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OBESITY AND ENDOMETRIAL HYPERPLASIA AND CANCER IN PREMENOPAUSAL WOMEN: A SYSTEMATIC REVIEW

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ABSTRACT

Background: *Endometrial cancer (EC) represents the most common malignancy of the female reproductive tract. The precursor lesion for endometrioid adenocarcinoma of the endometrium, which comprises the majority of ECs, is endometrial hyperplasia (EH). EH is a noninvasive, abnormal proliferation of the endometrial lining of the uterus and associated with a significant risk of concurrent EC or progression to EC. The leading symptoms of EH are bleeding disorders in premenopausal women and vaginal bleeding in postmenopausal women. The most important risk factor is chronic exposure to unopposed estrogen.*

The aim: *This study aims to show obesity and endometrial hyperplasia and cancer in premenopausal women.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 81 articles, whereas the results of our search on SagePub brought up 112 articles. The results of the search conducted for the last year of 2013 yielded a total 29 articles for PubMed and 78 articles for SagePub. The result from title screening, a total 5 articles for PubMed and 13 articles for SagePub. In the end, we compiled a total of 8 papers. We included five research that met the criteria.*

Conclusion: *The nomogram of EH/EC is significantly associated with risk factors, namely BMI, PCOS, anemia, infertility, menostaxis, AUB type, and endometrial thickness. The nomogram model can be used to predict the EH/EC risk and rapidly screen risk factors in a women population with high risk.*

Keyword: *Endometrial hyperplasia, endometrial cancer, obesity, premenopausal.*

INTRODUCTION

Endometrial hyperplasia (EH) involves an increase in the number of endometrial linings due to structural changes in endometrial glands and an imbalance (> 1:1) of glands and stroma. EH is associated with the risk of progression to endometrial endometrioid cancer (EEC). The incidence of EH is three times that of EEC. In 2014, the World Health Organization (WHO) categorized EH into EH without atypia and EH with atypia (AH). In the 2003 classification, EH is further classified into simple EH (SH) and complex EH (CH). A meta-analysis revealed that in SH patients, the probability of EEC development was 1%, and in CH patients, the probability was > 3%. The American College of Obstetricians and Gynecologists Committee reported that in AH patients, approximately 25–40% of patients experience EEC simultaneously, and the EEC risk was increased by 14–45 times.[1]

Among women, obesity is more strongly associated with the development of endometrial cancer than any other cancer type. In fact, approximately 57% of endometrial cancers in the United States are thought to be attributable to being overweight and obese. This association has been well established and follows a dose-response relationship, with the incidence of endometrial cancer increasing as body mass index (BMI) increases. In a meta-analysis of 26 studies by the American Institute for Cancer Research, for every increase of five BMI units, there was a 50% increase in the risk of developing endometrial cancer (relative risk [RR], 1.50; 95% CI, 1.42 to 1.59). Endometrioid endometrial cancer is the histologic subtype predominantly linked to obesity; however, the incidence of more aggressive, nonendometrioid subtypes (such as serous, clear cell, and carcinosarcoma) has also recently been found to increase with increasing BMI.[2,3]

In premenopausal women, endometrial proliferation due to cyclic estrogen expression of the ovarian tissue is essential for a healthy menstrual cycle. Naturally, estrogen levels decrease in the ovaries in postmenopausal women, and the role of peripheral and adipose tissue in estrogen synthesis gain in importance. Adipose tissue expresses aromatase, an enzyme that catalyzes the endogenous conversion of androgen to estrogen. Thus, with an increase in adipose tissue, estrogen levels increase. Similarly, the amount of sex hormone-binding globulin (SHBG), a hormone that binds and transports estrogen, decreases. Consequently, the level of bioactive estrogen in the circulating bloodstream increases further. In 1996, Potischman et al. showed that an increased risk of EC is directly associated with a high level of circulating, unopposed estrogen and a low plasma level of SHBG.[4]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast of obesity and endometrial hyperplasia and cancer in premenopausal women. It is possible to accomplish this by researching or investigating obesity and endometrial hyperplasia and cancer in premenopausal women. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about the obesity and endometrial hyperplasia and cancer in premenopausal women. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " obesity and endometrial hyperplasia and cancer in premenopausal women." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *((*"Endometrial hyperplasia*"[MeSH Subheading] OR* "Endometrial cancer*"[All Fields] OR* "Obesity in premenopausal women" *[All Fields]) AND (*"Obesity and endometrial hyperplasia*"[All Fields] OR* "Obesity and endometrial cancer*"[All Fields]) AND (*"Endometrial hyperplasia in menopausal*"[All Fields]) OR (*"Endometrial cancer in premenopausal" *[All Fields]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

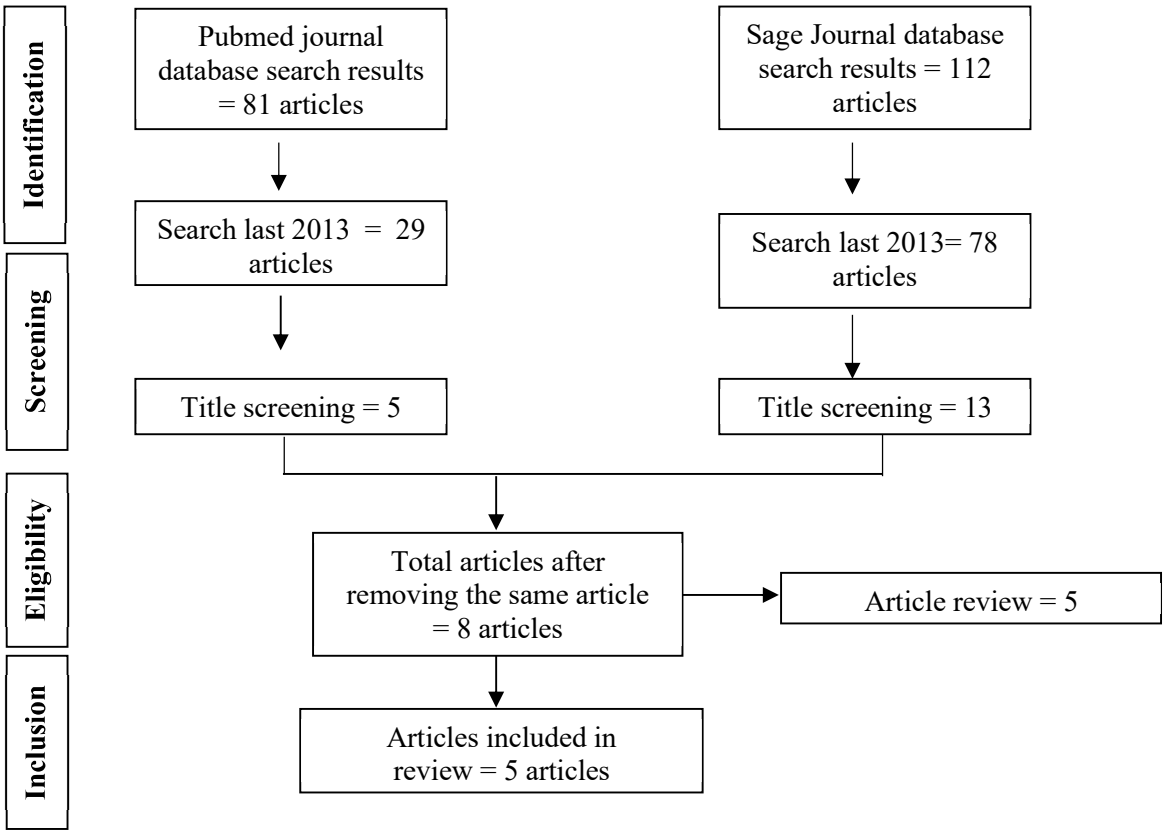

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 81 articles, whereas the results of our search on SagePub brought up 112 articles. The results of the search conducted for the last year of 2013 yielded a total 29 articles for PubMed and 78 articles for SagePub. The result from title screening, a total 5 articles for PubMed and 13 articles for SagePub. In the end, we compiled a total of 8 papers. We included five research that met the criteria.

Dottino, JA *et al* (2020)[5] showed obesity alone as a high-risk state and further studies are warranted to define individualized biomarker profiles for cancer risk. Evaluation of additional cohorts will be required to determine if compensatory mechanisms are at play in the endometrium of obese premenopausal women. Additional events to overcome this compensatory process may distinguish obese women who will develop complex atypical hyperplasia and cancer compared to those that do not. Biomarker differences in obese women with Lynch syndrome or insulin resistance suggest that these combined aberrations may result in an imbalance or disturbance in estrogen-responsive signals.

Beavis, AL *et al* (2020)[6] showed low levels of awareness of EH/EC symptoms and low perceived risk may contribute to the low reporting of symptoms. In a study of women presenting for bariatric surgery, half perceived their personal risk of developing uterine cancer as “not likely” or “not possible”. However, up to 14% of asymptomatic morbidly obese women have undiagnosed EH/EC. It is unclear if these women truly have no symptoms, or if they do not recognize their bleeding pattern as abnormal. The issue may lie in provider counseling: only a third of EC survivors reported that their provider

has told them about the link between obesity and EC, and while gynecologists generally recognize the importance of obesity counseling, many do not feel comfortable providing it.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Dottino, JA *et al.*,2020[5]	USA	Prospectively enrolled in a cross-sectional study	130 women	In addition to known systemic metabolic differences, histologically normal endometrium from obese women showed decreased gene expression of progesterone receptor (p=0.0027) and estrogen-induced genes - *RALDH2* (p=0.008), *IGF-1* (p=0.016), and survivin (p=0.042) compared to non-obese women. Endometrial biomarkers *IGF-1*, survivin, and progesterone receptor remained statistically significant in multivariate linear regression models. In contrast, obese women with Lynch syndrome had increased *IGF -1* (p=0.017). There were no differences in proliferation and limited endometrial immune differences were observed.
Beavis, AL *et al.*, 2020[6]	USA	A retrospective cohort study	103 women	The primary outcome of any EH/EC symptom was defined as follows: in premenopausal women, any recent abnormal uterine bleeding (AUB); in postmenopausal women: any bleeding/discharge. The prevalence of EH/EC symptoms was compared by menopausal status using Fisher's exact tests, and multivariable regression identified independent factors associated with having EH/EC symptoms. A total of 103 women were included, and 4 (4%) had a history of EH/EC. Of the 84 (n = 82%) of women with no prior hysterectomy, 57% (n = 33/58) of premenopausal women reported any EH/EC symptom compared to 15% (n = 15/26) of postmenopausal women ($p < 0.001$). Two-thirds of symptomatic premenopausal women had two or more symptoms, most commonly heavy menses (49% (n = 25/51)) and irregular periods (39% (n = 17/44)). Sixty percent (n = 20/33) had discussed these with a gynecologist, and one third had

				undergone an endometrial biopsy. A history of polycystic ovarian syndrome (RR:1.72, 95% CI 1.24–2.38) was associated with EH/EC symptoms, while being postmenopausal was not (RR:0.32, 95%CI: 0.12–0.87).
Giannella, L *et al*., 2019[7]	Italy	An observational retrospective study	240 women	12 women had EH/EC (5%). Stepwise logistic regression analysis showed that EH/EC associated significantly with BMI ≥ 30 (OR=7.70, 95% CI 1.90 to 31.17), diabetes (OR=9.71, 95% CI 1.63 to 57.81), and a thickened endometrium (OR=1.20, 95% CI 1.08 to 1.34, criterion > 11 mm). The AUC was 0.854 (95% confidence intervals 0.803 to 0.896, p<0.0001). Considering the pretest probability for EH/EC of 5%, the prediction model with a positive likelihood ratio of 8.14 showed a posttest probability of 30%. The simultaneous presence of two or three risk factors was significantly more common in women with EH/EC than controls (50% vs. 6.6 and 25% vs. 0%, respectively, p<0.0001).
Manap, NA *et al*., 2022[8]	Malaysia	A comparative, retrospective study	392	All subjects' histopathological examination result was confirmed, and their clinical data were extracted and transferred into a standardized data checklist and analysed. A total number of 392 cases was obtained from the Annual Cancer Registry Hospital Melaka. However, only 281 cases were studied, including 44.8% premenopausal and 55.2% postmenopausal women. In the premenopausal group, there were higher incidence of obesity (30.8 + 8.6 vs. 28.9 + 7.1), younger age at menarche (12.7 + 1.5 vs. 13.3 + 1.6), lesser parity (1.47 vs. 3.26), and a higher number of nulliparous women (46.8% vs. 19.4%) as compared to postmenopausal group. The premenopausal group tends to be presented with a well-differentiated grading of tumour (52.4%) and a higher incidence of having concomitant endometrial hyperplasia (41.3%). The mean survival among the

				premenopausal group (200.3 + 7.9 months) is higher compared to postmenopausal group (153.9 + 6.5 months).
Zhao, J *et al*., 2021[9]	China	A retrospective study	228 patients	A total of 228 EH patients were included, the incidence of EC in the EH patients was 31.58%. There were significant differences in the age, BMI, diabetes, hypertension and pathology of EH between EC and no EC groups (all $P < 0.05$), no significant differences in the hyperlipidemia, preoperative CA_{125}, number of deliveries, menopause and endometrial thickness between EC and no EC groups were found (all $P > 0.05$). Logistic regression analyses indicated that age > 50 y (OR 3.064, 95% CI 1.945–5.931), BMI ≥ 25 kg/m^2 (OR 2.705, 95% CI 1.121–3.889), diabetes (OR 3.049, 95% CI 1.781–5.114), hypertension (OR 2.725, 95% CI 1.108–3.431) and severe hyperplasia (OR 3.181, 95% CI 1.496–4.228) were the risk factors of EC in patients with EH (all $P < 0.05$).

Giannella, L *et al* (2019)[7] showed When premenopausal vaginal bleeding occurs in diabetic obese women with ET > 11 mm, the percentage of premalignant/malignant endometrial pathology increases by 25%. It is likely that the simultaneous presence of several risk factors is necessary to significantly increase the probability of endometrial pathology.

Manap, NA *et al* (2022)[8] showed The number of endometrial cancers in premenopausal group is in a rising trend; thus, a high index of suspicion of malignancy is needed in young women presenting with abnormal uterine bleeding associated with conditions that contribute to excessive unopposed oestrogen. However, most of the patients in the premenopausal group usually presented with an early disease with a favourable histological type, and generally, it is associated with a good prognosis and better survival.

Zhao, J *et al* (2021)[9] showed The risk of EC in EH patients is high, especially for those patients with age > 50 y, BMI ≥ 25 kg/m^2, diabetes, hypertension and severe hyperplasia, special attentions should be paid for occurrence of EC and early diagnosis and early treatment are needed for those patients.

DISCUSSION

EH describes the abnormal proliferation of endometrial glands with a greater gland-to-stroma-ratio than healthy proliferative endometrium but without endometrial stromal invasion. Diagnosis should be based upon histological assessment of a tissue sample obtained by endometrial biopsy, curettage, or hysterectomy. The most widely used classification system for EH is the 2014 World Health Organization (WHO) Classification System which differentiates between:[10]

- EH without atypia (benign EH) and
- atypical EH/endometrial intraepithelial neoplasia (EIN).

This distinction is particularly important because clinical management of the two conditions is different, depending on the presence or absence of nuclear atypia. Nuclear atypia is defined as nuclear enlargement with or without prominent nucleoli. EH without atypia constitutes a benign lesion without significant somatic genetic changes caused by extensive exposure to estrogen that is not counterbalanced by the protective effects of progestins. If physiological progesterone levels are resumed or if therapeutic progestins are used, the hyperplastic changes regress and the endometrium becomes healthy again in the majority of cases. EH without atypia seems to rarely progress to EC although evidence supporting this statement is poor.[10,11]

Endometrial cancer (EC) is the fourth most common cancer affecting women in the United Kingdom and its incidence is rising. Obesity is the strongest risk factor for type 1 EC and its precursor lesion, atypical hyperplasia (AH), with every 5 kg/m^2 increase in body mass index (BMI) conferring a 1.6-fold higher risk of EC. Consequently, women with class III-IV obesity (BMI ≥40 kg/m^2 and ≥50 kg/m^2, respectively) have an almost tenfold higher lifetime risk of EC compared to women of normal weight, with an estimated 40% of all EC directly attributable to obesity. Furthermore, women with class III-IV obesity who sustain long-term weight loss after bariatric surgery show enduring reduction in EC risk in both retrospective studies and the prospective Swedish Obesity Subjects study. The strength and consistency of the above relationships suggest that the obesity epidemic and the steep rise in EC rates are causally linked. Despite these epidemiological associations, the mechanisms linking obesity and EC are incompletely understood, but are likely to include the proliferative effects of excess estrogen unopposed by progesterone in noncycling premenopausal and postmenopausal endometrium, insulin resistance and the proinflammatory state observed with excess adiposity.[12,13]

CONCLUSION

The nomogram of EH/EC is significantly associated with risk factors, namely BMI, PCOS, anemia, infertility, menostaxis, AUB type, and endometrial thickness. The nomogram model can be used to predict the EH/EC risk and rapidly screen risk factors in a women population with high risk.

REFERENCES

[1] Kuai D, Tang Q, Tian W, Zhang H. Rapid identification of endometrial hyperplasia and endometrial endometrioid cancer in young women. Discov Oncol [Internet]. 2023;14(1). Available from: https://doi.org/10.1007/s12672-023-00736-w

[2] Onstad MA, Schmandt RE, Lu KH. Addressing the role of obesity in endometrial cancer risk, prevention, and treatment. J Clin Oncol. 2016;34(35):4225–30.

[3] Chu CS. Opportunity for Intervention. 2018;69(7):990–5.

[4] Kiesel L, Eichbaum C, Baumeier A, Eichbaum M. Obesity epidemic—the underestimated risk of endometrial cancer. Cancers (Basel). 2020;12(12):1–11.

[5] Jia M. 乳鼠心肌提取 HHS Public Access. Physiol Behav. 2017;176(3):139–48.

[6] Beavis AL, Najjar O, Cheskin LJ, Mangal R, Rositch AF, Langham G, et al. Prevalence of endometrial cancer symptoms among overweight and obese women presenting to a multidisciplinary weight management center. Gynecol Oncol Reports [Internet]. 2020;34(June):100643. Available from: https://doi.org/10.1016/j.gore.2020.100643

[7] Giannella L, Cerami LB, Setti T, Bergamini E, Boselli F. Prediction of Endometrial Hyperplasia and Cancer among Premenopausal Women with Abnormal Uterine Bleeding. Biomed Res Int. 2019;2019.

[8] Abdol Manap N, Ng BK, Phon SE, Abdul Karim AK, Lim PS, Fadhil M. Endometrial Cancer in Pre-Menopausal Women and Younger: Risk Factors and Outcome. Int J Environ Res Public Health. 2022;19(15).

[9] Zhao J, Hu Y, Zhao Y, Chen D, Fang T, Ding M. Risk factors of endometrial cancer in patients with endometrial hyperplasia: implication for clinical treatments. BMC Womens Health [Internet]. 2021;21(1):1–6. Available from: https://doi.org/10.1186/s12905-021-01452-9

[10] Nees LK, Heublein S, Steinmacher S, Juhasz-Böss I, Brucker S, Tempfer CB, et al. Endometrial hyperplasia as a risk factor of endometrial cancer. Arch Gynecol Obstet [Internet]. 2022;306(2):407–21. Available from: https://doi.org/10.1007/s00404-021-06380-5

[11] Grubman J, Mora V, Nguyen M, Ladwig N, Chen L may, Jacoby V. Impact of abnormal uterine bleeding care in premenopausal patients prior to endometrial malignancy diagnosis. Gynecol Oncol Reports [Internet]. 2023;50(October):101292. Available from: https://doi.org/10.1016/j.gore.2023.101292

[12] MacKintosh ML, Derbyshire AE, McVey RJ, Bolton J, Nickkho-Amiry M, Higgins CL, et al. The impact of obesity and bariatric surgery on circulating and tissue biomarkers of endometrial cancer risk. Int J Cancer. 2019;144(3):641–50.

[13] Papatla K, Huang M, Slomovitz B. The obese endometrial cancer patient: How do we effectively improve morbidity and mortality in this patient population? Ann Oncol [Internet]. 2016;27(11):1988–94. Available from: https://doi.org/10.1093/annonc/mdw310