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## Review article

# The risk of malignancy in uterine polyps: A systematic review and meta-analysis

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## ABSTRACT

**Background:** Endometrial polyps are a common condition. The risk of malignancy has often led to an overtreatment with high health care costs and huge psychological distress.

**Objective:** We conducted a systematic review and a meta-analysis in order to estimate the prevalence of premalignant and malignant lesions in women undergoing hysteroscopic polypectomy.

**Data source:** We developed the search using PubMed/MEDLINE and EMBASE databases to identify papers published between 2000– January 2019. The research strategy used on Pubmed was: (“polyps” (MESH) OR “endometrial polyp”) AND (“malignancy” OR “cancer” OR “histopathology” OR “hysteroscopy” OR “ultrasound”, OR “sonohysterography”). The same search was modified for EMBASE.

**Study eligibility:** We included all observational retrospective and prospective studies and studies were selected for the review if they met following inclusion criteria: pre-operative diagnosis of benign-looking endometrial polyps at ultrasound examination or at hysteroscopy, excision of endometrial polyps via surgical hysteroscopy, histopathological diagnosis of benign polyps, or hyperplasia without atypia, or premalignancy (atypical hyperplasia) or malignancy (endometrial cancer). Moreover, studies were included if number or percentage of subjects with and without malignancy was provided and if they reported data about menopausal and/or bleeding status. We excluded data presented exclusively as abstracts in national and international meetings, or case report or review articles that did not include original data and papers published in other than English language.

Our primary outcome was the prevalence of endometrial premalignant or malignant polyps in the total series, among premenopausal and postmenopausal women and among women with or without abnormal bleeding and then in subgroup analysis according to study design, diagnostic method, study region and calendar year of publication.

**Results:** A total of 51 studies reporting data on 35,345 women were included in this review. The prevalence of malignant polyps was 2.73% (95% CI 2.57–2.91) with very high heterogeneity among studies. The rates were lower for premenopausal women (1.12%) than post-menopausal ones (4.93%) and the difference was statistically significant (chi-square = 397.21,  $p < .0001$ ). The risk of malignancy was higher among symptomatic (5.14%) than asymptomatic ones (1.89%) (chi-square = 133.13  $p < .001$ ). We observed higher rate of malignant polyps in prospective studies. In the meta-analysis selecting 10 prospective studies the random pooled estimate was 5.88 (95% CI: 4.06–7.97) with heterogeneity among studies (heterogeneity chi square = 17.55  $P = .025$ ) whereas in retrospective studies the random pooled estimate was 2.94 (95% CI: 2.24–3.71) with high heterogeneity among studies ( $P < .001$ ). This finding can be due to more strict diagnostic criteria in prospective studies.

**Conclusion:** Symptomatic vaginal bleeding and postmenopausal status in women with endometrial polyps increased the risk of malignancy.

This finding could be an useful evidence to select patients who need to undergo hysteroscopic resection of endometrial polyps and women to whom, instead, an expectant management can be offer.

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## Introduction

Endometrial polyps are a common condition. Their prevalence in women examined with TransVaginal Sonography (TVS) and Saline Infusion Sonohysterography (SIS) or hysteroscopy for Abnormal Uterine Bleeding (AUB) in reproductive age is reported from 10 to 40% of cases [1]. For this reason these lesions are included in the Federation International of Gynecology and Obstetrics (FIGO) classification of causes of AUB in the reproductive years [2]. In addition, endometrial polyps are more found in subfertile eumenorrheic women with an estimated prevalence of 6–15% [3]. In these patients, the rationale for hysteroscopic polypectomy lies in correcting AUB or improving fertility.

Patients with postmenopausal bleeding and ultrasonographic diagnosis of endometrial polyps require hysteroscopic removal of the lesion. Indeed, only histological evaluation allows the differential diagnosis between benign endometrial polyps and focal neoplastic lesions, whose ultrasound characteristics may suggest the neoplastic nature of neof ormation [4–7].

However, it is controversial the indication to remove endometrial polyps in asymptomatic patients. The fear of misunderstanding a malignant polypoid lesion or neglecting a lesion with a potentially low malignancy – especially in postmenopausal, obese, diabetic or hypertensive women with an increased risk of endometrial cancer – has made the practice of "prudent removal" of endometrial polyps highly widespread also in asymptomatic patients.

The prevalence of endometrial polyps in asymptomatic patients of all ages is high [8] and it is likely to increase for the spread of transvaginal ultrasound, more frequently used as an integral part of gynecological examination.

It is widely believed that this excess of diagnosis entails an overtreatment of endometrial polyps, with significantly high health care costs, huge psychological burden and risks, in absence of safe benefits for patients' health.

We conducted a systematic review and a meta-analysis of published studies on the prevalence of histological diagnosis of malignant neoplasms in patients who had endometrial polyps removed, diagnosed with TVS, SIS and/or hysteroscopy, in premenopausal or postmenopausal women and in symptomatic or asymptomatic women.

In 2010 Lee et al have reviewed the frequency of oncologic potential of endometrial polyps [9]. In this paper we updated it, including new studies, with the aim of providing useful evidence to select patients who need to undergo hysteroscopic resection of endometrial polyps and women to whom, instead, an expectant management can be offer.

## Material and methods

We developed the search using PubMed/MEDLINE and EMBASE databases to identify papers published between 2000–January 2019. The research strategy used on Pubmed was:

("polyps" (MESH) OR "endometrial polyp\*") AND ("malignancy" OR "cancer" OR "histopathology" OR "hysteroscopy" OR "ultrasound", OR "sonohysterography"). The same search was modified for EMBASE. We included all observational retrospective and prospective studies and studies were selected for the review if they met following inclusion criteria: pre-operative diagnosis of benign-looking endometrial polyps at ultrasound examination (TVS, SIS) or at hysteroscopy, excision of endometrial polyps via surgical hysteroscopy, histopathological diagnosis of benign polyps, or hyperplasia without atypia, or premalignancy (atypical hyperplasia) or malignancy (endometrial cancer). Moreover, studies were included if number or percentage of subjects with and without malignancy was provided and if they reported data about menopausal and/or bleeding status. We excluded data presented exclusively as abstracts in national and international meetings, or case report or review articles that did not include original data and papers published in other than English language.

Moreover, bibliographies of the retrieved papers were reviewed, to identify any other relevant publication.

Our primary outcome was the prevalence of endometrial premalignant or malignant polyps in the total series, among premenopausal and postmenopausal women and among women with or without abnormal bleeding and then in subgroup analysis according to study design, diagnostic method, study region and calendar year of publication.

The present systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines [10].

Three authors (MF, AU and LB) conducted an independent screening of all titles and abstracts retrieved from peer-reviewed journals to exclude irrelevant or duplicate citations. Disagreements were solved by discussing the respective position on the issue. When we found more than one publication based on the same study population and data, we included only the one with most detailed information, or published most recently.

We used a data extraction form where from each publication we filled in the following information: author, year of publication, study design, number of patients enrolled, number of premenopausal/menopausal women, number of women with/without abnormal uterine bleeding and diagnostic step when patient was inserted in the study (ultrasound suggesting polyp, hysteroscopy with polyp diagnosis and resection, or histological evaluation of uterus or endometrium including polyp after surgical removal) and clinical and demographic factors.

Information on the methodological quality of selected studies was assessed using the Methodological Index for Non-Randomised Studies (MINORS), a validated instrument which is designed for assessment of methodological quality of non-randomized studies in surgery [11]. Briefly, the studies were judged on eight pre-defined items and maximum score was 16.

For each study with binary outcomes, we calculated the 95% confidence intervals (CIs) of the estimated percentages.

To evaluate the association between malignancy and menopausal status or presence of symptoms (bleeding), we computed Pearson Chi Square test for heterogeneity and relative p value.

We used Metaprop, a command implemented in Stata to compute meta-analysis of proportions.<sup>11</sup> Freeman-Tukey method was applied to include, in the computation, the studies with outcome proportion equal zero.<sup>12</sup> Estimates of proportion and 95% CI were calculated by using random effect model. To evaluate heterogeneity among studies, heterogeneity chi square value was also reported.

## Results

We identified 1289 articles: after screening and evaluation of abstract or full text 1166 articles were excluded; 123 were considered for eligibility and another 20 citations were found from reference lists. The flow diagram of the literature search results is shown in Fig. 1.

Overall, 92 publications were not included in the current review: 88 studies because did not meet the inclusion criteria and 4 because had the same population of another included studies.

Table 1 reported the selected studies. A total of 51 studies reporting data on 35,345 women were included in this review and meta-analysis [8,12–61]. Thirteen studies were conducted in Italy, seven in Brazil, seven in Israel, four in Spain, three in United Kingdom, three in Turkey, two in Netherlands, one in Greece, one in United States, one in Norway, one in Denmark, one in China, one in Japan, one in Korea, one in Thailand, one in Egypt, one in Portugal, one in Poland and one in France. Their quality was generally good to the MINORS criteria score ranged from 4 to 10 being 8 or 10 in 29 papers out of 51.

Table 2 considers the frequency of malignancy in the total series and separately in pre and post-menopausal women. The rate of malignancies ranged from 0 to 15%. Overall of the 35,345 surgically removed lesions, 965 (2.73%, 95% CI 2.57–2.91) were malignant. When we performed meta-analysis there was high heterogeneity among the studies (heterogeneity chi-square  $P < .0001$ ).

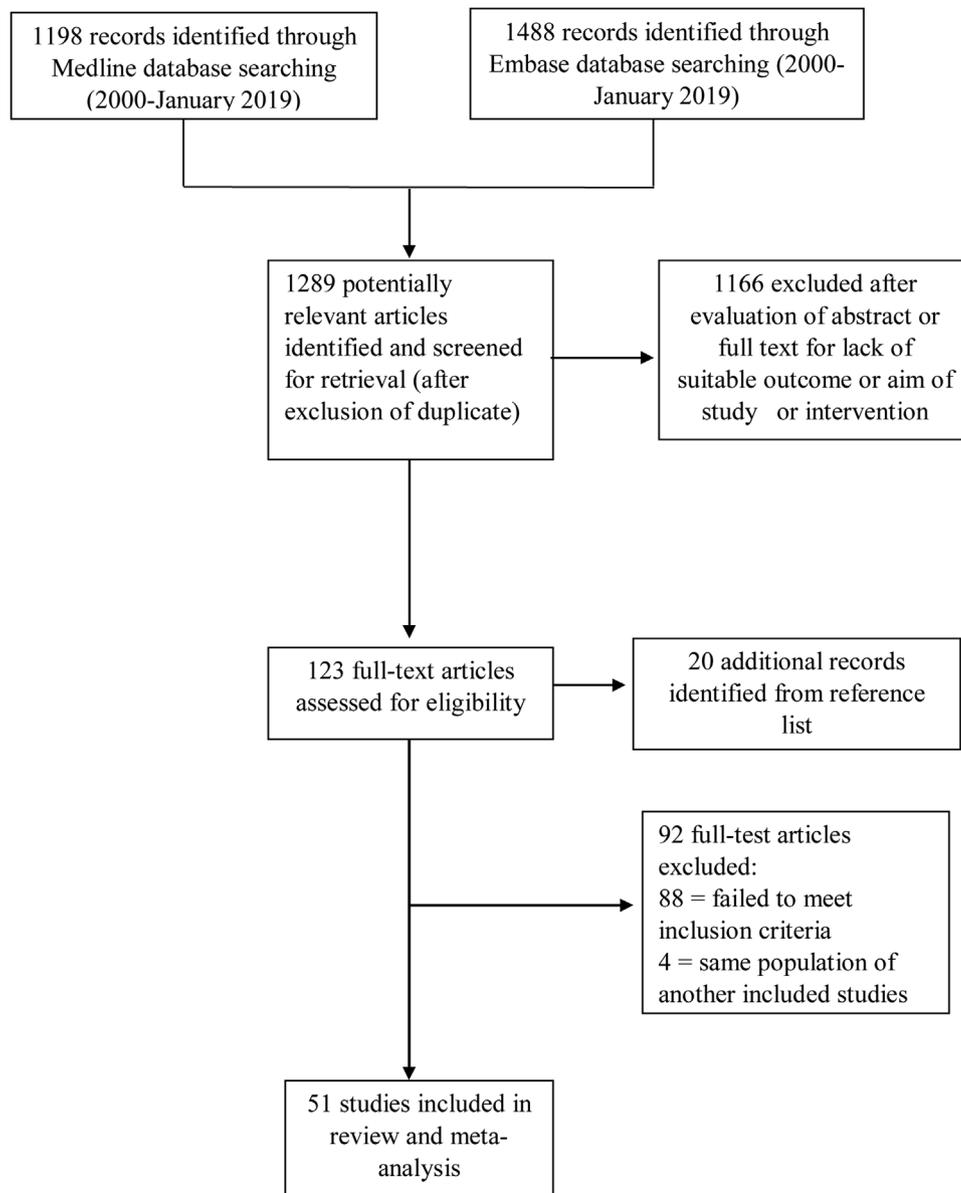


Fig. 1. Flowchart of the study selection process.

**Table 1**

Main characteristics of the selected studies.

Reference (First Author)	Year	Country	Patients (n)	Patients with malignant polyps(n)	Study Design	Population studied	included in study after diagnosis by	Other factors analysed
Bakour et al.	2000	UK	62	6	Prospective	Pre and post menopausal patients with abnormal uterine bleeding.	Hysteroscopy	HRT + Tamoxifene
de Almeida Silva Reis et al.	2001	Brazil	60	3	Retrospective	Postmenopausal patients	Hysteroscopy	
Goldstein et al.	2002	United States	61	7	Prospective	Patients with and without bleeding.	Ultrasound	Size of polyps (NS)
Gambacciani et al.	2003	Italy	139	0	Retrospective	Postmenopausal asymptomatic patients	Hysteroscopy	
Savelli et al.	2003	Italy	509	20	Retrospective	Pre e postmenopausal patients with and without abnormal bleeding	Hysteroscopy	BMI(NS)Parity (NS)Diabetes mellitus (NS) Hypertension (p = 0.001) HRT (NS) Tamoxifen (NS) Oral contraceptives (NS)
Ben-Arie et al.	2004	Israel	420	27	Retrospective	Pre e postmenopausal patients with and without abnormal bleeding	Hysteroscopy	Tamoxifen (NS), HRT(NS) Size of polyp >1.5 cm (p < 0.0001)
Martinez et al.	2004	Spain	1822	16	Retrospective	Pre and postmenopausal patients with and without abnormal uterine bleeding.	Hysteroscopy	HRT(NS), Tamoxifene
Shushan et al.	2004	Israel	300	5	Retrospective	Pre and postmenopausal patients with and without bleeding	Hysteroscopy	Size, multiple polyps, tamoxifene (NS)
Lev-Sagie et al.	2005	Israel	82	0	Retrospective	Postmenopausal asymptomatic patients	Ultrasound	
Machtlinger et al.	2005	Israel	438	11	Retrospective	Pre and postmenopausal patients with or without bleeding	Hysteroscopy	Tamoxifen (NS) HRT(NS)
Preutthipan et al.	2005	Thailand	240	1	Retrospective	Pre and postmenopausal patients with and without bleeding	Hysteroscopy	
Antunes et al.	2006	Brazil	455	18	Retrospective	Pre and postmenopausal patients > 40 years old, with and without bleeding.	Hysteroscopy	HRT (NS), BMI(NS), Parity(NS), Diabetes(NS) Hypertension (NS), Tamoxifene(NS, age>60 p < 0,014)
Fernandez-Parra et al.	2006	Spain	653	10	Retrospective	Pre and postmenopausal patients with and without bleeding	Hysteroscopy	Parity (NS), HRT (NS)
Lieng et al.	2007	Norway	411	14	Retrospective	Pre and postmenopausal patients with and without bleeding	Hysteroscopy	BMI(NS) Tamoxifene(NS) HRT(NS)
Papadia et al.	2007	Italy	90	8	Prospective	Pre and postmenopausal patients with and without bleeding	Hysteroscopy	.
Andia-Ortiz et al.	2008	Spain	303	19	Prospective	Pre and postmenopausal patients with AUB or without bleeding.	Hysteroscopy	Age p > 0,001, Tamoxifene(NS)
Kassab et al.	2008	UK	102	15	Retrospective	Postmenopausal patients with postmenopausal bleeding	Ultrasound	BMI(NS) Parity(NS) Size of polyp (NS) Tamoxifen (p = 0,5) HRT(p = .03)
Baiocchi et al.	2009	Italy	1,242	60	Retrospective	Pre and postmenopausal patients with or without bleeding	Hysteroscopy	Diabetes (NS) Hypertension (p < .05) HRT (NS) Tamoxifen (NS)
Domingues et al.	2009	Portugal	481	22	Retrospective	Postmenopausal patients with or without bleeding	Hysteroscopy	HRT(NS) Hypertension(NS) Diabetes mellitus(NS)
Dreisler et al.	2009	Denmark	61	2	Planned Study Population	Pre and postmenopausal patients without bleeding	Ultrasound	
Ferrazzi et al.	2009	Italy	1,922	64	Retrospective	Postmenopausal patients with and without bleeding	Hysteroscopy	Parity(NS) BMI(NS) HRT(NS) Hypertension(NS) Diabetes mellitus (NS) Size of polyp(p = .0002) Obesity(p = .001)Diabetes mellitus (p = .04) Size of polyp (NS), HRT(NS) Tamoxifene(NS), Hypertension(NS)
Gregoriou et al.	2009	Greece	516	16	Retrospective	Pre and postmenopausal patients with or without bleeding	Hysteroscopy	Past use of contraception (NS) AEH on background endometrium in 7,3 % overall and 12% in postmenopausal patients
Rahimi et al.	2009	Italy	694	54	Retrospective	Pre and postmenopausal patients	Hysteroscopy	
Van Dongen et al.	2009	Netherlands	21	0	Prospective	Premenopausal patients with abnormal uterine bleeding	Hysteroscopy	
Wang et al.	2010	China	766	29	Prospective	Pre and postmenopausal patients with and without abnormal bleeding	Hysteroscopy	BMI(NS) Parity(NS) Size of polyp > 1 cm (p = .001) Multiple polyps(p = .01)

Table 1 (Continued)

Reference (First Author)	Year	Country	Patients (n)	Patients with malignant polyps(n)	Study Design	Population studied	included in study after diagnosis by	Other factors analysed
Golan et al.	2010	Israel	1,124	23	Retrospective	Pre and postmenopausal patients with and without bleeding	Hysteroscopy	Hypertension(NS) Diabetes mellitus (NS) HRT(NS) Tamoxifene(NS) HRT(NS) Tamoxifene(NS)
Mossa et al.	2010	Italy	351	10	Retrospective	Pre e postmenopausal patients with and without bleeding	Hysteroscopy	
Costa Paiva et al.	2011	Brazil	870	36	Retrospective	Pre and postmenopausal patients with and without bleeding.	Hysteroscopy or Ultrasound	BMI, hypertension, polyp size<15 mm p < 0,05 Tamoxifene NS, breast cancer NS HRT NS
Kilicdag et al.	2011	Turkey	417	9	Retrospective	Premenopausal patients with or without AUB	Hysteroscopy	Diabetes mellitus(NS) Hypertension (NS) Size of polyp(NS) PCOS(p < .01) Polyp number(p < .01)
Daniele et al.	2013	Italy	345	6	Retrospective	Pre and postmenopausal patients with and without bleeding	Hysteroscopy	
Godoy Junior et al.	2013	Brazil	521	23	Retrospective	Postmenopausal patients	Hysteroscopy	Polyp size(p = .002)
Lasmar et al.	2013	Brazil	1,136	1	Retrospective	Asymptomatic premenopausal patients	Hysteroscopy	Polyp size(p = .05) associated with hyperplasia Age(NS)
Cavkaytar et al.	2014	Turkey	328	26	Retrospective	Postmenopausal patients with postmenopausal bleeding	Hysteroscopy	Polyp size (p < .001) Parity(NS) BMI(NS)Diabetes mellitus(NS) Hypertension(NS)
Gambadauro et al.	2014	Spain	1,390	16	Retrospective	Pre and postmenopausal patients with and without bleeding	Ultrasound	
Lenciet al.	2014	Brazil	1,020	5	Retrospective	Pre and postmenopausal patients with and without bleeding	Hysteroscopy	.
Litta et al.	2014	Italy	813	47	Retrospective	Pre and postmenopausal patients with and without bleeding	Hysteroscopy	Nulliparity, diabetes, Tamoxifene, breast cancer, HRT NS Age hypertension BMI p < 0,001
Ricciardi et al.	2014	Italy	973	41	Retrospective	Pre and postmenopausal patients with and without bleeding.	Hysteroscopy	Age Diabetes, Hypertension, tamoxifene, HRT BMI NS
Uglietti et al.	2014	Italy	1,284	36	Retrospective	Pre and postmenopausal patients with and without bleeding	Ultrasound	Age BMI Tamoxifene Hypertension diabete HRT, NS.
Elfayomy et al.	2015	Egypt	150	7	Prospective	Only premenopausal patients	Hysteroscopy	PCOS e polyp volume > 10 ml p > 0,001 multiple polyps p > 0,1 AUB, BMI, age NS
Ciavattini et al.	2016	Italy	146	12	Retrospective	Only patients overweight (BMI 25-29) or obese (BMI > 30)	Hysteroscopy	
de Azevedo et al.	2016	Brazil	352	10	Retrospective	Pre and postmenopausal patients with and without bleeding	Ultrasound	BMI, Hypertension, diabetes, polips size, Tamoxifene HRT NS
Radowicka et al.	2016	Poland	412	14	Retrospective	Pre and postmenopausal patients with and without bleeding	Ultrasound	Age BMI parity NS
Bel et al.	2017	France	631	30	Retrospective	Only menopausal patients, with or without bleeding	Ultrasound or diagnostic hysteroscopy	Age > 59 OR 1,06 AUB family history OR 2,4 e 2,8
Ghoubara et al.	2017	UK	421	24	Prospective	Only patients with PMB	Hysteroscopy	BMI(BMI=>32p=.002), Hypertension, Diabetes, Tamoxifene.
Kuribayashi et al.	2017	Japan	1035	10	Retrospective	Only premenopausal, infertile patients	Hysteroscopy	
Van Hanegem et al.	2017	Netherlands	50	6	Prospective Randomized	Only patients with PMB	Hysteroscopy	
Karakaya et al.	2018	Turkey	133	19	Retrospective	Only postmenopausal patients >65 years old	Hysteroscopy	Age,Parity,BMI, Hypertension, Diabetes. Uterine bleeding(15/19) and endometrial thickness >16 mm p < 0,001
Trojano et al.	2018	Italy	198	0		Only postmenopausal asymptomatic patients	Hysteroscopy	
Yuk et al.	2018	Korea	8368	87	Retrospective	Pre and postmenopausal patients	Hysteroscopy	
Namazov et al.	2019	Israel	472	18	Retrospective	Only asymptomatic postmenopausal patients	Hysteroscopy	Age at mp, hypertension, diabetes, tamoxifene, breast and colon ca history, HRT, size of polyp (NS)

**Table 1** (Continued)

Reference (First Author)	Year	Country	Patients (n)	Patients with malignant polyps(n)	Study Design	Population studied	included in study after diagnosis by	Other factors analysed
Shor et al.	2019	Israel	556	31	Retrospective	Pre e postmenopausal, with and without bleeding	Hysteroscopy	Age, parity, hypertension, diabetes, breast cancer history, tamoxifene (NS)

As shown in Table 2, the rates were lower for premenopausal women (1.12%, 200 of 17,885) than post-menopausal ones (4.93%, 696 of 14,108) and the difference was statistically significant (chi-square = 397.21  $p < .0001$ ).

The risk of malignancy was higher among symptomatic (5.14%) than asymptomatic ones (1.89%) (chi-square = 133.13  $p < .001$ ) (see Table 3).

We performed subgroup analyses according to study design: in the meta-analysis selecting 41 retrospective studies the random pooled estimate was 2.94 (95% CI:2.24–3.71) with high heterogeneity among studies ( $P < .001$ ). In the meta-analysis selecting 10 prospective studies the random pooled estimate was 5.88 (95% CI:

4.06–7.97) with heterogeneity among studies (heterogeneity chi square = 17.55  $P = .025$ ). When in the sensitivity analysis we excluded two studies (Goldstein and Van Hanegem) considered outliers comparing with the remaining studies the random pooled estimate was 5.05 (95% CI:3.54–6.77) with no heterogeneity among studies (heterogeneity chi square = 10.37  $P = .11$ ).

We performed subgroup analyses according to diagnostic method: in the meta-analysis selecting studies where diagnosis was based on ultrasound examination the random pooled estimate was 3.26 (95% CI:1.56–5.48) with high heterogeneity among studies ( $P < .001$ ). In the meta-analysis selecting studies where diagnosis was based on hysteroscopy the random pooled estimate

**Table 2**

Frequency of malignant polyps according menopausal status.

Authors	Years	Postmenopausal women				Premenopausal women			
		Patients with malignancy (n)	Total	% Malignancy	95 % Confidence Interval	Patients with malignancy (n)	Total	% Malignancy	95 % Confidence Interval
de Almeida Silva Reis et al.	2001	3	60	5.00	1.72–13.70				
Gambacciani et al.	2003	0	139	0.00					
Savelli et al.	2003	18	317	5.68	3.62–8.80	2	192	1.04	0.29–3.72
Ben-Arie et al.	2004	22	218	10.09	6.76–14.81	5	184	2.72	1.17–6.20
Martinez et al.	2004	14	994	1.41	0.84–2.35	2	828	0.24	0.07–0.88
Shushan et al.	2004	2	90	2.22	0.71–3.84	2	210	0.95	0.26–3.41
Lev-Sagie et al.	2005	0	82	0.00					
Machtinger et al.	2005	10	201	4.98	2.73–8.91	1	237	0.42	0.07–2.35
Preuththipan et al.	2005	1	50	2.00	0.35–10.49	0	190	0.00	
Antunes et al.	2006	14	326	4.29	2.58–7.08	4	129	3.10	1.21–7.70
Fernandez-Parra et al.	2006	10	376	2.66	1.45–4.83	0	277	0.00	
Lieng et al.	2007	9	204	4.41	2.34–8.17	5	207	2.42	1.04–5.53
Papadia et al.	2007	4	53	7.55	2.97–17.86	4	37	10.81	4.29–24.71
Kassab et al.	2008	15	102	14.71					
Baiocchi et al.	2009	49	585	8.38	6.39–10.90	11	657	1.67	0.94–2.97
Domingues et al.	2009	22	481	4.57	3.04–6.83				
Ferrazzi et al.	2009	64	1922	3.33	2.62–4.23				
Gregoriou et al.	2009	14	393	3.56	2.13–5.89	2	123	1.63	0.45–5.74
Rahimi et al.	2009	32	241	13.28	9.57–18.14	22	453	4.86	3.23–7.24
Van Dongen et al.	2009					0	21	0.00	
Wang et al.	2009	16	104	15.38	9.70–23.54	13	662	1.96	1.15–3.33
Golan et al.	2010	16	641	2.50	1.54–4.02	7	483	1.45	0.70–2.96
Mossa et al.	2010	6	149	4.03	1.86–8.51	4	202	1.98	0.77–4.98
Costa Paiva et al.	2011	31	663	4.68	3.31–6.56	5	205	2.44	1.05–5.58
Kilicdag et al.	2011					9	417	2.16	
Daniele et al.	2013	5	222	2.25	0.97–5.16	1	123	0.81	0.14–4.46
Godoy Junior et al.	2013	23	521	4.41	2.96–6.54				
Lasmar et al.	2013					1	1136	0.09	0.02–0.50
Cavkaytar et al.	2014	26	328	7.93	5.47–11.36				
Elfayomy et al.	2014					7	150	4.67	2.28–9.32
Litta et al.	2014	38	392	9.69	7.14–13.03	9	421	2.14	1.13–4.01
Ricciardi et al.	2014	25	341	7.33	5.02–10.60	16	632	2.53	1.56–4.07
Uglietti et al.	2014	30	481	6.24	4.40–8.76	6	803	0.75	0.34–1.62
Ciavattini et al.	2016	10	89	11.24	6.22–19.46	2	57	3.51	0.97–11.92
Marques da Rocha de Azevedo et al.	2016	9	177	5.08	2.70–9.38	1	162	0.62	0.11–3.41
van Hanegem et al.	2016	6	50	12.00	5.62–23.81				
Bel et al.	2017	30	631	4.75	3.35–6.71				
Ghoubara et al.	2017	24	421	5.70	3.86–8.34				
Kuribayashi et al.	2017					10	1035	0.97	0.53–1.77
Karakaya et al.	2018	18	133	13.53	8.74–20.38				
Namazov et al.	2018	11	472	2.33	1.31–4.12				
Trojano et al.	2018	0	197	0.00					
Yuk et al.	2018	44	940	4.68	3.51–6.23	43	7428	0.58	0.43–0.78
Shor et al.	2019	25	322	7.76	5.31–11.21	6	224	2.68	1.23–5.72
TOTAL			696	4.93	4.04–6.01	200	17,885	1.12	0.84–1.84

**Table 3**  
Patients with malignancy: symptomatic and asymptomatic subjects.

First Author	Symptomatic uterine bleeding	95 % Confidence Interval	Asymptomatic	95 % Confidence Interval
Bakour et al.	6/62 (9.68)	4.51–19.55		
Goldstein et al.	4/42 (9.52)	3.77–22.06	3/19 (15.79)	5.52–37.56
Savelli et al.	11/274 (4.01)	2.26–7.04	9/235 (3.83)	2.03–7.12
Ben Arie et al.	12/188 (6.38)	3.69–10.82	15/214 (6.47)	3.96–10.39
Martinez et al.	12/998 (1.20)	0.69–2.09	4/824 (0.49)	0.19–1.24
Shushan et al.	4/227 (1.76)	0.69–4.44	0/73 (0)	
Lev-Sagie et al.			0/82 (0)	
Macthinger et al.	10/230 (4.35)	2.38–7.82	1/238 (0.42)	0.07–2.34
Fernandez-Parra et al.	10/470 (2.13)	1.16–3.87	0/183 (0)	
Lieng et al.	7/265 (2.64)	1.29–5.35	7/144 (4.86)	2.37–9.69
Papadia et al.	4/50 (8.00)	3.15–18.84	4/40 (10.00)	3.96–23.05
Kassab et al.	15/102 (14.71)	9.12–22.86		
Baiocchi et al.	39/397 (9.82)	7.27–13.15	21/845 (2.49)	1.63–3.77
Domingues et al.	21/181 (11.6)	7.72–17.09	1/175 (0.57)	0.10–3.17
Ferrazzi et al.	46/770 (5.97)	4.51–7.88	18/1152 (1.56)	0.99–2.46
Gregoriou et al.	5/313 (1.60)	0.68–3.68	11/203 (5.42)	3.05–9.44
Golan et al.	16/548 (2.92)	1.81–4.69	7/576 (1.22)	0.59–2.49
Mossa et al.	10/209 (4.78)	2.62–8.58	0/142 (0)	
Wang et al.	23/426 (5.40)	3.62–7.97	6/340 (1.76)	0.81–3.80
Costa Paiva et al.	21/255 (8.24)	5.45–12.26	9/389 (2.31)	1.22–4.34
Kilicdag et al.	1/96 (1.04)	0.18–5.67	8/321 (2.49)	1.27–4.84
Cavkaytar et al.	26/328 (7.93)	5.47–11.36		
Elfayomy et al.	5/57 (8.77)	3.81–18.94	2/93 (2.15)	0.59–7.51
Lenci et al.	2/364 (0.55)	0.15–1.98	3/656 (0.46)	0.16–1.34
Litta et al.	28/267 (10.49)	7.36–14.74	19/546 (3.48)	2.24–5.37
Uglietti et al.	24/615 (3.90)	2.64–5.74	12/669 (1.79)	1.03–3.11
Bel et al.	20/338 (5.92)	3.86–8.96	10/293 (3.41)	1.86–6.17
Ciavattini et al.	5/61 (8.20)	3.55–17.80	7/85 (8.24)	4.05–16.04
Radowicka et al.	5/205 (2.44)	1.05–5.58	9/207 (4.35)	2.30–8.06
De Azavedo et al.	10/237 (4.22)	2.31–7.59	0/115 (0)	
Van Hanegem et al.	6/50 (12.0)	5.62–23.81		
Ghoubara et al.	24/421(5.70)	3.86–8.34		
Trojano et al.			0/197 (0)	
Namazov et al.			11/472 (2.33)	1.31–4.12
Shor et al.	19/144 (13.19)	8.61–19.69	6/153 (3.92)	1.81–8.29
<b>Total</b>	<b>452/9501 (4.76)</b>	<b>4.35–5.20</b>	<b>226/9838 (2.29)</b>	<b>2.02–2.61</b>

was 3.27 (95% CI: 2.50–4.12) with high heterogeneity among studies ( $P < .001$ ).

We performed subgroup analyses according to study region: in the meta-analysis selecting European studies the random pooled estimate was 3.60 (95% CI: 2.68–4.63) with high heterogeneity among studies ( $P < .001$ ). In the meta-analysis selecting American studies the random pooled estimate was 2.87 (95% CI: 1.03–5.48) with high heterogeneity among studies ( $P < .001$ ). In the meta-analysis selecting Asian studies the random pooled estimate was 2.86 (95% CI: 1.74–4.23) with high heterogeneity among studies ( $P < .001$ ).

We performed subgroup analyses according to calendar year of publication: in the meta-analysis selecting studies published from 2000 to 2009 the random pooled estimate was 3.46 (95% CI: 2.41–4.68) with high heterogeneity among studies ( $P < .001$ ). In the meta-analysis selecting studies where diagnosis was based on hysteroscopy the random pooled estimate was 3.12 (95% CI: 2.25–4.13) with high heterogeneity among studies ( $P < .001$ ).

## Discussion

Before discussing the results of this analysis, potential limitations should be considered.

The selected studies reported large differences in frequency of malignant condition; this fact can be explained by the patient selection and in the difference in studies design but we cannot completely explain in terms of clinical characteristics. In fact, also considering similar population we found statistically significant heterogeneity among studies also in subgroup analysis. Although absolute homogeneity among studies might appear desirable, it should not however preclude generalization to a broad clinical

population; nevertheless, understanding the sources of heterogeneity remains important.

Another limitation is the different way to classify polyps by the authors: in fact the diagnosis was based on ultrasound examination and/or hysteroscopy.

We considered only publications published in English. Authors may be more prone to publish in an international, English-language journal if results are more new and “exceptional” as, for example, characterized by particularly low or high rates of malignancy [62]. Another limitation is the limited sample size of several considered papers.

The results of this analysis confirm previous reviews showing a low rate (about 3%) of malignant conditions among patients with a diagnosis of uterine polyps [9,63]. However, in presence of symptomatic vaginal bleeding and postmenopausal status the proportion of malignant conditions increased: the risk of malignancy was about 5% among postmenopausal ones and about 5% among symptomatic ones. We observed higher rate of malignant polyps in prospective studies. This finding can be due to more strict diagnostic criteria in these studies. Taking into account potential difference in diagnostic criteria across the world and calendar period we performed subgroup analysis according to region (Europe, Asia and America) and calendar year of publication (2000–2009 and from 2010 to 2019).

The findings of the present systematic review have clinical implications in terms of balance between potential benefits, potential harms and costs. The potential benefit of surgery in asymptomatic women consists in the prevention of endometrial cancer deaths providing early diagnosis of the disease. The clinical risks include mainly the surgical ones.

The age of the patient may influence the decision independently of the operative risk. In fact, although in perimenopausal women the risk of malignancy is lower, in young women a long follow-up period should be anticipated if expectant management is chosen. This generally causes strict ultrasonographic follow up every 6–12 months. This introduces the issue of patient preferences. In fact, the planned length of follow-up may tip the balance in favor of expectant management or in favor of surgery. Some women, and possibly also some gynecologists, may be reluctant to discontinue surveillance after one to two years and, even after medical reassurance, individual psychological distress may be associated also with uncertainties regarding the no longer checked endometrial status. On the other hand, prolonging the follow-up indefinitely results in progressively unfavorable healthcare economic evaluations. When facing the same risk, different women may choose differently. The caring gynaecologists should explaining clearly the pros and cons of observation and surgery, defining risks and benefits in absolute terms. Within the context of a policy aimed at limiting oncological risk, the ultimate challenge is, on one hand, preventing overdiagnosis and overtreatment and, on the other hand, limiting the long-term burden of treatment associated with prolonged surveillance. The final choice should be individualized based on the combination of each patient's overall risk profile as well as personal priorities

In conclusion the balance between surgery and expectant management is always a clinical issue. The results of this analysis offer quantitative estimates in order to identify group of patients with a diagnosis of uterine polyps which may benefit of different clinical approach: surgery or expectant management.

#### Authors' contribution

Anna Uglietti: Protocol/project development, Manuscript writing/editing.

Laura Buggio: Data collection or management, Protocol/project development.

Marilena Farella: Data collection or management.

Francesca Chiaffarino: Data analysis, Manuscript writing/editing.

Dhouha Dridi: Data collection or management.

Paolo Vercellini: Protocol/project development.

Fabio Parazzini: Protocol/project development, Manuscript writing/editing.

#### Compliance with ethical standards

The Authors declare no conflict of interest.

The study does not contain any studies with human participants or animals performed by any of the authors.

Informed consent is not applicable in this study.

#### Conflict of interest

The authors declare that they have no conflict of interest.

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#### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ejogrb.2019.04.009>.

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