11204 patients had their polyp removed with histopathological confirmation. Two hundred and eighty-seven polyps were malignant (2.75%), 182 (1.8%) had hyperplasia with atypia, and 520 (5.2%) had hyperplasia without atypia within the polyp and/or the endometrium [Tables 2 and 3].

The odd ratio of having premalignancy/malignancy among those who used tamoxifen was 0.50 (95% CI 0.26–0.94: $I^2$ 12%, $P = 0.03$), [Figure 2a]. In the sensitivity analysis, we excluded the largest weight study by Baiocchi *et al.*[13] The results showed an OR of 0.74 (95% CI 0.38, 1.44; $I^2 = 0\%$, $P = 0.38$). This suggests that tamoxifen use could reduce the probability of endometrial premalignancy/malignancy, although the statistical significance was driven by the largest study [Figure 2b].

Concerning HRT, the OR of having premalignancy/malignancy among those who used HRT was 0.35 (95% CI 0.20–0.61; $I^2$ 12%) [Figure 3a]. However, a sensitivity analysis by removing Arslan *et al.*,[21] the largest weight study, showed an OR of 0.56 (95% CI 0.30, 1.06; $I^2$ 0%, $P = 0.07$) [Figure 3b]. This also suggests that the role of HRT in reducing the probability of endometrial premalignancy/malignancy was driven by the largest study. Among 200 subjects diagnosed with premalignant or malignant conditions, 159 were menopausal. Menopausal women had a likelihood of having premalignancy/malignancy 5.63 (95% CI 3.87–8.20, $I^2 = 0\%$, $P < 0.001$) higher than the nonmenopausal women [Figure 4]. A sensitivity analysis by excluding the study by Baiocchi yielded similar results: OR 5.76 (95CI 3.65, 9.08, $I^2 = 0\%$, $P < 0.001$) [Figure 5], which confirmed that menopause was a risk factor for endometrial premalignancy/malignancy.

There were two conflicting studies regarding polyp diameter and the pooled mean difference was inconclusive with a very wide CI and high heterogeneity (–0.49 mm, 95% CI –8.70–7.72 mm, $I^2 = 89\%$, $P = 0.06$) [Figure 5]. The endometrial thickness

**Table 3: Summary of prevalence of benign: endometrial polyp, or hyperplasia without atypia in polyp premalignant/ malignant: hyperplasia with atypia, or endometrial carcinoma for included studies**

| Author(s) | Population (Inclusion criteria) | Polyp with endometrial hyperplasia without atypia | Polyp with endometrial hyperplasia with atypia | Polyp with endometrial carcinoma |
|---|---|---|---|---|
| Akış *et al*. 2022[18] | 229 patients who underwent hysteroscopic polypectomy after pre-diagnosis on saline infusion sonohysterography | 13 (3.65) | 4 (1.1%) | 2 (0.9%) |
| Antunes A *et al*. 2007[12] | 475 postmenopausal women who underwent hysteroscopic polypectomy | 64 (13.5%) | 5 (1.1%) | 13 (2.7%) |
| Arslan *et al*. 2003[21] | 181 postmenopausal women with endometrial polyp | 30 (16.6%) | 4 (2.2%) | None |
| Baiocchi *et al*. 2009[13] | 1242 postmenopausal women with endometrial polyp | None | 15 (1.3%) | 45 (3.5%) |
| Bel *et al*. 2017[23] | 631 menopausal patients over 45 years who underwent hysteroscopic polypectomy | 11 (1.74%) | 11 (1.74%) | 30 (4.75%) |
| Ben-Arie *et al*. 2004[19] | 420 patients with endometrial polyp (symptomatic and asymptomatic) | 48 (11.5%) | 14 (3.3%) | 13 (3.0%) |
| Ciavattini *et al*. 2015[22]* | 146 overweight and obese women with endometrial polyp diagnosed at transvaginal ultrasound and then underwent hysteroscopy polypectomy | 5 (3.4%)* | | 7 (4.8%) |
| Domingues *et al*. 2009[20] | 481 postmenopausal women over 40 years with and without abnormal uterine bleeding | 11 (2.3%) | 9 (1.8%) | 5 (1.0%) |
| Ferrazzi *et al*. 2009[14] | 1152 asymptomatic postmenopausal women and 770 patients with abnormal uterine bleeding | 103 (5.4%) | 31 (1.6%) | 33 (1.7%) |
| Fernandez-Parra *et al*. 2006[11] | 637 women with endometrial polyp (hysteroscopic polypectomy or hysterectomy) | None | None | 10 (1.5%) |
| Ghoubara, *et al*. 2018[24] | 431 women with endometrial polyps and postmenopausal bleeding | 10 (2.3%) | 20 (4.7%) | 4 (1.0%) |
| Gregoriou *et al*. 2009[16] | 425 women with abnormal uterine bleeding or asymptomatic women with endometrial polyp. | 75 (14.5%) | 6 (1.2%) | 10 (1.9%) |
| Hileeto *et al*. 2005[6] | 513 cases with endometrial polyp | None | None | 66 (13%) |
| Karakaya *et al*. 2018[25] | 133 women over >65 years with pathological diagnosis of endometrial polyp | 7 (5.3%) | 7 (5.3%) | 12 (9.0%) |
| Lasmar *et al*. 2013[5]* | 1136 asymptomatic patients aged 15–52 years with a hysteroscopic diagnosis of endometrial polyp. | 102 (9.0%)* | | None |
| Orvieto *et al*. 1999[8] | 146 postmenopausal women with polyp | 11 (7.5%) | 4 (2.7%) | None |
| Savelli *et al*. 2003[10] | 509 patients who underwent hysteroscopic polypectomy over a 48-month period | 131 (25.74) | 16 (3.14) | 4 (0.79) |
| Shushan *et al*. 2004[17] | 300 patients who underwent hysteroscopic polypectomy | None | None | 4 (1.3%) |
| Uglietti *et al*. 2014[27] | 481 postmenopausal with endometrial polyp on ultrasound. Those diagnosed at hysteroscopy but not suspected at ultrasound were excluded. | 53 (4%) | 11 (1%) | 25 (2%) |
| Wang al. 2010[15] | 766 women who underwent hysteroscopic polypectomy with exclusion criteria of endometrial carcinoma with polypoid features | 84 (11%) | 25 (3.3%) | 4 (0.5%) |

*Combined atypical and non-atypical hyperplasia

was a risk factor contributing to malignancy potential within polyps. The pooled estimate of endometrial thickness showed that the endometrium in premalignancy/malignancy cases was significantly thicker than in the benign polyp (mean difference 4.21 mm, 95% CI 0.77–7.64 mm, $I^2 = 18\%$, $P = 0.02$) [Figure 6].

Women with AUB had a likelihood of having premalignancy/ malignancy 1.89 (95% CI 1.06–3.35, $I^2 = 78\%$, $P = 0.03$) higher than those without AUB [Figure 7a]. A sensitivity analysis by excluding the largest study by Baiocchi showed an OR of 1.77 (95% CI 0.92, 3.38: $I^2$ 79%, $P = 0.09$) [Figure 7b]. It suggests that endometrial premalignancy/malignancy is more likely with the presence of AUB, although the statistical significance was driven by the largest study.

### Bias assessment for the included studies

#### *Quality assessment*

Of 20 studies, all articles explicitly demonstrated their objectives and research questions. With regards to study population, 16 (80%) studies accurately defined their chosen study populations. Several studies did not specify their population.[19-21,23] Concerning participation rates, only 5% of the articles achieved a participation rate of at least 50%. All articles selected and recruited subjects from the same or a comparable population. In addition, inclusion and exclusion criteria were clearly and systematically clarified in every article. 85% of the articles accurately validated exposure measures consistently and reliably across all study participants. However, 15% failed to maintain consistency in their approach [Supplementary Table 2].

## Discussion

The results of our study are similar to those of a systematic review published in 2010[26] suggesting that premalignant and malignant endometrial lesions are more likely to occur

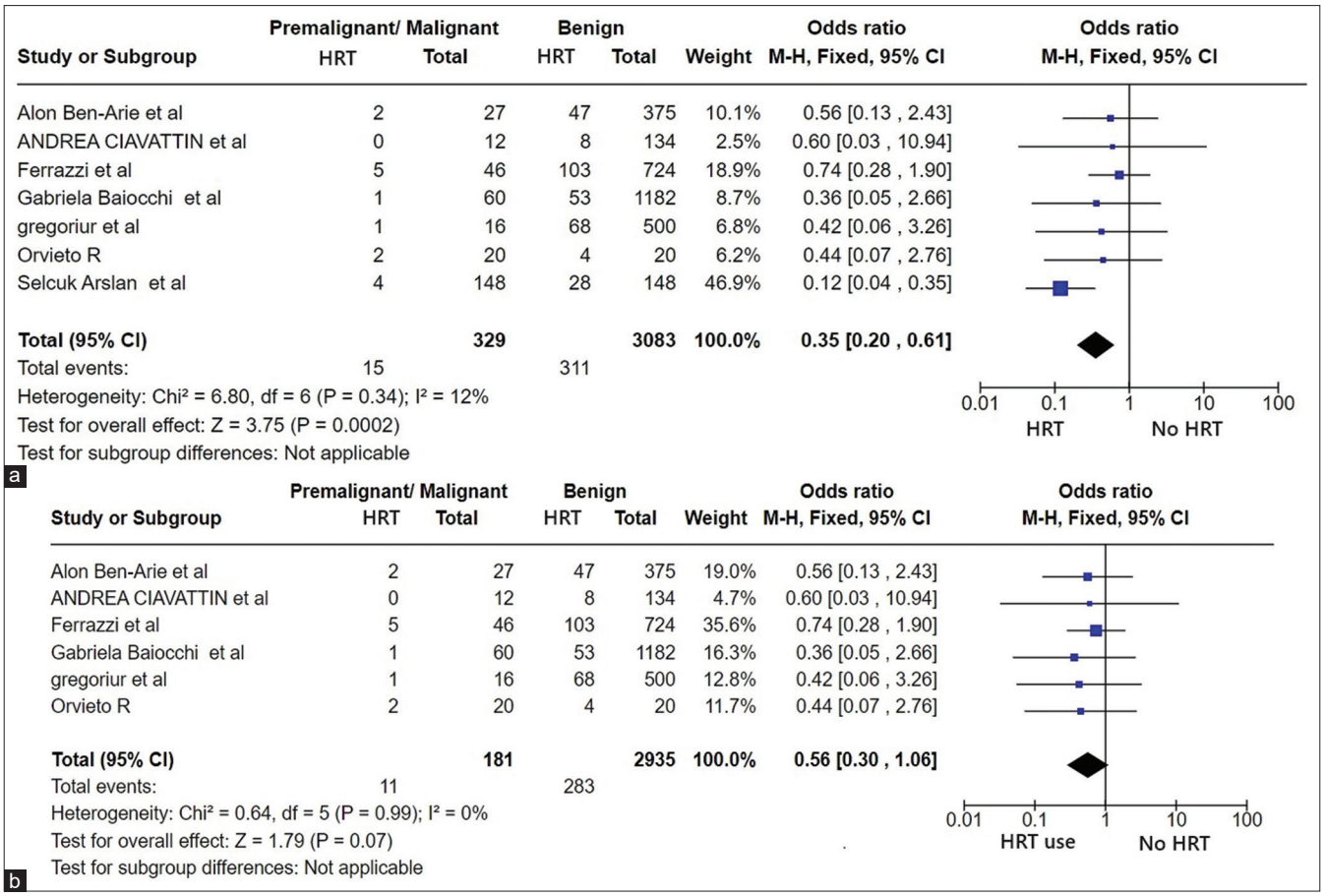


**Figure 3:** Forest plots for hormone replacement therapy (HRT) (a); Forest plots for HRT after excluding a study by Arslan *et al*. (b)

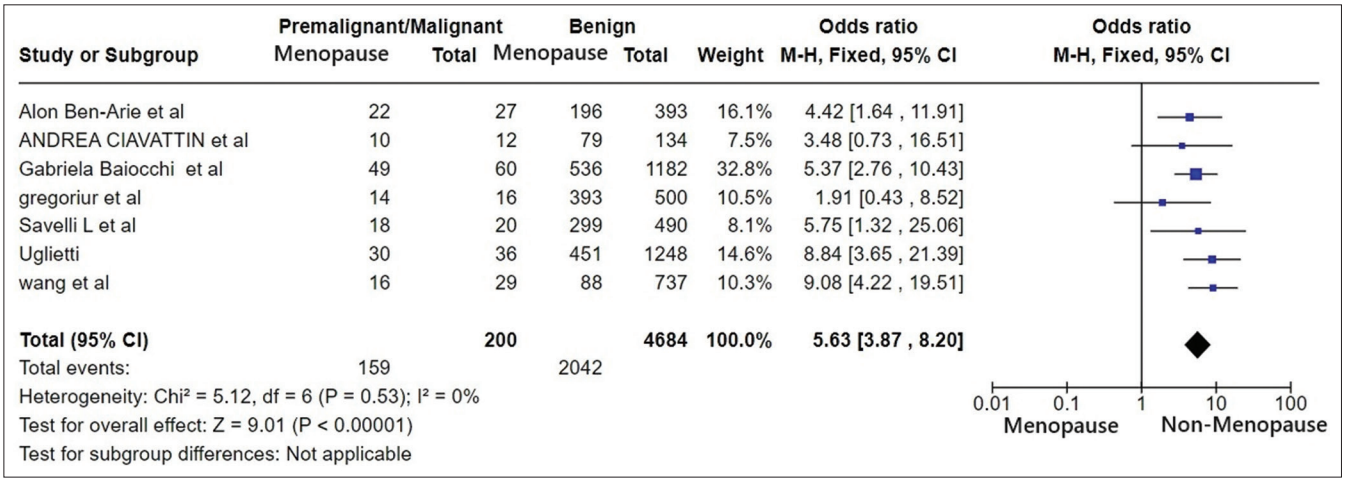


**Figure 4:** Forest plots for menopause

in postmenopausal women with endometrial polyp than in premenopausal women.[26] Menopausal women had a 5.6-fold higher likelihood of having premalignancy/malignancy than the nonmenopausal women. The sensitivity analysis yielded similar results (OR 5.76, $P < 0.001$). This could be related to the fact that advancing age is associated with a lack of progesterone in postmenopausal women. This age-related hormonal shift creates an imbalance between estrogen and progesterone leading to decreased regression as seen in young individuals.[6]

Of ten chart-reviews evaluating the association between body mass index (BMI) and the risks of malignancy,[10,12,14-16,22-25,27] only two reported significant associations between BMI and the likelihood of developing cancer[16,17] Similarly, in the previous review, only one study included in their meta-analysis found

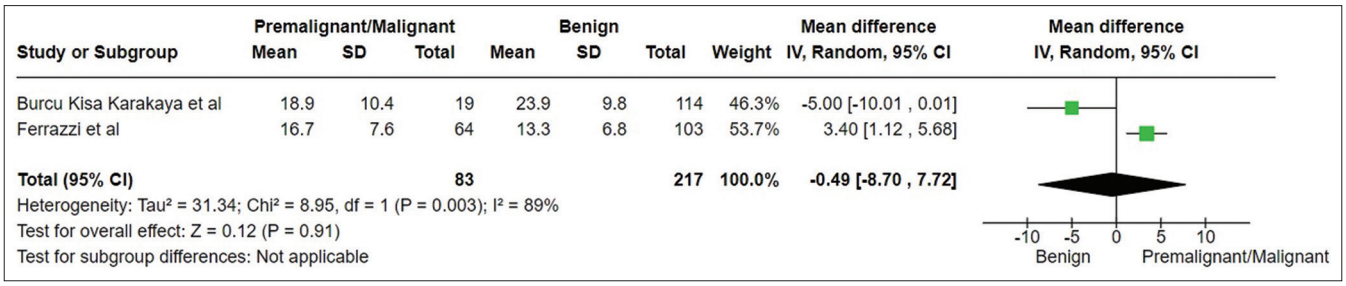


**Figure 5:** Forest plots for polyp diameter random effect

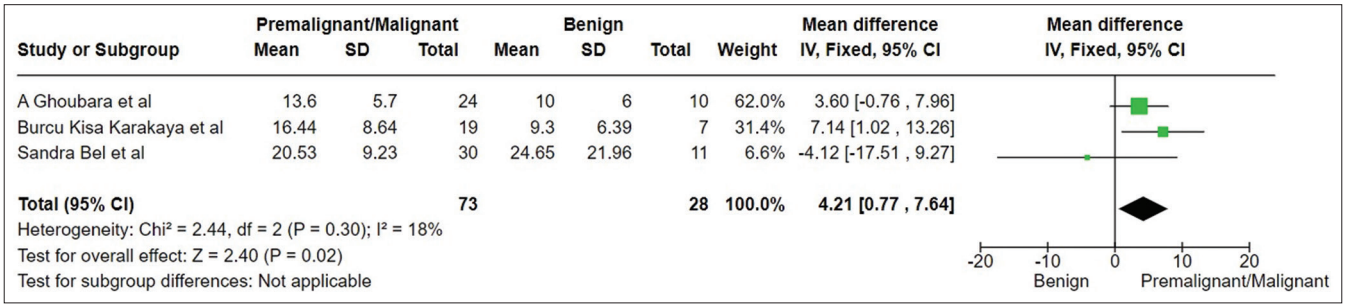


**Figure 6:** Forest plots for endometrial thickness

a statistically significant association between obesity and malignancy. The established association between obesity and endometrial cancer, attributed to the estrogenic environment may not extend to the malignancy potential of endometrial polyp.[16]

Six of eleven chart reviews reported increased malignancy risk in those with abnormal bleeding,[11-15,17,21,23-25,27] and our pooled result showed that AUB presented more in patients with premalignant/malignant lesions. Patients experiencing bleeding symptoms are more likely to seek medical attention leading to earlier diagnosis.

It has been reported that women with thickened endometrium are at increased risk of harboring cancer cells compared to their counterparts. The pooled estimate of three studies examining this risk[13,24,25] demonstrated a significant association with a mean difference of 4.2 mm ($P = 0.02$) thicker endometrium in the premalignant/malignant subjects. This could be due to the underlying factors that increase endometrial thickness. A thick endometrium might impede visualization of endometrial polyp on imaging studies, potentially delaying their detection, and providing more time for malignant transformation to occur within the polyp. In addition, without sonohysterography, the presence of a polyp inside the uterine cavity might give an impression of thick endometrium on transvaginal ultrasound.

Eight chart reviews[5,11,14-19] explored the association between polyp size and malignancy within endometrial polyps. Five of them found a significant association between polyp size and malignant potential within the polyp.[5,14,15,18,19] They reported a cutoff size of 10–22.5 mm with a size exceeding their cutoff point carried a significant risk of malignant transformation within the polyp.[14] Each study used a different cutoff and hence, we could not calculate the pooled estimate. It has been assumed that there seems to be a direct relationship between the quantity of cells and the mutation rate that leads to the development of malignancy.[28] It is also possible that larger polyps have more blood supply, facilitating the delivery of nutrients and oxygen to rapidly dividing cells facilitating malignant transformation. However, regardless of the presence or absence of a polyp, perimenopausal patients with AUB should undergo endometrial sampling. Empirically, polypectomy is indicated in asymptomatic women with endometrial polyp of ≥10 mm. In a retrospective study, Garcia *et al*. reported that benign endometrial of over 15 mm tends to recur.[29]

Hypertension and diabetes mellitus, although previously being considered as risk factors for endometrial carcinoma, were not associated with malignant transformation of endometrial polyp in several studies.[8,12,14,15,17,20,22,24,25] Likewise, in agreement with Lee *et al*.'s study, only one of five studies investigating hypertension in relation to endometrial malignancy risk found a significant association.[10] Biaocchi *et al*.[13] identified hypertension as a significant factor, while Gregoriou *et al*. underscored diabetes as an important contributor.[16]

Regarding hormonal use, eight authors studied the relationship between tamoxifen use and polyp malignancy,[10,13,15,16,18,22-24] and seven included the use of HRT.[8,13,14,16,19,21,22] All those studies demonstrated that tamoxifen use reduced the likelihood of endometrial premalignancy/malignancy. We also found a

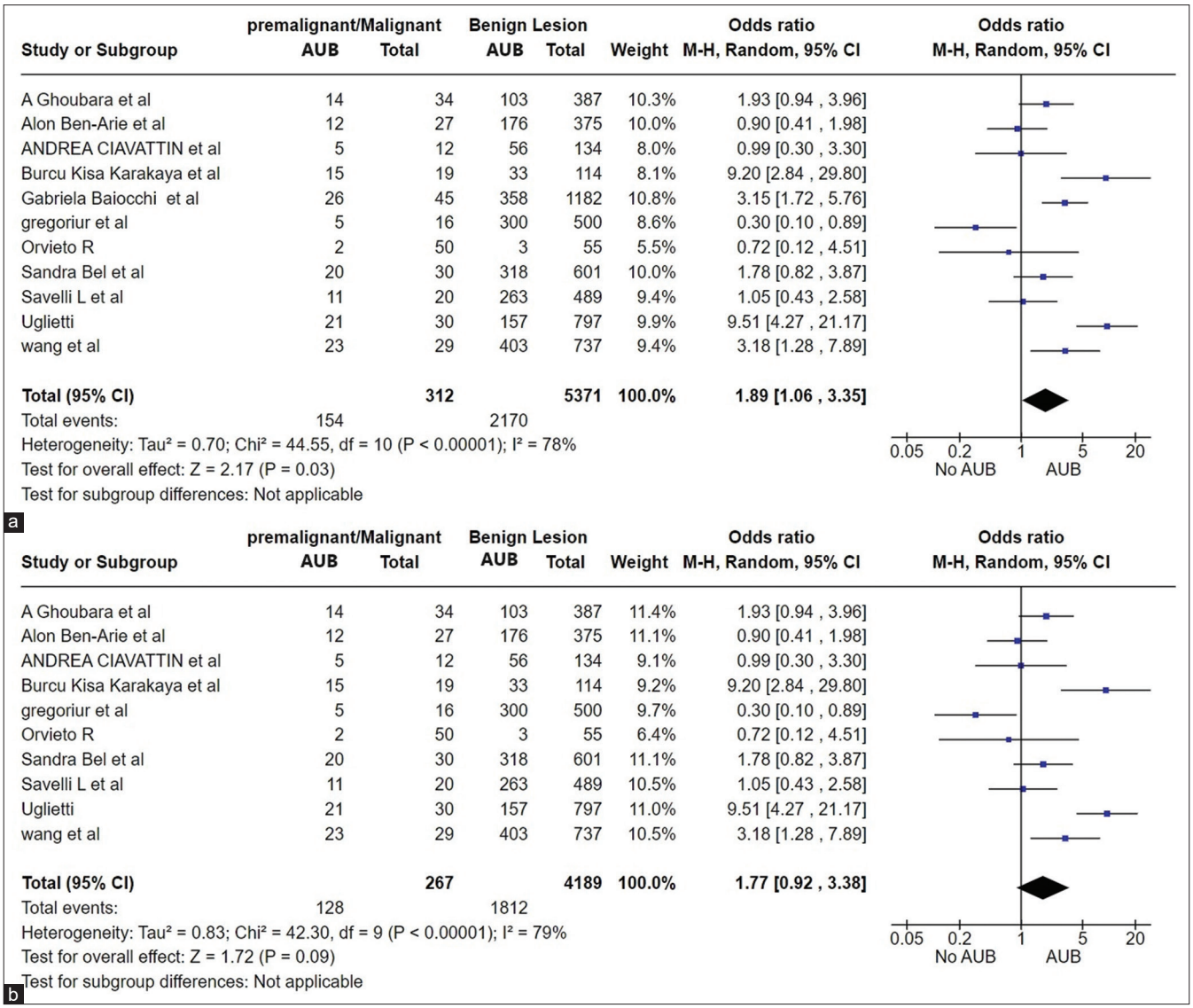


**Figure 7:** Forest plots for abnormal uterine bleeding (AUB) (a); Forest plots for AUB, Sensitivity analysis excluding a study by Baiocchi *et al*. (b)

lower probability of malignancy in endometrial polyps among HRT users. Because tamoxifen is associated with a reduction in estrogen receptors (ER) and an elevation in progesterone receptors within the polyp, McGurgan *et al*. postulated that a decrease in apoptosis facilitates the growth of polyp.[30]

It is possible that the lower prevalence of endometrial polyps in women treated with HRT could be due to the use of progestins in HRT. According to a recent systematic review by Tempfer *et al*., encompassing 8 case–control studies, 2 randomized control studies, and 9 cohort studies on the use of HRT in postmenopause women, the use of HRT, specifically continuous-combined menopausal hormone therapy with synthetic progestins), 9/19 studies showed reduction of the endometrial cancer risk with ORs/HR ranged between 0.24 and 0.71).[31] Studies showed that menopausal hormone therapy (continuous-combined or single progestins) could reduce the endometrial cancer risk in women with higher BMI index.[29]

The prevalence of premalignant endometrial lesions was 6.9% in studies published before 2010[26] and 8% in more recent studies [Table 2]. Similarly, an upward trend in the incidence of endometrial atypical hyperplasia was observed. The prevalence was 1.6% in studies before 2010, and 2.8% in those conducted after 2010. In general, this increasing trend could be due to several factors including obesity, estrogen replacement therapy, delayed childbearing, nulliparity, poor lifestyles including poor diet, sedentary lifestyles or smoking, environmental toxins, or increased awareness and early detection.

## Strengths and limitations

The strengths of our study include the comprehensive search strategy adopted encompassing multiple databases and manual searches. The process of study selection, involving independent screening and resolution of discrepancies, further strengthens the reliability of the included literature. In addition, our inclusion criteria were rigorous, restricting the enrollment of patients with endometrial polyp/s or those who underwent endometrial polyp removal with histopathology diagnosis by either biopsy or hysterectomy, ensuring a more reliable diagnostic framework.

Our meta-analysis provides valuable insights into both the prevalence of malignancy in endometrial polyps and specific risk factors that elevate the likelihood of hyperplasia occurring within endometrial polyp, being one of the few observational-based studies in the medical literature. However, despite the thoroughness of our search strategy, we only found 20 chart-review studies, which is considered low-quality evidence and potentially limits the generalizability and interpretation of findings.

Given the nature of the design, we could not establish temporal associations between polyp, risk factors, and the occurrence of malignancy. We were also unable to further explore the types, doses, and frequency of HRT and tamoxifen use and their impact on the progress of malignancy. Due to the low incidence of malignancy, prospective studies require a large number of patients and will take many years to complete. We propose creation of a longitudinal data base with a large number of patients.

# Conclusions

In women with endometrial polyps, menopausal age and thickened endometrium might increase the probability while tamoxifen or HRT use might lower the likelihood of endometrial premalignancy/malignancy; and the presence of AUB might signal endometrial premalignancy/malignancy.

## Author contributions

- SA: Data Collection, Literature review search, Analysis, Writing, Review and Editing
- MM: Data Collection, Literature review search, Analysis, Writing, Review and Editing
- HK: Analysis, Writing, Review and Editing
- ES: Conceptualization, Methodology, Data Collection, Analysis, Writing, Review, supervision, and Editing
- JR: Data Collection, Literature review search, Writing, Review and Editing
- TT: Conceptualization, Methodology, Data Collection, Analysis, Writing, Review, supervision, and Editing.

All authors have read and agreed to the final version of the manuscript.

## Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author.

## Financial support and sponsorship

Nil.

## Conflicts of interest

Dr. Togas Tulandi, an editorial board member at *Gynecology and Minimally Invasive Therapy*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

# References

1. Nijkang NP, Anderson L, Markham R, Manconi F. Endometrial polyps: Pathogenesis, sequelae and treatment. SAGE Open Med 2019;7:2050312119848247.
2. de Rijk SR, Steenbergen ME, Nieboer TE, Coppus SF. Atypical endometrial polyps and concurrent endometrial cancer: A systematic review. Obstet Gynecol 2016;128:519-25.
3. Namazov A, Gemer O, Ben-Arie A, Israeli O, Bart O, Saphier O, *et al.* Endometrial polyp size and the risk of malignancy in asymptomatic postmenopausal women. J Obstet Gynaecol Can 2019;41:912-5.
4. Jacobs I, Tibosch R, Geomini P, Coppus S, Bongers MY, van Hanegem N. Atypical endometrial polyps and the incidence of endometrial cancer: A retrospective cohort study. BJOG 2020;127:994-9.
5. Lasmar BP, Lasmar RB. Endometrial polyp size and polyp hyperplasia. Int J Gynaecol Obstet 2013;123:236-9.
6. Hileeto D, Fadare O, Martel M, Zheng W. Age dependent association of endometrial polyps with increased risk of cancer involvement. World J Surg Oncol 2005;3:8.
7. Uglietti A, Buggio L, Farella M, Chiaffarino F, Dridi D, Vercellini P, *et al.* The risk of malignancy in uterine polyps: A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 2019;237:48-56.
8. Orvieto R, Bar-Hava I, Dicker D, Bar J, Ben-Rafael Z, Neri A. Endometrial polyps during menopause: Characterization and significance. Acta Obstet Gynecol Scand 1999;78:883-6.
9. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016;5:210.
10. Savelli L, De Iaco P, Santini D, Rosati F, Ghi T, Pignotti E, *et al.* Histopathologic features and risk factors for benignity, hyperplasia, and cancer in endometrial polyps. Am J Obstet Gynecol 2003;188:927-31.
11. Fernández-Parra J, Rodríguez Oliver A, López Criado S, Parrilla Fernández F, Montoya Ventoso F. Hysteroscopic evaluation of endometrial polyps. Int J Gynaecol Obstet 2006;95:144-8.
12. Antunes A Jr., Costa-Paiva L, Arthuso M, Costa JV, Pinto-Neto AM. Endometrial polyps in pre- and postmenopausal women: Factors associated with malignancy. Maturitas 2007;57:415-21.
13. Baiocchi G, Manci N, Pazzaglia M, Giannone L, Burnelli L, Giannone E, *et al.* Malignancy in endometrial polyps: A 12-year experience. Am J Obstet Gynecol 2009;201:462.e1-4.
14. Ferrazzi E, Zupi E, Leone FP, Savelli L, Omodei U, Moscarini M, *et al.* How often are endometrial polyps malignant in asymptomatic postmenopausal women? A multicenter study. Am J Obstet Gynecol 2009;200:235.e1-6.
15. Wang JH, Zhao J, Lin J. Opportunities and risk factors for premalignant and malignant transformation of endometrial polyps: Management strategies. J Minim Invasive Gynecol 2010;17:53-8.
16. Gregoriou O, Konidaris S, Vrachnis N, Bakalianou K, Salakos N, Papadias K, *et al.* Clinical parameters linked with malignancy in endometrial polyps. Climacteric 2009;12:454-8.
17. Shushan A, Revel A, Rojansky N. How often are endometrial polyps malignant? Gynecol Obstet Invest 2004;58:212-5.
18. Akış S, Kıran G, Göçmen A. The clinical importance of polyp size measurement through two-dimensional saline infusion

sonohysterography prior to hysteroscopic resection in predicting premalignant and malignant endometrial lesions. Int J Gynaecol Obstet 2022;157:582-7.
19. Ben-Arie A, Goldchmit C, Laviv Y, Levy R, Caspi B, Huszar M, *et al.* The malignant potential of endometrial polyps. Eur J Obstet Gynecol Reprod Biol 2004;115:206-10.
20. Domingues AP, Lopes H, Dias I, De Oliveira CF. Endometrial polyps in postmenopausal women. Acta Obstet Gynecol Scand 2009;88:618-20.
21. Arslan S, Gökmen O, Tuncay G. The office hysteroscopic evaluation of postmenopausal patients. Arch Gynecol Obstet 2004;270:31-3.
22. Ciavattini A, DI Giuseppe J, Clemente N, Moriconi L, Carpini GD, Montik N, *et al.* Thickness of preperitoneal fat as a predictor of malignancy in overweight and obese women with endometrial polyps. Oncol Lett 2016;11:2278-82.
23. Bel S, Billard C, Godet J, Viviani V, Akladios C, Host A, *et al.* Risk of malignancy on suspicion of polyps in menopausal women. Eur J Obstet Gynecol Reprod Biol 2017;216:138-42.
24. Ghoubara A, Sundar S, Ewies AA. Predictors of malignancy in endometrial polyps: Study of 421 women with postmenopausal bleeding. Climacteric 2018;21:82-7.
25. Karakaya BK, Ozkan NT, Kansu-Celik H, Coskun B, Saridogan E, Evliyaoglu O, *et al.* Malignancy risk of endometrial polyps among geriatric women. Int J Gerontol 2018;12:215-7.
26. Lee SC, Kaunitz AM, Sanchez-Ramos L, Rhatigan RM. The oncogenic potential of endometrial polyps: A systematic review and meta-analysis. Obstet Gynecol 2010;116:1197-205.
27. Uglietti A, Mazzei C, Deminico N, Somigliana E, Vercellini P, Fedele L. Endometrial polyps detected at ultrasound and rate of malignancy. Arch Gynecol Obstet 2014;289:839-43.
28. Takeda T, Banno K, Kobayashi Y, Adachi M, Yanokura M, Tominaga E, *et al.* Mutations of RAS genes in endometrial polyps. Oncol Rep 2019;42:2303-8.
29. Cea García J, Jiménez Caraballo A, Ríos Vallejo MD, Zapardiel I. Retrospective cohort study on the symptomatic recurrence pattern after hysteroscopic polypectomy. Gynecol Minim Invasive Ther 2020;9:209-14.
30. McGurgan P, Taylor LJ, Duffy SR, O'Donovan PJ. Does tamoxifen therapy affect the hormone receptor expression and cell proliferation indices of endometrial polyps? An immunohistochemical comparison of endometrial polyps from postmenopausal women exposed and not exposed to tamoxifen. Maturitas 2006;54:252-9.
31. Tempfer CB, Hilal Z, Kern P, Juhasz-Boess I, Rezniczek GA. Menopausal hormone therapy and risk of endometrial cancer: A systematic review. Cancers (Basel) 2020;12:2195.

## Supplementary Material

**Supplementary Table 1: Bias Evaluation with NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE for Cohort studies**

| Study | Case-cohort representative | Selection of the non-exposed cohort | Ascertainment of exposure | Outcome negative at start | Comparability by design | Comparability by analysis | Outcome assessment | Score |
|---|---|---|---|---|---|---|---|---|
| Ciavattini *et al*. | * | * | * | * | * | | * | 6 |
| Uglietti *et al*. | * | * | * | * | * | * | * | 7 |
| Baiocchi *et al.* | | * | * | * | * | * | * | 6 |
| Ferrazzi *et al*. | | * | * | * | * | * | * | 6 |

**Supplementary Table 2: Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies**

| Criteria | Saveli *et al*. | Hileeto *et al*. | Lasmar *et al*. | Akış *et al*. | Arslan *et al*. | Oriveto *et al* | Bel *et al*. | Antunes A *et al*. | Ghoubara *et al*. |
|---|---|---|---|---|---|---|---|---|---|
| 1. Was the research question or objective in this paper clearly stated? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 2. Was the study population clearly specified and defined? | Yes | Yes | Yes | yes | No | Yes | No | Yes | yes |
| 3. Was the participation rate of eligible persons at least 50%? | NM | NM | No | Yes | NM | No | NM | NM | NM |
| 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 5. Was a sample size justification, power description, or variance and effect estimates provided? | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 6. For the analyses in this paper, were the exposure (s) of interest measured prior to the outcome (s) being measured? | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? | N/A | N/A | yes | N/A | N/A | yes | N/A | N/A | N/A |
| 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Yes |
| 10. Was the exposure (s) assessed more than once over time? | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes | No | No | No | yes | yes | Yes | Yes | Yes |
| 12. Were the outcome assessors blinded to the exposure status of participants? | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| 13. Was loss to follow-up after baseline 20% or less? | N/A | N/A | NA | N/A | NA | NA | NA | NA | NA |
| 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure (s) and outcome (s)? | yes | NM | NM | NM | NM | NM | NM | NM | NM |

*Contd...*

**Supplementary Table 2: Contd...**

| Criteria | Karakaya *et al*. | Fernandez-Parra *et al*. | Wang *et al*. | Gregoriur *et al*. | Shushan *et al*. | Ben-Arie *et al*. | Dominiques *et al*. |
|---|---|---|---|---|---|---|---|
| 1. Was the research question or objective in this paper clearly stated? | Yes | Yes | yes | yes | yes | yes | yes |
| 2. Was the study population clearly specified and defined? | Yes | Yes | Yes | Yes | Yes | No | No |
| 3. Was the participation rate of eligible persons at least 50%? | NM | NM | NM | NM | NM | NM | NM |
| 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? | Yes | Yes | yes | yes | yes | yes | yes |
| 5. Was a sample size justification, power description, or variance and effect estimates provided? | NA | NA | N/A | N/A | N/A | N/A | N/A |
| 6. For the analyses in this paper, were the exposure (s) of interest measured prior to the outcome (s) being measured? | N/A | NA | N/A | N/A | N/A | N/A | N/A |
| 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | N/A | NA | N/A | N/A | N/A | N/A | N/A |
| 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? | yes | N/A | N/A | N/A | N/A | N/A | N/A |
| 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | No | Yes | Yes | yes | yes | yes | yes |
| 10. Was the exposure (s) assessed more than once over time? | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 12. Were the outcome assessors blinded to the exposure status of participants? | NA | N/A | N/A | N/A | N/A | N/A | N/A |
| 13. Was loss to follow-up after baseline 20% or less? | NA | N/A | N/A | N/A | N/A | N/A | N/A |
| 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure (s) and outcome (s)? | NM | 1 | NM | NM | NM | NM | NM |