Risk Factors Analysis of Endometrial Cancer at Dr. Soetomo Hospital in Surabaya, Indonesia

Rimbani Dwi Irnasih[a], Willy Sandhika[b]*, Ratna Dwi Jayanti[c]

[a] Email: rimbani.dwi.nasih-2022@fk.unair.ac.id
[a]Midwifery Study Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[b]Department of Anatomic Pathology, Faculty of Medicine, Universitas Airlangga; Dr. Soetomo General Academic Hospital, Surabaya, Indonesia; The international Academy of Phatology, Indonesian Division
[c]Midwifery Study Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Abstract

Endometrial cancer is a common gynecological cancer that occurs frequently in perimenopausal and postmenopausal women. Several factors influence the incidence of endometrial cancer, such as age, family history of cancer, Body Mass Index, parity, diabetes mellitus, age at menarche, menopausal status, and age at first birth. This study aims to determine the risk factors associated with endometrial cancer in Dr. Soetomo's hospital in Surabaya. This research uses an analytical observational design with a case-control approach. The subjects were chosen by convenience sampling, and 70 patients in the case group and 69 in the control group were obtained. Bivariate analysis using Mann-Whitney and Chi-square, then multivariate analysis using the logistic regression test with significance $p<0.05$. The results showed that age, family history of cancer, diabetes mellitus, menopausal status, and age at first birth were related to endometrial cancer. Body mass index, parity, and age at menarche are variables not associated with endometrial cancer. Diabetes mellitus is the most dominant factor in increasing endometrial cancer incidence with Odd Ratio (OR)= 7.085 (95% CI; 1.299-38.637). This research provides information about what factors are related to and influence the incidence of endometrial cancer. The development of these findings needs to be carried out in a larger sample size and using a cohort study.

Keywords: Endometrial Cancer, age, Diabetes Mellitus, menopausal status

1. Introduction

A prevalent gynecological malignancy that often affects postmenopausal and perimenopausal women is endometrial cancer [1]. Generally, endometrial cancer prognosis is good because the majority of women present at an early stage. However, it is estimated 20% of patients are dying as a result of this disease, which is associated with women who present and diagnosed at an advanced age so that the prognosis for recurrence is poor [2], [3].

Endometrial cancer growth is brought on by genetic mutations, prolonged estrogen stimulation, and lifestyle modifications. Prolonged exposure to estrogen without resistance from progesterone triggers endometrial cancer [4], [5]. A high increase in the incidence of endometrial cancer has been linked to multiple studies that have found a relationship between estrogen exposure factors and obesity, nulliparity, early menarche, menopausal status, anovulation or oligo ovulation, polycystic ovary syndrome (PCOS), and a family history of endometrial and colorectal cancer [6], [7]. Genetic mutations linked to Lynch syndrome, Cowden syndrome, and polymerase prof-reading polyposis are among the genetic variables that are also risk

factors for endometrial cancer [8]. The high incidence coincides with several lifestyle factors such as increasing obesity, increasing age and older age at first birth [9]. The growth of endometrial cancer can also be caused by hyperinsulinemia and increased levels of the insulin hormone growth factor in patients with diabetes mellitus, resulting in increased endometrial proliferation [6].

Apart from risk factors, there are protective factors, several study results also state that late menarche, early menopause and the application of hormonal contraception has the potential to lower endometrial cancer risk [10]. Each pregnancy is additionally linked to a decline in endometrial cancer, both from parity and gestational age where very high progesterone levels during pregnancy can reverse premalignant changes [11].

Endometrial cancer cases increase by 1-2% every year [2]. Data from 2020 shows that uterine cancer in the world recorded 417,368 new cases, or 10.8 new cases per 100,000 population. Meanwhile in Indonesia there were 7,773 new cases of uterine cancer or 2% of all new cases of cancer, with a total of 2,026 deaths. Apart from the relatively high mortality rate, late treatment of cancer patients causes the cost burden to increase. For the 2019-2020 period, government insurance cover the cost of cancer approximately 7.6 trillion rupiah [12], [13]. Dr. Soetomo hospital is an academic hospital and referral center in the city of Surabaya, where the hospital has an Oncology Polyclinic service as a center for outpatient services, especially cancer. The number of new patients with endometrial cancer at Dr. Soetomo hospital in 2020 was 57 patients, in 2021 there were 86 patients and in 2022 there were 96 patients.

Based on the findings above, researchers are looking into risk factors that might be correlated to a rise in endometrial cancer cases at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

2. Methods

This study uses a case-control methodology and is an observational analytical investigation that was carried out from July to October 2022 following receiving approval for the study from the Dr. Soetomo Hospital's ethics committee (0719/KEPK/VII/2023), which was published on July 17, 2023. The study population was all patients diagnosed with endometrial cancer at the oncology clinic (case group) and patients diagnosed with something other than cancer at the obstetrics-gynecology clinic (control group) who were undergoing treatment visits. Calculation of the case: control sample size (1:1 ratio), using the n4study application with the case-control study formula and obtained a minimum sample size of 67:67. The inclusion criteria for the case group in this study were patients with endometrial cancer proven by anatomical pathology results. The control group was patients diagnosed with something other than cancer. Histological analysis is a basic test to determine whether it is benign or malignant [14]. All research subjects have agreed by providing informed consent. The exclusion criteria for this study were patients who could not speak and were seriously ill, so they could not provide the information the researchers needed. The sampling technique used was convenience sampling. This study's dependent variable is endometrial cancer, and the independent variables are age, family history, Body mass index (BMI), parity, Diabetes Mellitus (DM), age at first birth, age at menarche, and menopausal status. Data collection through interviews using questionnaires. Bivariate (chi-square and Mann-Whitney) and multivariate (binary logistic regression) data were analyzed using IBM Corp. Released in 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp. The alpha significance value used in this research is 0.05.

3. Result

In this study, there were 70 patients with endometrial cancer and 69 patients without cancer, according to the inclusion criteria. The number of patients included in the analysis were patients who had given birth, resulting in the number of respondents being endometrial cancer patients being 48 and 51 non-cancer patients.

Table 1 shows that people with endometrial cancer are often found in women who are pre-elderly, have a BMI that is more than normal, are multiparous, have normal menarche and have gone through menopause. Respondents who were found to have a history of cancer in their families were all people with cancer, and as many as 14 (87.5%) DM sufferers were found to have endometrial cancer. The age at first birth comparison can be seen in Table 2, which shows that the median age at first birth of endometrial cancer sufferers is younger than non-cancer sufferers.

Significant values show the relationship of independent variables with endometrial cancer in Table 1 and Table 2. Variables that have p-value < 0,05 are age (p=0.000), family history of cancer (p=0.028), DM (p=0.002), menopause (p=0.000) and age at first birth (p=0,004). Variables that have p-value>0,05 are BMI (0.067), parity (p=0.199), and age at menarche (p=0.194).

Based on the result of the binary logistic regression test in Table 3, it shows that the independent variables that have a significant effect on endometrial cancer with p-value <0.05 are the age (1) with OR=5,351 (95% CI; 1,863-15,370), DM (1) with OR= 7,085 (95% CI; 1,299-38,639) and menopausal status with OR= 6,894(95% CI; 2,036-23,336) directly significantly influence endometrial cancer. Age (1) is the difference between DM type II and non-DM, and menopause is the menopause group.

Table 1. Distribution of characteristic of subject on risk factor

Characteristic subject	Endometrial cancer (n=70),n(%)	Non-cancer (n=69), n(%)	Significant value
Age (years old)			
Adults (19-44)	9 (16.1)	47 (83.9)	0.000
Pre-elderly (45-59)	45 (72.6)	17 (27.4)	
Elderly (>60)	16 (76.2)	5 (23.8)	
Family History of cancer			
No history	64 (48.1)	69 (51.9)	0.028
There is history	6 (100)	0 (0)	
BMI			
Underweight (< 18.5 Kg/m^2)	3 (60)	2 (40)	0.067
Normal (18.5-22.9 Kg/m^2)	11 (33.3)	22 (66.7)	
Overweight (23 – 24.9 Kg/m^2)	16 (53.3)	14 (46.7)	
Obesity I (25-29.9 Kg/m^2)	21 (52.5)	19 (47.5)	
Obesity II (≥30 Kg/m^2)	19 (61.3)	12 (38.7)	
Parity			
Nulliparous	19 (48,7)	20 (51,3)	0.199
Primiparous	12 (35.3)	22 (64.7)	
Multiparous	35 (60.3)	23 (39.7)	
Grand multiparous	4 (50.0)	4 (50.0)	
DM history			
Not DM	56 (45.5)	67 (54.5)	0.002
DM type II	14 (87.5)	2 (12.5)	
Menarche age (years old)			
Early (<10)	1 (100)	0 (0)	0.194
Normal (10-16)	66 (51.2)	63 (48.8)	
Late (>16)	3 (33.3)	6 (66.7)	
Menopausal status			
Not yet menopause	23 (28)	59 (72)	0.000
Menopause	47 (82.5)	10 (17.5)	

Table 2. Distribution of age at first birth

Age at first birth (years old)	Endometrial cancer	Non-cancer	p-value
Min-Max	16-41	17-39	0.004
Median	20	24.5	

Table 3. Regression binary logistic analysis

Variable	B	p- value	Exp(B)	95% CI for EXP (B)
Age		0.004		
Age (1)	1.677	0.002	5.351	1.863-15.370
Age (2)	0.758	0.390	2.135	0.378-12.051
DM (1)	1.958	0.024	7.085	1.299-38.639
Menopause	1.931	0.002	6.894	2.036-23.336
Constant	-3.749	0.000	0.024	

4. Discussion

This study presents findings regarding factors that impact the prevalence of endometrial cancer. The results of chi-square and Mann-Whitney tests showed a statistically significant correlation between age, family history of cancer, DM, menopausal status and age at first birth with the incidence of endometrial cancer. However, BMI, parity, and age at menarche did not have a significant relationship. Type I endometrial cancer is most commonly diagnosed, and 80% is caused by excessive estrogen exposure [15].

The perimenopause age group (40-55 years) is a period where there is an imbalance in DNA mismatch repair (MMR) activity and estrogen activity. Low MMR activity causes estrogen to increase endometrial cell growth and cause carcinogenesis [9], [16]. Wu et al., 2019 indicate that endometrial cancer is more common in women above 46.5 years of age [17]. Another study also said that those aged ≥ 55 years are predicted to get endometrial cancer with OR 4.69 (95% CI: 2.16-10.1) [18]. These findings show that endometrial cancer prevention can be done from a young age to prevent this disease from developing in old age.

A family history of endometrial cancer increases the risk of this disease two to three times higher [6], [19]. Phosphatase and tensin homolog (PTEN) germline mutations in autosomal dominant syndrome/Cowden syndrome encode a phosphatase involved in the signaling pathway Phosphoinositide 3-kinase (PI3K/Akt) cells that influence proliferation, apoptosis, and energy metabolism [19], [20]. Approximately 25% of patients with Cowden syndrome have germline PTEN loss-of-function variants [19].

Comparable studies also demonstrate that a first-degree family history of cancer [18], [21] and second-degree [21] show a strong association with endometrial cancer. The odds ratio (OR) for endometrial cancer in women with first-degree relatives is 3.5% (95% CI 2.8-4.2) [22]. Women who have a history of cancer in their family must be more alert and take precautions against endometrial cancer.

Women with type II diabetes are more likely than those without the disease to acquire endometrial cancer [6]. Endometrial cancer develops primarily through three primary pathways: hormone imbalance, insulin resistance, and systemic inflammation. Insulin resistance causes hyperglycemia and hyperinsulinemia, which, when combined with chronic inflammation, increase the proliferative and anti-apoptotic properties of insulin and insulin growth factor (IGF-1) on endometrial cells, hence promoting endometrial tumorigenicity and metastasis [23]. This study supports the findings of Saed et al., 2019, who found that DM is linked to a statistically significant increase in the risk of endometrial cancer with RR: 1.72 (95% CI 1.21-2.01). Type II DM is not only caused by genetic factors but also lifestyle factors [24]. This requires attention to women to have a good lifestyle to prevent DM in order to lower the risk of endometrial cancer.

Women who have gone through menopause are exposed to estrogen longer than women who have not gone through menopause, so endometrial cell proliferation increases. Long periods of menstruation increase the risk of endometrial cancer [6]. Postmenopausal bleeding is a common symptom of endometrial cancer. The prevalence of postmenopausal women with endometrial cancer was 91% (95%CI, 87%-93%) regardless of stage [25]. Tran, Kim and Park, 2023 in their research linked menopause with frequent metabolic syndrome problems (such as central adiposity, increased blood glucose, increased blood pressure and decreased

HDL(high density lipoprotein)), which can increase the risk of endometrial cancer with HR=1.47 (95 % CI; 1.32-1.63) [26]. These findings suggest to women that apart from unavoidable exposure to endogenous estrogen, metabolic syndrome can be prevented with a better lifestyle starting from a young age so that at menopause, they can avoid metabolic syndrome, which can increase endometrial cancer risk.

Childbearing age is linked to a term pregnancy. The high progesterone level in the last trimester has a resistance effect against estrogen, thereby suppressing endometrial cell mitosis. In addition, the shedding of the endometrial layer can eliminate preneoplastic endometrial cells [21]. In their cohort study, Sugawara et al., 2018 found that increasing the age at first birth reduced the risk of endometrial cancer. Compared to the group of women who gave birth to their first child at the age of <22, the risk of endometrial cancer was higher in the group of women who gave birth to their first child between the ages of 23 and 25 (Hazard Ratio (HR) = 0.79 (95% CI; 0.49-1.26) and in the group of women who gave birth to their first child between the ages of >26 and <22 (HR = 0.53 (95% CI; 0.28-1.00) [27]. However, the findings in the research of Katagiri et al., 2023 found that the age at first birth and the risk of endometrial cancer were not significantly correlated [28]. The risk of endometrial cancer can be lowered by being older when one first gives birth. However, this is still a matter of debate in previous studies.

A BMI that is more than normal is reflected in the accumulation of body fat. Excessive conversion of androstenedione to estrone and The decrease in sex hormone-binding globulin (SHBG) protein causes the concentration of free estrogens to rise, which in turn promotes the growth of cancer and endometrial hyperplasia [29]. Many studies are similar, and the results are quite consistent that BMI is associated with endometrial cancer. There exists a correlation between a high body mass index and the likelihood of developing further gynecological illnesses such as polycystic ovary syndrome, infertility, pelvic organ prolapse, urinary incontinence, postmenopausal bleeding, menstrual disorders (oligomenorrhea, hypomenorrhea, irregular cycles, polymenorrhea, menorrhagia and premenstrual syndrome), and pregnancy with preeclampsia [30], [31], [32]. As many as 37.1% of the non-cancer group had gynecological problems as a result of excessive BMI, and this may be the reason why the research results on the BMI variable did not have significant differences, thereby allowing for bias.

According to Mehta and Singla, 2019 and Jia et al., 2020 Endometrial cancer is linked to the number of anovulatory cycles in nulliparous women, which raises estrogen levels in infertile women [6], [33]. Nulliparity is linked to a two-fold rise in endometrial cancer. In contrast to research conducted by Yang et al, 2015, nulliparous women had an increased risk of endometrial cancer with OR=1.22 (95% CI: 1.13-1.33) [34]. Raglan et al., 2019, in their meta-analysis, stated that women who give birth decrease the risk of endometrial cancer in comparison to women who are nulliparous by 40% [35]. Previous studies consistently state that there is a strong correlation between endometrial cancer and parity. This lack of significant differences is due to some respondents in the non-cancer group having gynecological problems that cause infertility, such as endometriosis, PCOS, amenorrhea and ovarian cysts, thus allowing bias.

Several studies say that endometrial cancer risk rises with early menarche [6]. Early menarche age is linked to earlier estrogen exposure. Endometrial tumors express estrogen receptors, and greater exposure to circulating estrogens is linked to somatic mutation of endometrial cells through enhanced DNA replication and mitotic activity, which results in the malignant transformation of cells [36]. A meta-analysis from Gong, Wang and Ma, 2015 revealed that age at menarche is associated with endometrial cancer, where each delay of menarche every two years is associated with a 4% reduced risk (Risk Ratio=0.96; 95%CI:0.94 -0.98). Researchers have not found research results with similar results [37]. As time goes by, the age of menarche tends to occur earlier, thus influencing the differences between the results of this study and previous studies. The decline in the age of menarche occurred in several countries, such as America, in 1900; menarche occurred at an average age of 14.2 years to 12.45 years in 2010. The average menarche age in Indonesia ranged from 15 years in 1932 to 12.69 years in 1992 [38].

This research provides knowledge about the factors that influence the prevalence of endometrial cancer. Then this can be the reason why it is necessary to adopt a healthy lifestyle to avoid type II DM, have better planning for having children, and be more alert to avoid the risk of endometrial cancer. However, this research is not free from limitations. This research uses non-probability sampling techniques, so it does not provide an equal opportunity for each member of the population to become a research sample. The control group was taken from obstetrics and gynecology patients with various obstetric and gynecological problems other than cancer, some of whom had several of the same characteristics as endometrial cancer patients, such as BMI and parity, thereby allowing bias in some of the analysis results.

Strength and Limitation

This research provides knowledge about the factors that influence the prevalence of endometrial cancer. Then this can be the reason why it is necessary to adopt a healthy lifestyle to avoid type II DM, have better planning for having children, and be more alert to avoid the risk of endometrial cancer. However, this research is not free from limitations. This research uses non-probability sampling techniques, so it does not provide an equal opportunity for each member of the population to become a research sample. The control group was taken from obstetrics and gynecology patients with various obstetric and gynecological problems other than cancer, some of whom had several of the same characteristics as endometrial cancer patients, such as BMI and parity, thereby allowing bias in some of the analysis results.

5. Conclusion

This study revealed a valuable correlation between age, family history, DM, menopausal status and age at first birth on endometrial cancer. DM appears to have the most significant influence on endometrial cancer. Further research using probability sampling techniques and cohort studies is needed for more accurate results.

Acknowledgements

The author would like to thank the Department of Obstetrics and Gynecology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

References

[1] T. J. Courtney M, R. D. Beauchamp MD, B. M. Ever MD, and K. L. Mattox MD, “Sabiston: Textbook of Surgery: The Biological basic of Modern Surgical Practice, Twenty First Edition,” in Sabiston: Textbook of Surgery: The Biological basic of Modern Surgical Practice, Twenty First Edition, 21st ed., Elsevier, 2022, p. 28.

[2] A. Maryam et al., Perempuan Dan Permasalahannya Dalam Sistem Reproduksi. Media Sains Indonesia, 2021.

[3] B. Barczyński, K. Frąszczak, A. Wnorowski, and J. Kotarski, “Menopausal Status Contributes to Overall Survival in Endometrial Cancer Patients,” Cancers, vol. 15, no. 2, p. 451, Jan. 2023, doi: 10.3390/cancers15020451.

[4] K. Yoriki et al., “Genistein induces long-term expression of progesterone receptor regardless of estrogen receptor status and improves the prognosis of endometrial cancer patients,” Sci Rep, vol. 12, no. 1, p. 10303, Jun. 2022, doi: 10.1038/s41598-022-13842-6.

[5] M. Zhang et al., “Analysis of prognostic factors of metastatic endometrial cancer based on surveillance, epidemiology, and end results database,” Front. Surg., vol. 9, p. 1001791, Jan. 2023, doi: 10.3389/fsurg.2022.1001791.

[6] S. Mehta and A. Singla, Preventive Oncology for the Gynecologist. Springer, 2019.

[7] K.-S. Mak, K.-G. Huang, and H.-H. Kuo, “An incidental diagnosis of endometrial cancer in a young and underweight female with isolated symptom of amenorrhea,” Taiwanese Journal of Obstetrics and Gynecology, vol. 61, no. 2, pp. 399–401, Mar. 2022, doi: 10.1016/j.tjog.2022.02.039.

[8] H. K. Yasin, A. H. Taylor, and T. Ayakannu, “A Narrative Review of the Role of Diet and Lifestyle Factors in the Development and Prevention of Endometrial Cancer,” Cancers, vol. 13, no. 9, p. 2149, Apr. 2021, doi: 10.3390/cancers13092149.

[9] S. Mehta and B. Gupta, Recent Advances in Endometrial Cancer. Springer Nature, 2020.

[10] S. D’Urso et al., “Mendelian randomization analysis of factors related to ovulation and reproductive function and endometrial

cancer risk," BMC Med, vol. 20, no. 1, p. 419, Nov. 2022, doi: 10.1186/s12916-022-02585-w.
[11] S. J. Jordan et al., "Pregnancy outcomes and risk of endometrial cancer: A pooled analysis of individual participant data in the Epidemiology of Endometrial Cancer Consortium," Intl Journal of Cancer, vol. 148, no. 9, pp. 2068–2078, May 2021, doi: 10.1002/ijc.33360.
[12] Kemenkes, "Kementerian Kesehatan Republik Indonesia." Accessed: Dec. 10, 2022. [Online]. Available: https://www.kemkes.go.id/article/view/22020400002/health-care-equality-for-breast-cancer-patients.html
[13] GLOBOCAN, "Cancer today." Accessed: Dec. 10, 2022. [Online]. Available: http://gco.iarc.fr/today/home
[14] Y. Shen, W. Yang, J. Liu, and Y. Zhang, "Minimally invasive approaches for the early detection of endometrial cancer," Molecular Cancer, vol. 22, no. 1, p. 53, Mar. 2023, doi: 10.1186/s12943-023-01757-3.
[15] A. C. Holland, A. Hodges, K. S. Catron, K. S. Bevis, N. R. Berman, and K. Meneses, "Endometrial Cancer: Using Evidence to Impact Practice and Policy," The Journal for Nurse Practitioners, vol. 12, no. 6, pp. 395–402, Jun. 2016, doi: 10.1016/j.nurpra.2016.04.006.
[16] E. S. Mulia SST M. Keb, D. M.Keb SST, Y. F. M.Biomed SST, A. N. H. M.Kes SST, Y. M.Kes S. S. T., and D. Y. M.Keb S. ST, Buku Ajar Perimenopause Kebidanan. Mahakarya Citra Utama Group, 2022.
[17] Y. Wu, W. Sun, H. Liu, and D. Zhang, "Age at Menopause and Risk of Developing Endometrial Cancer: A Meta-Analysis," BioMed Research International, vol. 2019, 2019, doi: 10.1155/2019/8584130.
[18] W. I. udayangani Jayawickcrama and C. Abeysena, "Risk factors for endometrial carcinoma among postmenopausal women in Sri Lanka: a case control study," BMC Public Health, vol. 19, no. 1, p. 1387, Oct. 2019, doi: 10.1186/s12889-019-7757-2.
[19] T. Dörk, P. Hillemanns, C. Tempfer, J. Breu, and M. C. Fleisch, "Genetic Susceptibility to Endometrial Cancer: Risk Factors and Clinical Management," Cancers (Basel), vol. 12, no. 9, p. 2407, Aug. 2020, doi: 10.3390/cancers12092407.
[20] Y. Zhuang et al., "MDH2 Stimulated by Estrogen-GPR30 Pathway Down-Regulated PTEN Expression Promoting the Proliferation and Invasion of Cells in Endometrial Cancer," Translational Oncology, vol. 10, no. 2, pp. 203–210, Apr. 2017, doi: 10.1016/j.tranon.2017.01.009.
[21] S. Johnatty et al., "Family history of cancer predicts endometrial cancer risk independently of Lynch Syndrome: Implications for genetic counselling," Gynecologic Oncology, vol. 147, Aug. 2017, doi: 10.1016/j.ygyno.2017.08.011.
[22] A. K. Win, J. C. Reece, and S. Ryan, "Family History and Risk of Endometrial Cancer: A Systematic Review and Meta-analysis," Obstetrics & Gynecology, vol. 125, no. 1, p. 89, Jan. 2015, doi: 10.1097/AOG.0000000000000563.
[23] K. Njoku, H. J. Agnew, and E. J. Crosbie, "Impact of Type 2 Diabetes Mellitus on Endometrial Cancer Survival: A Prospective Database Analysis," Frontiers in Oncology, vol. 12, 2022, Accessed: Dec. 18, 2022. [Online]. Available: https://www.frontiersin.org/articles/10.3389/fonc.2022.899262
[24] L. Saed et al., "The effect of diabetes on the risk of endometrial Cancer: an updated a systematic review and meta-analysis," BMC Cancer, vol. 19, no. 1, p. 527, May 2019, doi: 10.1186/s12885-019-5748-4.
[25] M. A. Clarke, B. J. Long, A. Del Mar Morillo, M. Arbyn, J. N. Bakkum-Gamez, and N. Wentzensen, "Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis," JAMA Internal Medicine, vol. 178, no. 9, pp. 1210–1222, Sep. 2018, doi: 10.1001/jamainternmed.2018.2820.
[26] T. X. M. Tran, S. Kim, and B. Park, "Changes in metabolic syndrome and the risk of breast and endometrial cancer according to menopause in Korean women," Epidemiol Health, vol. 45, p. e2023049, May 2023, doi: 10.4178/epih.e2023049.
[27] Y. Sugawara, K. Sugiyama, Y. Tomata, S. Kanemura, A. Fukao, and I. Tsuji, "Age at First Birth and the Risk of Endometrial Cancer Incidence: A Pooled Analysis of Two Prospective Cohort Studies among Japanese Women," J Cancer, vol. 9, no. 23, pp. 4422–4429, Oct. 2018, doi: 10.7150/jca.26242.
[28] R. Katagiri et al., "Reproductive Factors and Endometrial Cancer Risk Among Women," JAMA Network Open, vol. 6, no. 9, p. e2332296, Sep. 2023, doi: 10.1001/jamanetworkopen.2023.32296.
[29] A. Słabuszewska-Jóźwiak, A. Lukaszuk, M. Janicka-Kośnik, A. Wdowiak, and G. Jakiel, "Role of Leptin and Adiponectin in Endometrial Cancer," Int J Mol Sci, vol. 23, no. 10, p. 5307, May 2022, doi: 10.3390/ijms23105307.
[30] I. Kalliala et al., "Obesity and gynaecological and obstetric conditions: umbrella review of the literature," BMJ, vol. 359, p. j4511, Oct. 2017, doi: 10.1136/bmj.j4511.
[31] C. van Drünick, L. de Waard, C. J. B. Muller, and G. Theron, "Association between gynaecological disorders and body mass index in a South African cohort: a retrospective observational study," Journal of Obstetrics and Gynaecology, vol. 42, no. 6, pp. 2420–2425, Aug. 2022, doi: D'Urso.
[32] M. Agrawal, A. Goyal, P. Gupta, and A. Agrawal, "Study of menstrual disorders and its correlation with BMI in adolescents," International Journal of Reproduction, Contraception, Obstetrics and Gynecology, vol. 12, no. 5, pp. 1399–1404, Apr. 2023, doi: 10.18203/2320-1770.ijrcog20231232.
[33] X. Jia, L. Yang, P. Xu, N. Li, C. Chen, and H. Wang, "Endometrial cancer combined with polycystic ovary syndrome in 9 women under 40-years old: A case report," Biomedical Reports, vol. 13, no. 5, pp. 1–1, Nov. 2020, doi: 10.3892/br.2020.1357.
[34] H. P. Yang et al., "Infertility and incident endometrial cancer risk: a pooled analysis from the epidemiology of endometrial cancer consortium (E2C2)," Br J Cancer, vol. 112, no. 5, pp. 925–933, Mar. 2015, doi: 10.1038/bjc.2015.24.
[35] O. Raglan et al., "Risk factors for endometrial cancer: An umbrella review of the literature," International Journal of Cancer, vol. 145, no. 7, pp. 1719–1730, 2019, doi: 10.1002/ijc.31961.
[36] Y. Lv et al., "Health outcomes of age at menarche in European women: a two-sample Mendelian randomization study," Postgraduate Medical Journal, vol. 99, no. 1175, pp. 993–999, Sep. 2023, doi: 10.1093/postmj/qgad023.
[37] T.-T. Gong, Y.-L. Wang, and X.-X. Ma, "Age at menarche and endometrial cancer risk: a dose-response meta-analysis of

prospective studies," Sci Rep, vol. 5, p. 14051, Sep. 2015, doi: 10.1038/srep14051.
[38] N. N. Fadhilah and K. Katmini, "Studi Literatur : Determinan Menarche Dini Pada Siswi," JIK JURNAL ILMU KESEHATAN, vol. 5, no. 2, Art. no. 2, Oct. 2021, doi: 10.33757/jik.v5i2.414.