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Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women
A Systematic Review and Meta-analysis

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IMPORTANCE As the worldwide burden of endometrial cancer continues to rise, interest is growing in the evaluation of early detection and prevention strategies among women at increased risk. Focusing efforts on women with postmenopausal bleeding (PMB), a common symptom of endometrial cancer, may be a useful strategy; however, PMB is not specific for endometrial cancer and is often caused by benign conditions.

OBJECTIVE To provide a reference of the prevalence of PMB in endometrial cancers and the risk of endometrial cancer in women with PMB.

DATA SOURCES For this systematic review and meta-analysis, PubMed and Embase were searched for English-language studies published January 1, 1977, through January 31, 2017.

STUDY SELECTION Observational studies reporting the prevalence of PMB in women with endometrial cancer and the risk of endometrial cancer in women with PMB in unselected populations were selected.

DATA EXTRACTION AND SYNTHESIS Two independent reviewers evaluated study quality and risk of bias using items from the Newcastle-Ottawa Quality Assessment Scale and the Quality Assessment of Diagnostic Accuracy Studies tool. Studies that included highly selected populations, lacked detailed inclusion criteria, and/or included 25 or fewer women were excluded.

MAIN OUTCOMES AND MEASURES The pooled prevalence of PMB in women with endometrial cancer and the risk of endometrial cancer in women with PMB.

RESULTS A total of 129 unique studies, including 34 432 unique patients with PMB and 6358 with endometrial cancer (40 790 women), were analyzed. The pooled prevalence of PMB among women with endometrial cancer was 91% (95% CI, 87%-93%), irrespective of tumor stage. The pooled risk of endometrial cancer among women with PMB was 9% (95% CI, 8%-11%), with estimates varying by use of hormone therapy (range, 7% [95% CI, 6%-9%] to 12% [95% CI, 9%-15%]; $P < .001$ for heterogeneity) and geographic region (range, 5% [95% CI, 3%-11%] in North America to 13% [95% CI, 9%-19%] in Western Europe; $P = .09$ for heterogeneity).

CONCLUSIONS AND RELEVANCE Early detection strategies focused on women with PMB have the potential to capture as many as 90% of endometrial cancers; however, most women with PMB will not be diagnosed with endometrial cancer. These results can aid in the assessment of the potential clinical value of new early detection markers and clinical management strategies for endometrial cancer and will help to inform clinical and epidemiologic risk prediction models to support decision making.

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Invited Commentary
Supplemental content

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Endometrial cancer is the most common gynecologic cancer in developed countries and accounts for nearly 5% of cancer cases and more than 2% of deaths due to cancer in women worldwide.[1] In regions such as North America and parts of Europe, the incidence of endometrial cancer is disproportionately higher than in other developed countries, which may be attributed to higher rates of obesity, as well as other important risk factors such as aging, early menarche, late menopause, nulliparity, and postmenopausal estrogen therapy use.[2] Unlike most cancers, the incidence of endometrial cancer and associated mortality rates have increased in recent years[3-7] and are projected to rise during the next 10 years.[8-11]

Most endometrial cancers are diagnosed at a localized stage and are often curable with surgery, with a 5-year survival of approximately 95%. In contrast, 5-year survival for late-stage (stage IV) endometrial cancer ranges from 16% to 45%.[12-14] However, studies evaluating early detection strategies for endometrial cancer are lacking, and at present no recommendation for population-based screening exists. In the era of precision prevention, emphasis on identifying individuals at high risk to maximize the positive outcomes of clinical interventions while avoiding unnecessary harms is growing.[15-17] Rather than targeting the whole population, early detection strategies for endometrial cancer could focus on women at high risk of developing endometrial cancer, while excluding most women at low risk. Postmenopausal bleeding (PMB) is a common symptom of endometrial cancer and accounts for approximately two-thirds of all gynecologic visits among perimenopausal and postmenopausal women.[18] Women presenting with PMB undergo additional clinical testing using a combination of transvaginal ultrasonography (TVUS), hysteroscopy, endometrial biopsy, and/or dilation and curettage, and workup varies widely among different settings.[18-20] However, PMB is often associated with benign conditions such as endometrial polyps or may result from unscheduled bleeding in women using hormone therapy (HT).[18,21] The risk of endometrial cancer in women with PMB varies widely in individual studies from 3% to 25%.[22-27]

Accurate estimates of the prevalence of PMB in endometrial cancers (equal to the sensitivity of PMB for detecting endometrial cancer) and the risk of endometrial cancer in women with PMB (equal to the positive predictive value [PPV] of PMB for detecting endometrial cancer) are needed to evaluate whether targeting women with PMB for early detection is a useful strategy, particularly because endometrial cancer rates are increasing in the population. A high sensitivity of PMB would ensure that most cases of endometrial cancer are being captured by targeting this population. A high PPV of PMB, which translates into a low number needed to diagnose (1/PPV) to find 1 case of endometrial cancer, would support diagnostic workup of women with PMB, whereas a low PPV would signify the need for additional triage to improve performance of early detection. Furthermore, these estimates would provide the foundation for evaluating clinical and epidemiologic risk prediction models[28] and are necessary for evaluating novel molecular markers that are currently under development against established methods.[29-33]

We conducted a systematic review and meta-analysis to evaluate the prevalence of PMB in women with endometrial cancer and the risk of endometrial cancer among women with PMB. Our estimates could inform the evaluation of clinical scenarios to assess the utility of early detection strategies for endometrial cancer.

Key Points

Question What is the prevalence of postmenopausal bleeding in women with endometrial cancer and the risk of endometrial cancer in women with postmenopausal bleeding?

Findings This systematic review and meta-analysis of 40 790 unique patients in 129 unique studies suggests that postmenopausal bleeding occurs in approximately 90% of women with endometrial cancer; however, only 9% of women with postmenopausal bleeding were diagnosed with endometrial cancer. These estimates varied by geographic region, hormone use, and calendar time.

Meaning These findings provide a foundation for evaluating early detection strategies for endometrial cancer and can support risk-informed decision making in clinical management of postmenopausal bleeding.

Methods

Search Strategy and Selection Criteria

We conducted this systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (eFigure 1 in the Supplement).[34] We included original studies with primary data reporting the prevalence of PMB in women with endometrial cancer and the risk of endometrial cancer among women with PMB. We searched English-language, peer-reviewed studies published before February 1, 2017, in the MEDLINE database via PubMed and Embase using search terms described in eMethods in the Supplement. We also reviewed the reference lists of articles identified in the primary search for additional relevant studies. Titles and abstracts were independently screened for inclusion by 3 investigators (M.A.C., A.D.M., and B.J.L.). Full-text versions of eligible articles were reviewed by 2 investigators (M.A.C. and B.J.L.) to determine eligibility; any questions regarding the inclusion of studies were resolved by the senior author (N.W.). We evaluated data on patient selection criteria, sample size, and exposure and outcome ascertainment to determine study quality and generalizability; we excluded studies that included special populations (eg, defined by comorbid conditions or specific histologic findings), lacked detailed inclusion criteria, and/or included 25 or fewer women.

Data Extraction and Quality Assessment

We extracted information on aggregate study-level participant characteristics (age, body mass index, years since menopause, parity, frequency of bleeding, HT use, tamoxifen use, and other comorbidities) and endometrial biopsy results, including stage and histologic data when available. Geographic regions were defined by the World Health Organization for those with 2 or more countries represented.[1] Study designs were classified as retrospective

or prospective if follow-up time was specified or as cross-sectional (or case series). We assessed study quality using items from the Newcastle-Ottawa Quality Assessment Scale[35] and the Quality Assessment of Diagnostic Accuracy Studies tool[36] (eMethods in the Supplement). We provide the detailed algorithms of how PMB was evaluated for each study in eTable 1 in the Supplement. Studies were classified as having potential verification bias if receipt or interpretation of the diagnostic test (eg, endometrial biopsy) depended on the results of a prior clinical test (eg, TVUS) (eMethods in the Supplement).

Data Synthesis and Analysis

We estimated pooled prevalence and 95% CIs using multilevel logistic-normal random-effects models to account for interstudy heterogeneity. Between-study variance was quantified using the τ^2 statistic.[37,38] We visualized variation in study-specific estimates using forest plots and performed subgroup analyses (described in eMethods in the Supplement) to evaluate the influence of (1) study exclusion criteria for HT use (analysis of risk of endometrial cancer in women with PMB only); (2) geographical region; and (3) study enrollment period, using the last year of study enrollment or publication date as a proxy, grouped as before 1990, 1990 to 1999, 2000 to 2009, and 2010 to 2017. We use the *P* value for heterogeneity to compare subgroup estimates, with significance at $P < .05$. The influence of continuous study-level (mean) characteristics, including age, years since menopause, and percentage using HT, was explored using multilevel logistic random-effects models for studies with available data. We conducted sensitivity analyses to assess the influence of clinical setting (tertiary center vs other), study design, and the potential for publication bias using Egger regression analyses.[29] For the analysis of the prevalence of PMB in women with endometrial cancer, we excluded 2 studies[39,40] that selected cases based on stage at diagnosis; however, these studies were included in the stage-specific analysis. For the analysis of the risk of endometrial cancer among women with PMB, we conducted a secondary analysis in a subset of 10 studies[41-50] that excluded women with measurements below a minimum endometrial thickness determined by TVUS (range, 4-5 mm) and a separate subset of 7 studies[51-57] that evaluated the risk of endometrial cancer in women with polyps.

As an ancillary analysis, we simulated the performance of 2 approaches for early detection of endometrial cancer in a hypothetical population of 10 000 women with PMB to demonstrate how our results can be used to evaluate current testing strategies and the potential clinical value of early-stage biomarkers for endometrial cancer detection: TVUS (cutoff of ≤3 mm), which is a well-established, clinically validated test,[18] and an experimental methylation marker assay[31,32] (eMethods in the Supplement). All analyses were performed in Stata, version 13 (StataCorp). For pooling of proportions, we used the program metaprop_one.[38]

Results

We identified 2398 studies, of which 129 were eligible for our analysis,[22-27,39-162] with 40 790 unique patients, including 1 study[58] that was eligible for both analyses (overlap of 45 women with endometrial cancers and 45 women with PMB) (eFigure 1 in the Supplement). Studies were published from January 1, 1977, through January 1, 2017, and most were cross-sectional and conducted in Northern (26 [20.2%]) and Southern Europe (24 [18.6%]). Among eligible studies, 21[39,40,58-72,74-77] were included for analysis of the prevalence of PMB in women with endometrial cancer (3792 cases of endometrial cancer, of which 3257 were in women with PMB, including the 2 studies restricted to stages III-IV cancers[39,40]) and 92[22-27,58,78-162] were included for analysis of the risk of endometrial cancer in women with PMB (31 220 women with PMB and 2611 cases of endometrial cancer).

Prevalence of PMB in Women With Endometrial Cancer

Study-specific and pooled estimates of the prevalence of PMB in women with endometrial cancer are shown in **Figure 1**. The prevalence of PMB was 90% (95% CI, 84%-94%), with substantial between-study variance ($\tau^2 = 1.14$). Removal of a potential outlier[74] resulted in a similar pooled prevalence of 91% (95% CI, 87%-93%), but strong reduction of variance between studies ($\tau^2 = 0.47$); therefore we excluded the outlier study from the remaining analyses. Among 5 studies[66,70,72,75,76] with information on stage I tumors, the proportion of PMB was 94% (95% CI, 72%-99%; $\tau^2 = 4.03$). Among the 7 studies[39,40,66,70,72,75,76] with information on stages II to IV tumors, the proportion of PMB was 84% (95% CI, 71%-92%; $\tau^2 = 0.93$). We found no significant difference in prevalence of PMB by stage ($P = .20$ for heterogeneity) (eFigure 2 in the Supplement).

In an analysis stratified by geographic region, the prevalence of PMB ranged from 94% (95% CI, 84%-97%) in North America to 90% in Western Asia (95% CI, 85%-94%) and Eastern Asia (95% CI, 83%-94%) ($P = .55$ for heterogeneity) (eFigure 3 in the Supplement). The pooled prevalence of PMB among women with endometrial cancer varied significantly by study enrollment period ($P < .001$ for heterogeneity). The prevalence of PMB in women with endometrial cancer was higher in studies that enrolled women before 1990 (94%; 95% CI, 92%-95%) and in 1990 to 1999 (96%; 95% CI, 87%-99%) compared with studies that enrolled women in 2000 to 2009 (85%; 95% CI, 78%-90%) and in 2010 to 2017 (86%; 95% CI, 82%-90%) (eFigure 4 in the Supplement).

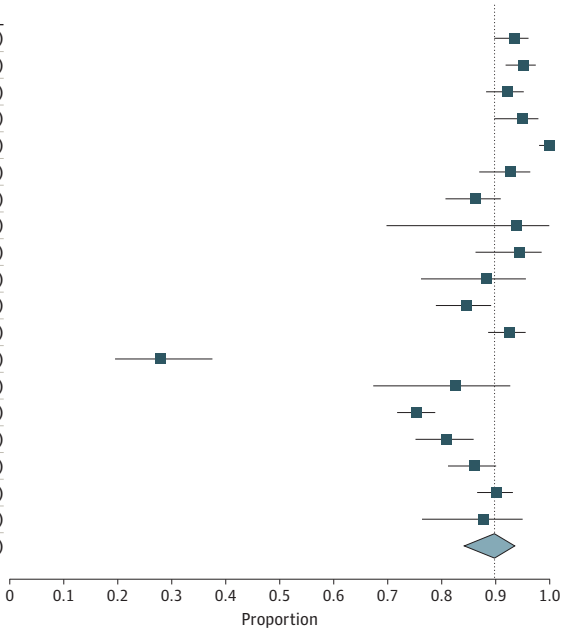
In a sensitivity analysis restricted to 11 studies[59,62,64,66-68,70-72,75,76] (67%) that ascertained PMB through retrospective medical record review, the pooled prevalence of PMB was 91% (95% CI, 85%-94%), similar to our overall findings. The prevalence of PMB did not vary significantly by clinical setting. No evidence of publication bias was found among studies reporting the prevalence of PMB in women with endometrial cancer (Egger regression intercept, 0.15; $P = .90$).

Risk of Endometrial Cancer in Women With PMB

Study-specific and pooled estimates of the risk of endometrial cancer in women with PMB are shown in **Figures 2** and **3**. In 92 studies,[22-27,58,78-162] the risk of endometrial cancer ranged from 0% to 48%, yielding an overall pooled estimate of 9% (95% CI, 8%-11%), with moderate variability observed between studies ($\tau^2 = 0.56$).

Figure 1. Prevalence of Postmenopausal Bleeding (PMB) in Women With Endometrial Cancer

Source	ES (95% CI)
Sharon et al,[64] 1977	0.93 (0.90-0.96)
Horwitz and Feinstein,[61] 1978	0.95 (0.92-0.97)
Hulka et al,[65] 1980	0.92 (0.88-0.95)
Franceschi et al,[60] 1983	0.95 (0.90-0.98)
Liu et al,[66] 1995	1.00 (0.98-1.00)
Krissi et al,[76] 1996	0.93 (0.87-0.96)
Piura et al,[67] 1997	0.86 (0.81-0.91)
Tsuda et al,[69] 1997	0.94 (0.70-1.00)
Schneider et al,[68] 1998	0.94 (0.86-0.98)
Ciatto et al,[58] 2002	0.88 (0.76-0.96)
Kimura et al,[75] 2004	0.85 (0.79-0.89)
Kodama et al,[59] 2005	0.93 (0.88-0.96)
Dvalishvili et al,[74] 2006	0.28 (0.20-0.38)
Le et al,[63] 2009	0.82 (0.67-0.93)
Seebacher et al,[72] 2009	0.75 (0.72-0.79)
Barak et al,[70] 2013	0.81 (0.75-0.86)
Chandavarkar et al,[71] 2013	0.86 (0.81-0.90)
Khunnarong et al,[62] 2016	0.90 (0.86-0.93)
Pakish et al,[77] 2016	0.88 (0.76-0.95)
LR test random- vs fixed-effects model; χ^2 = 303.9: *P*<.001	0.90 (0.84-0.94)



The pooled prevalence of PMB is indicated by the dotted line. ES indicates effect size; LR, likelihood ratio; and diamond, pooled risk.

The pooled risk of endometrial cancer was significantly higher among the 41 studies[22,24,58,82,89,92-94,98,99,101-106,112,115,116,118,120,121,127,133,136-138,140,141,143-147,149,150,152,158,160-162] that excluded women using HT (12%; 95% CI, 9%-15%; τ^2 = 0.64) (**Figure 4**) compared with the 51 studies that included women using HT[21,23,25-27,78-81,83-88,90,91,95-97,100,107-111,113,114,117,119,122-126,128-131,134,135,139,142,148,151,153-157,159] (7%; 95% CI, 6%-9%; τ^2 = 0.38; *P* < .001 for heterogeneity) (eFigure 8 in the Supplement).

The risk of endometrial cancer in women with PMB was lowest in North America (5%; 95% CI, 3%-11%; τ^2 = 0.78) and Northern Europe (7%; 95% CI, 5%-8%; τ^2 = 0.24) and highest in Western Europe (13%; 95% CI, 9%-19%; τ^2 = 0.61) (*P* = .09 for heterogeneity) (eFigure 5 in the Supplement). In an analysis restricted to European countries only, the risk of endometrial cancer was significantly higher in Western Europe compared with Northern and Southern Europe (*P* = .03 for heterogeneity). After stratifying by exclusion of women who used HT, significant regional differences persisted in both strata (*P* = .02 for heterogeneity in studies that included women using HT; *P* < .001 for heterogeneity in studies that excluded women using HT).

The risk of endometrial cancer was significantly higher in studies with enrollment periods before 1990 (13%; 95% CI, 10%-17%; τ^2 = 0.18) and in 1990 to 1999 (11%; 95% CI, 8%-13%; τ^2 = 0.57) compared with 2000 to 2009 (7%; 95% CI, 5%-9%; τ^2 = 0.47) and 2010 to 2017 (8%; 95% CI, 5%-12%; τ^2 = 0.59) (*P* < .001 for heterogeneity) (eFigure 6 in the Supplement). The risk of endometrial cancer was not significantly associated with mean age, number of years since menopause, and percentage of women using HT.

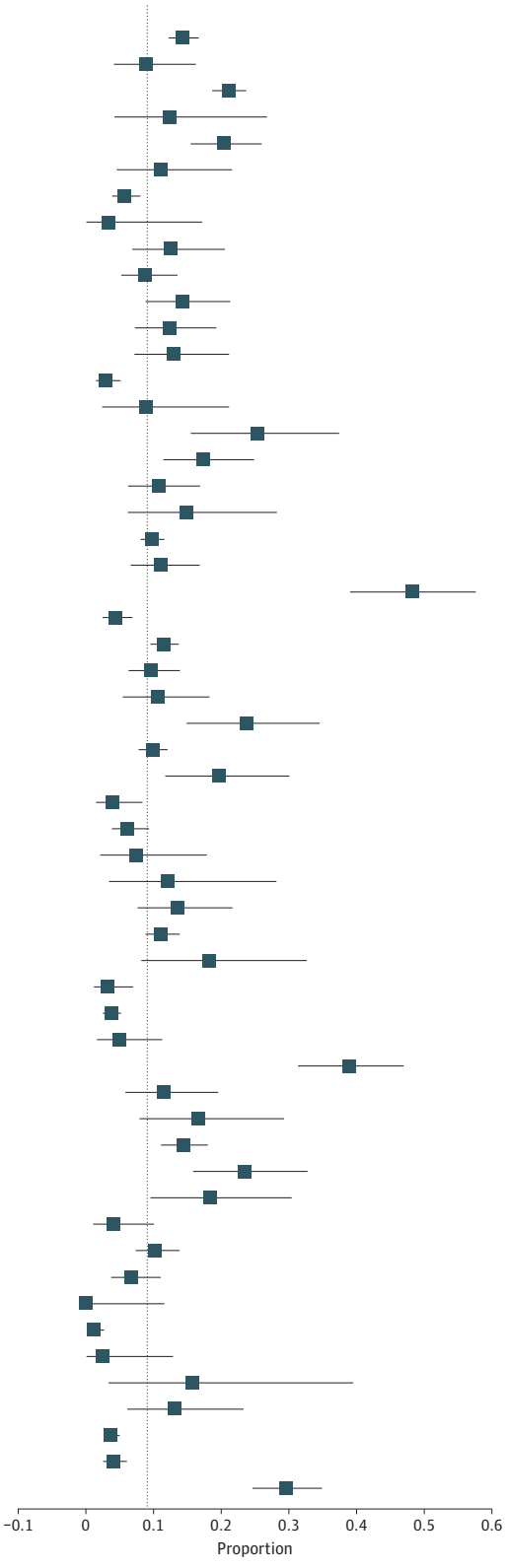
The risk of endometrial cancer was significantly lower in prospective[22,26,27,58,88,105,122-124,135,138-140,150] (6%; τ^2 = 0.34) and retrospective[23,25,83,94,97,113,125,131,134,147,148,151,153,155,158,161] (6%; τ^2 = 0.37) studies compared with cross-sectional studies[78-82,84-87,90-93,95,96,98-104,106-112,114-121,126-130,132,133,136,137,141-146,149,152,154,156,157,159,160,162] (11%; τ^2 = 0.49; *P* < .001 for heterogeneity) and was significantly higher in 6 studies[24,110,121,130,152,157] conducted in tertiary centers (23%; 95% CI, 17%-31%; τ^2 = 0.18; *P* < .001 for heterogeneity), compared with studies conducted in other settings. Evidence of publication bias suggested that small studies may overestimate the risk of endometrial cancer in women with PMB (Egger regression intercept, 0.75; *P* = .001). In an analysis based on the assessment of study quality, verification bias could be excluded in 71 studies[24-26,58,78,79,81-96,98-106,108,110-115,117-122,125,126,128,130-133,135-137,139-141,143-147,149,150,152,154,156-158,161,162] and was potentially present in 13 studies[22,27,107,109,123,124,127,129,138,142,148,155,159] (8 were unclear). The risk of endometrial cancer was significantly lower in studies with potential verification bias (6%; 95% CI, 4%-9%) compared with those with no verification bias (10%; 95% CI, 8%-12%) (eTable 2 and eFigure 7 in the Supplement).

In the 10 studies[41-50] that included women with PMB and a minimum endometrial thickness (n = 2087), the pooled risk of endometrial cancer was 19% (95% CI, 14%-25%; τ^2 = 0.28). In 7 studies[51-57] restricted to women with PMB and polyps (n = 2801), the pooled risk of endometrial cancer was 3% (95% CI, 3%-4%; τ^2 = 0).

To demonstrate how the estimates from this meta-analysis can be used to evaluate strategies for endometrial cancer detection in women with PMB, we evaluated the performance of TVUS, a well-established clinical test for evaluating PMB[18] and an experimental methylation assay for endometrial cancer detection[31,32] in a hypothetical population of 10 000 women with PMB. We evaluated endometrial cancer risk estimates of 5%, 10%, and 15%, representing the range of risks observed in different geographic regions

Figure 2. Risk of Endometrial Cancer in Women With Postmenopausal Bleeding

Source	ES (95% CI)
Mantalenakis et al,[25] 1977	0.14 (0.12-0.17)
Swingler et al,[78] 1979	0.09 (0.04-0.16)
Schindler and Schmidt,[23] 1980	0.21 (0.19-0.24)
Goldberg et al,[79] 1982	0.13 (0.04-0.27)
Alberico et al,[81] 1989	0.20 (0.16-0.26)
Nasri and Coast,[80] 1989	0.11 (0.05-0.22)
Allen et al,[83] 1990	0.06 (0.04-0.08)
Goldstein et al,[85] 1990	0.03 (0.00-0.17)
Osmers et al,[82] 1990	0.13 (0.07-0.21)
Granberg et al,[84] 1991	0.09 (0.05-0.14)
White,[86] 1991	0.14 (0.09-0.21)
Auslender et al,[89] 1993	0.12 (0.07-0.19)
Dørum et al,[87] 1993	0.13 (0.07-0.21)
Lin et al,[88] 1993	0.03 (0.01-0.05)
Cacciatore et al,[91] 1994	0.09 (0.02-0.21)
Chan et al,[92] 1994	0.25 (0.16-0.37)
Sladkevicius et al,[90] 1994	0.17 (0.11-0.25)
Conoscenti et al,[94] 1995	0.11 (0.06-0.17)
Emanuel et al,[95] 1995	0.15 (0.06-0.28)
Karlsson et al,[96] 1995	0.10 (0.08-0.12)
Lee et al,[97] 1995	0.11 (0.07-0.17)
Malinova and Pehlivanov,[93] 1995	0.48 (0.39-0.58)
Cecchini et al,[100] 1996	0.04 (0.03-0.07)
Ferrazzi et al,[98] 1996	0.12 (0.10-0.14)
Grigoriou et al,[102] 1996	0.10 (0.06-0.14)
Gruboeck et a[105] 1996	0.11 (0.05-0.18)
Giusa-Chiferi et al,[110] 1996	0.24 (0.15-0.35)
Güner et al,[108] 1996	0.10 (0.06-0.15)
Haller et al,[99] 1996	0.20 (0.12-0.30)
Nagele et al,[103] 1996	0.04 (0.01-0.08)
Valli et al,[107] 1996	0.06 (0.04-0.09)
Wolman et al,[101] 1996	0.07 (0.02-0.18)
Bronz et al,[109] 1997	0.12 (0.03-0.28)
Fistonic et al,[104] 1997	0.14 (0.08-0.22)
Iatrakis et al,[111] 1997	0.11 (0.09-0.14)
Kekre et al,[106] 1997	0.18 (0.08-0.33)
Briley et al,[116] 1998	0.03 (0.01-0.07)
Gemer et al,[113] 1998	0.04 (0.03-0.05)
O'Connell et al,[114] 1998	0.05 (0.02-0.11)
Weber al,[112] 1998	0.39 (0.31-0.47)
Bakour et al,[117] 1999	0.11 (0.06-0.20)
Büyük et al,[115] 1999	0.17 (0.08-0.29)
Garuti et al,[119] 1999	0.14 (0.11-0.18)
Loverro et al,[118] 1999	0.24 (0.16-0.33)
Amit et al,[121] 2000	0.18 (0.10-0.30)
Bree et al,[122] 2000	0.04 (0.01-0.10)
Gull et al,[123] 2000	0.10 (0.07-0.14)
Sheikh et al,[120] 2000	0.07 (0.04-0.11)
Cameron et al,[126] 2001	0.00 (0.00-0.12)
Dunn et al,[124] 2001	0.01 (0.00-0.03)
Hunter and McClure,[125] 2001	0.02 (0.00-0.13)
Jones and Bourne,[127] 2001	0.16 (0.03-0.40)
Sousa et al,[128] 2001	0.13 (0.06-0.23)
Ciatto et al,[58] 2002	0.04 (0.03-0.05)
Panda,[129] 2002	0.04 (0.03-0.06)
Randelzhofer et al,[24] 2002	0.30 (0.25-0.35)



The pooled risk of endometrial cancer in all 92 studies is indicated by the dotted line. ES indicates effect size.

(**Table**). We show the magnitude of the increase in PPV of both tests with increasing risk of endometrial cancer in women with PMB, supporting the evaluation of early-detection strategies in various populations.

Figure 3. Risk of Endometrial Cancer in Women With Postmenopausal Bleeding

Source	ES (95% CI)
Yaman et al,[130] 2002	0.10 (0.03-0.21)
Arslan et al,[133] 2003	0.07 (0.03-0.13)
Bachman et al,[135] 2003	0.04 (0.03-0.07)
Elliot et al,[131] 2003	0.03 (0.02-0.05)
Mossa et al,[132] 2003	0.09 (0.06-0.14)
de Wit et al,[134] 2003	0.04 (0.02-0.08)
Bruchim et al,[137] 2004	0.09 (0.04-0.17)
Critchley et al,[26] 2004	0.04 (0.01-0.07)
Phillip et al,[136] 2004	0.11 (0.05-0.20)
Litta et al,[139] 2005	0.06 (0.03-0.10)
Minagawa et al,[138] 2005	0.18 (0.08-0.34)
Wilailak et al,[140] 2005	0.10 (0.04-0.19)
Spicer et al,[142] 2006	0.05 (0.02-0.11)
Taşkin et al,[141] 2006	0.09 (0.04-0.16)
Mansour et al,[143] 2007	0.16 (0.11-0.22)
van Doorn et al,[22] 2007	0.10 (0.08-0.13)
Yildirim et al,[144] 2007	0.14 (0.07-0.25)
Tinelli et al,[145] 2008	0.02 (0.01-0.04)
Yaman et al,[146] 2008	0.20 (0.15-0.27)
Sadoon et al,[147] 2007	0.05 (0.02-0.10)
Ewies and Musonda,[148] 2010	0.06 (0.03-0.09)
Jillani et al,[149] 2010	0.16 (0.07-0.29)
Liberis et al,[150] 2010	0.05 (0.03-0.08)
Menzies et al,[151] 2011	0.05 (0.03-0.08)
Zaki et al,[152] 2011	0.38 (0.30-0.46)
Burbos et al,[27] 2012	0.06 (0.05-0.07)
Cho et al,[156] 2013	0.10 (0.06-0.16)
Damle et al,[154] 2013	0.10 (0.02-0.26)
Ragupathy et al,[153] 2013	0.05 (0.04-0.07)
Abid et al,[157] 2014	0.09 (0.02-0.21)
Kim et al,[160] 2015	0.16 (0.11-0.22)
Loiacono et al,[158] 2015	0.10 (0.06-0.15)
Van den Bosch et al,[159] 2015	0.07 (0.05-0.09)
Ozer et al,[161] 2016	0.05 (0.01-0.16)
Seckin et al,[162] 2016	0.03 (0.01-0.06)
Wong et al,[155] 2016	0.04 (0.03-0.04)
LS test: random- vs fixed-effects model: χ^2 = 1153.3; *P*<.001	0.09 (0.08-0.11)

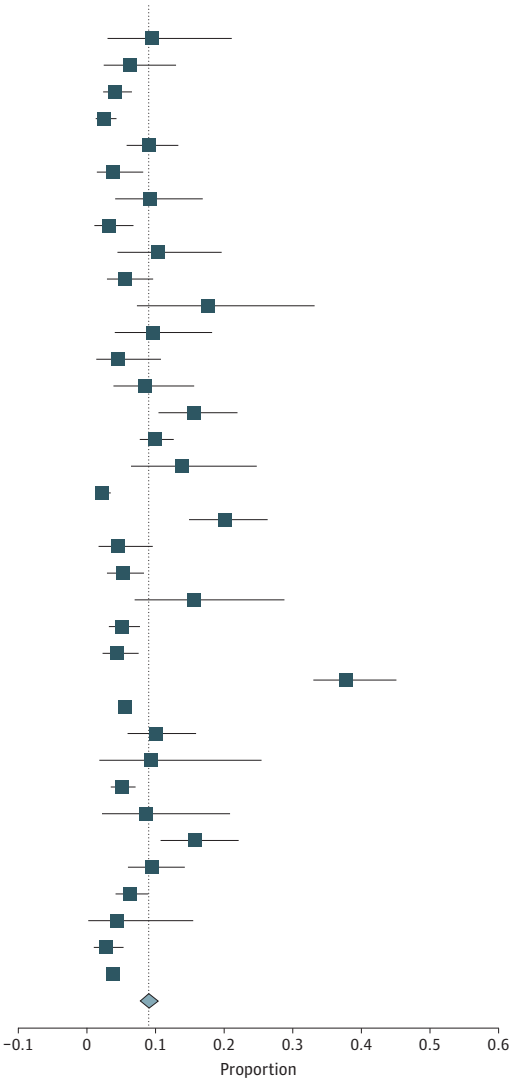


Figure 3 is a continuation of Figure 2. The pooled risk of endometrial cancer in all 92 studies is indicated by the dotted line. ES indicates effect size; LR, likelihood ratio; and diamond, pooled risk.

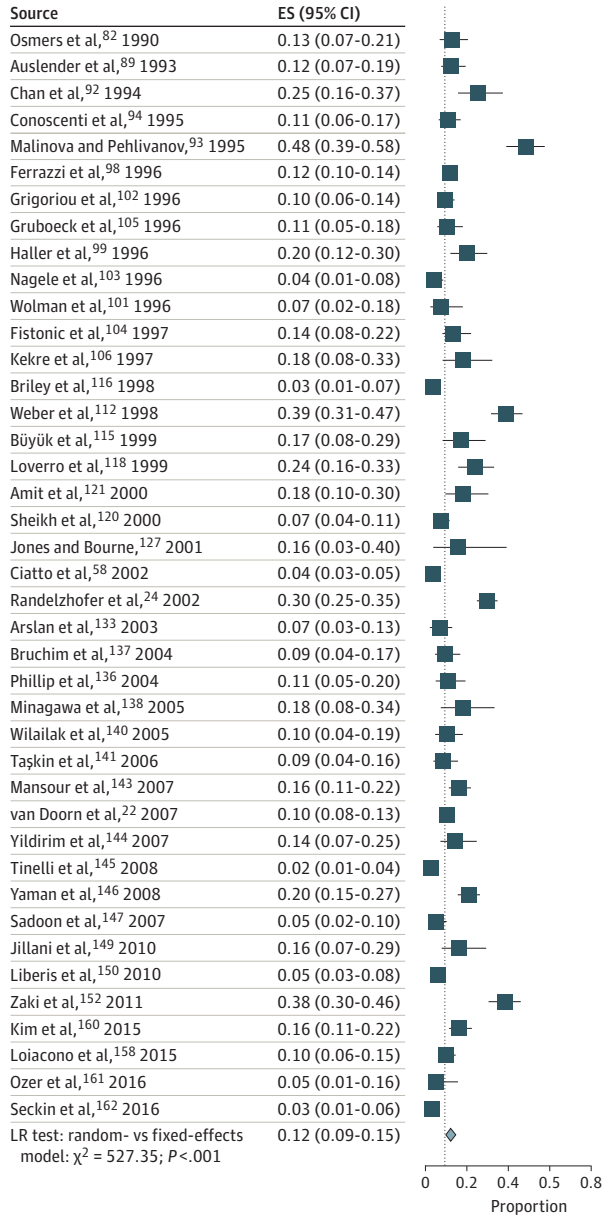
Discussion

The projected rise in endometrial cancer incidence and mortality underscores the importance of strategies for early detection and prevention. Focusing on women at highest risk of endometrial cancer can greatly improve the performance of a diagnostic test and avoid unnecessary testing and associated harms among women at low risk. Our systematic review and meta-analysis demonstrates that PMB is very sensitive for endometrial cancer detection, occurring in approximately 90% of cases. However, our findings indicate that among women with PMB, only approximately 9% will be diagnosed with endometrial cancer, with estimates varying substantially by HT use, geographic region, and the presence of endometrial polyps. Current practice guidelines recommend workup to rule out endometrial cancer among all women with PMB. Our findings support this recommendation by providing reassurance that targeting this high-risk group of women for early detection and prevention strategies will capture most endometrial cancers. However, the low PPV of PMB emphasizes the need for additional triage tests with high specificity to improve management of PMB and avoid unnecessary biopsies in low-risk women.

The prevalence of PMB in endometrial cancer and the risk of endometrial cancer in women with PMB were higher before 2000 compared with after 2000. When interpreting these results, it is important to distinguish population risk, which has generally increased over time, from the risk in women with PMB. The number of endometrial cancers without PMB and the number of women with PMB with benign conditions may both have increased over time. This increase could be influenced by factors such as changes in HT use, changes in prevalence of obesity, or changes in clinical management thresholds for abnormal bleeding.

The risk of endometrial cancer among women with PMB was notably lower in studies that included HT users compared with those that excluded these women. Use of HT may

Figure 4. Risk of Endometrial Cancer in Women With Postmenopausal Bleeding in Studies That Excluded Women Using HT



The pooled risk of endometrial cancer in all 92 studies is indicated by the dotted line. ES indicates effect size; HT, hormone therapy; LR, likelihood ratio; and diamond, pooled risk.

affect this association at multiple levels. Certain combined formulations of estrogen plus progestin therapy are established to have a protective effect on the endometrium.[163] Furthermore, irregular uterine bleeding is a common adverse effect of HT, particularly within the first 6 months of use.[164] The underlying causes of HT-induced bleeding is thought to involve changes in the size of endometrial blood vessels and regulation of vascular growth and integrity.[165] Because this type of bleeding is generally not associated with abnormal endometrial histologic findings, most guidelines recommend against clinical workup of women using HT who experience irregular uterine bleeding within the first 6 months. However, little consensus exists about how to best treat these women if bleeding persists, and a considerable number of women with HT-associated bleeding will undergo procedures to rule out endometrial cancer.[165] Our data emphasize the importance of considering a woman's HT status to inform clinical decision making, potentially supporting a less aggressive management approach in HT users.

We noted striking geographic differences in endometrial cancer risk among women with PMB, ranging from 13% in Western Europe to 5% in North America and 7% in Northern Europe. At present, consensus regarding the optimal approach for evaluating PMB is lacking. Practice may vary depending on resources, clinical expertise and judgment, and patient preferences. The threshold for evaluating PMB may be lower in North American countries compared with other countries in Europe and elsewhere. In many European countries, guidelines recommend TVUS as the first-line test, with histologic assessment indicated for women with a thickened endometrium based on cutoffs ranging from 3 to 5 mm.[18,166,167] In the United States, guidelines recommend TVUS or endometrial biopsy as the first step in evaluating PMB.[19] In sensitivity analyses, we observed a lower risk of endometrial cancer in studies with partial disease verification (ie, not all women received a biopsy) compared with studies with complete diagnostic verification, suggesting that disease may have been missed in women with negative findings for the first-line test (eg, TVUS). However, we cannot exclude that in some settings, women only received a first-line test such as TVUS if they had a lower risk of endometrial cancer. In the subset of studies included in our meta-analysis that included women with PMB and a minimum endometrial thickness, the pooled risk of endometrial cancer was 19%, more than double the risk observed in our main analysis.

Our findings also suggest substantial variation in the risk of endometrial cancer depending on the underlying cause of PMB. Endometrial polyps are one of the most common causes of PMB. Although polyps have been associated with risk of endometrial cancer in women with PMB,[168] other studies have suggested that this association is more likely attributed to detection bias, resulting from incidental findings during the diagnostic workup of PMB caused by endometrial polyps.[169] Our meta-analysis confirms a lower risk of endometrial cancer among women with PMB and polyps.

Strengths and Limitations

To our knowledge, this systematic review and meta-analysis is the first to evaluate the prevalence of PMB in endometrial cancer and the risk of endometrial cancer in women with PMB, 2 important variables for evaluating the role of PMB in early detection of endometrial cancer. Our findings can support risk-informed decision making in clinical management of women with PMB. As an example, we simulated the performance of TVUS, an established diagnostic tool, and methylation markers, an early-phase biomarker, for early detection of endometrial cancer. We provided estimates of how many women would be referred for endometrial biopsy for combinations of endometrial cancer risk

Table. Clinical Performance of Transvaginal Ultrasonography and an Experimental Assay for Endometrial Cancer Detection Across Risk Estimates in a Hypothetical Population of 10 000 Women With PMB[a]

Endometrial Cancer Risk in PMB, %	Test Sensitivity, %	Test Specificity, %	PPV, %	cNPV, %	No. of Patients With Biopsy	No. of Biopsies per case of Cancer
5						
Transvaginal ultrasonography	98.0	35.0	7.4	0.3	6665	13.6
Methylation assay	90.0	50.0	8.7	1.0	5200	11.6
10						
Transvaginal ultrasonography	98.0	35.0	14.3	0.3	6830	7.0
Methylation assay	90.0	50.0	16.7	2.2	5400	6.0
15						
Transvaginal ultrasonography	98.0	35.0	21.0	1.0	6995	4.8
Methylation assay	90.0	50.0	24.1	3.4	5600	4.1

Abbreviations: cNPV, complement of the negative predictive value; PMB, postmenopausal bleeding; PPV, positive predictive value.

[a] Assumes 10 000 women with PMB; sensitivity and specificity estimates for transvaginal ultrasonography and methylation were obtained from the literature.

in women with PMB, and we showed how many women would need to undergo endometrial biopsy to identify 1 case.

However, a few study limitations are worth noting. In general, data on study-level variables such as years since menopause and body mass index were inconsistently reported, limiting our ability to evaluate them. In addition, insufficient data were available to explore differences by histologic findings, stage, and grade. Whether cancers with more favorable histologic findings (eg, endometrioid type I tumors) are more likely to present with PMB compared with more aggressive histologic subtypes (eg, serous type II tumors) remains unknown. Our results suggest that approximately 10% of women diagnosed with endometrial cancer do not present with PMB. Given the cross-sectional nature of most studies included in this meta-analysis, additional studies linking clinical records with cancer registry data may be warranted to validate our findings. With respect to the analysis of the risk of endometrial cancer in women with PMB, most studies were cross-sectional, and few included prospective follow-up; thus, we were unable to evaluate long-term risk of endometrial cancer in these studies. Finally, our results suggested a lower prevalence of endometrial cancer in retrospective and prospective cohort studies compared with cross-sectional studies. Cross-sectional studies may have been more likely to include women with recurrent bleeding; however, few studies distinguished between incident vs recurrent PMB.

Conclusions

The widespread practice of referring all women with PMB for TVUS and/or endometrial biopsy carries a considerable burden and cost. Given the rise in endometrial cancer incidence and mortality, our findings raise the important question of how to best manage PMB to optimize the benefit of early detection approaches while avoiding unnecessary harms. Interest has increased in the use of biomarkers, such as DNA methylation, to improve early detection of endometrial cancer.[31,32,170,171] To obtain reliable estimates of the clinical performance of molecular assays, diagnostic tests, and management algorithms, we must know the prior risk of endometrial cancer in the population.[29,172]

Our study represents an important and timely evaluation of the risk of endometrial cancer in women with PMB and can serve as a reliable reference for the prevalence of PMB in women with endometrial cancer and the risk of endometrial cancer in women with PMB, 2 requisite prior probabilities for prediction of endometrial cancer risk and secondary and tertiary prevention. As new markers are discovered or new clinical management strategies are evaluated, our results can aid in the assessment of their potential clinical value and will help to inform clinical and epidemiologic risk prediction models to support clinical decision making.

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