Factors Related to Type of Endometrial Cancer in RSUP Dr. M. Djamil Padang

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Abstract
Objective: This study aims to determine the relationship of risk factors with type of endometrial cancer.
Methods: This study used a cross sectional design in patients with endometrial cancer. Sampling uses total sampling technique, with a total sample of fifty six people. Data were obtained from the anatomical pathology section and medical records of Dr. RSUP M. Djamil Padang from 2016 until 2018. Analysis of data using Chi-Square test and logistic regression
Result: In this study, type I endometrial cancer is 75% cases while type II is 25% cases. Age, parity, diabetes mellitus, hypertension, genetics history and exclusive breastfeeding have no association with the type of endometrial cancer. The age of menarche and BMI have a relationship with the type of endometrial cancer. The dominant factor associated with the type of endometrial cancer is BMI (p = 0.042; OR = 6.547; 95% CI = 1.067-40.169), age (p = 0.037; OR = 4.854; 95% CI = 1.096-21.493), and age of menarche (p = 0.054; OR = 4.590; 95% CI = 0.974-21.635).
Conclusion: On this research, BMI, age and age of menarche are the most dominant factor associated with the type of endometrial cancer.

Key words: Endometrial Cancer , Risk Factor

Faktor yang Berhubungan dengan Tipe Kanker Endometrium di RSUP Dr. M. Djamil Padang

Abstrak
Tujuan: Penelitian ini bertujuan untuk mengetahui hubungan faktor risiko dengan tipe kanker endometrium.
Hasil: Pada penelitian ini ditemukan 75% kasus merupakan kanker endometrium tipe 1 dan 25% kanker endometrium tipe II. Usia, paritas, diabetes mellitus, hipertensi, riwayat genetik dan pemberian asi eksklusif tidak memiliki hubungan dengan tipe kanker endometrium. Usia menarche dan IMT memiliki hubungan dengan tipe kanker endometrium. Faktor yang dominan berhubungan dengan tipe kanker endometrium adalah IMT (p = 0,042; OR = 6,547; 95% CI = 1,067-40,169), usia (p = 0,037; OR = 4,854; 95% CI = 1,096-21,493), dan usia menarche (p = 0,054; OR = 4,590; 95% CI = 0,974-21,635).
Kesimpulan: Pada penelitian ini, IMT, usia dan usia menarche merupakan faktor yang paling dominan mempengaruhi tipe kanker endometrium

Kata kunci: Kanker Endometrium, Faktor Risiko.
Introduction

Endometrial cancer is the sixth most often cancer in women throughout the world after breast, colon, lung, cervix and thyroid cancer. It is estimated that the incidence of this cancer reached 382,069 cases or about 4.4% of all cancer cases in women throughout the world in 2018.1

The prevalence of endometrial cancer in developing countries is 4-5 times lower than in developed countries. At Dr. Cipto Mangunkusumo Hospital, Jakarta, 346 (7.76%) cases of endometrial cancer from all cases of gynecological cancer in January 2011–August 2016 were found.2 Based on data from study conducted by Dewi and Budiana in Sanglah General Hospital, Denpasar, from August 2012 to July 2014, the proportion of endometrial cancer compared to other gynecological cancers was 9.2% (56 of 578 cases).3

Endometrial cancer occurs during reproduction and menopause phase. The average age of patients with endometrial cancer is 63 years old, with the majority of patients aged 50–59 years old. Only about 5% of women who suffer from endometrial cancer are less than 40 years old.4

The causes of endometrial cancer are still not fully known, but most risk factors are associated with changes in hormonal patterns that occur throughout woman’s life. Estrogen has been proved to affect cells proliferation in the endometrium while progesterone has the opposite effect.5 There are several factors that increase the risk of endometrial cancer i.e. age, parity, early menarche, obesity, diabetes mellitus, hypertension, and genetic history.5

Endometrial cancer consists of two types with different risk factors and prognosis. Type I endometrial cancer is associated with exposure to estrogen either endogenous or exogenous and begins with endometrial hyperplasia.7 Patients with type I endometrial cancer are younger and have a better prognosis than type II.8 In contrast, type II endometrial cancer is not estrogen-dependent and develops independently from the pathway of endometrial hyperplasia. The incidence of type II endometrial cancer is less common than type I and the risk factors are less identified so that it is often detected at more advanced stage and tends to be more aggressive.9 Clinical features of type I endometrial cancer are conditions with increased estrogen exposure, similar as in nulliparous women, early menarche and obesity. Type II endometrial cancer often occurs in multiparous women, and is not obese.8

Type I endometrial cancer is more common and has endometrioid histopathological appearance.10 Endometrial type II cancer has a less common histopathological appearance such as mucous, serous, clear cell, squamous, small cell, transitional cell, undifferentiated, and mixed cell carcinoma.11

Methods

This study is an analytical observation study with a cross sectional approach. The study was conducted at the medical record installation and anatomy pathology laboratory of RSUP dr. M. Djamil Padang. The study was conducted from May 2018 to March 2019.

The population was patients with endometrial cancer at RSUP Dr. M. Djamil Padang in the period of 2016-2018. The sample was population that meets the inclusion criteria and does not have exclusion criteria. Inclusion criterium for the subject is all patients with endometrial cancer at RSUP Dr. M. Djamil Padang in 2016-2018 who had a histopathological examination. Subject exclusion criteria are patient medical record data that is incomplete or cannot be read clearly. Study samples were taken using total sampling techniques.

The data was collected from the medical
record installation of RSUP Dr. M. Djamil Padang in 2016-2018. Data taken are as follows: medical record number, patient’s age, parity, age of menarche, weight, height, body mass index, blood sugar level, blood pressure, history of cancer suffered by patients and families, history of breastfeeding and type of histopathological endometrial cancer.

Data that has been collected by the researcher will be processed using a computer program. Data analysis was performed statistically using chi-square test and logistic regression.

**Results**

The study is conducted in the anatomy pathology laboratory and medical record installation at RSUP dr. M. Djamil Padang. The total sample of the study that fulfilled the inclusion criterium and did not have exclusion criteria were 56 patients. Based on the existing medical record data, the results are shown as follows. The frequency distribution of characteristics of endometrial cancer patients can be seen in table 1.

<table>
<thead>
<tr>
<th>No</th>
<th>Characteristics</th>
<th>F</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤50 th</td>
<td>33</td>
<td>58,9</td>
</tr>
<tr>
<td></td>
<td>&gt;50 th</td>
<td>23</td>
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<tr>
<td></td>
<td>Total</td>
<td>56</td>
<td>100</td>
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<tr>
<td>2</td>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nulliparous (0)</td>
<td>14</td>
<td>25,0</td>
</tr>
<tr>
<td></td>
<td>Parous (≥1)</td>
<td>42</td>
<td>75,0</td>
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<td></td>
<td>Total</td>
<td>56</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>Age of Menarche</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Early Menarche (≤12 th)</td>
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<td>51,8</td>
</tr>
<tr>
<td></td>
<td>Normal (&gt;12)</td>
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<td>48,2</td>
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<tr>
<td></td>
<td>Total</td>
<td>56</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>BMI</td>
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<td>Obesity (≥30)</td>
<td>23</td>
<td>41,1</td>
</tr>
<tr>
<td>5</td>
<td>Diabetes Mellitus</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>a. Yes</td>
<td>9</td>
<td>16,1</td>
</tr>
<tr>
<td></td>
<td>b. No</td>
<td>47</td>
<td>83,9</td>
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<tr>
<td></td>
<td>Total</td>
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<td>100</td>
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<tr>
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<td>a. Yes</td>
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<tr>
<td></td>
<td>b. No</td>
<td>36</td>
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<td></td>
<td>Total</td>
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<td>100</td>
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<td>History of Genetic Disease</td>
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<td></td>
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<tr>
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<td>a. Yes</td>
<td>13</td>
<td>23,2</td>
</tr>
<tr>
<td></td>
<td>b. No</td>
<td>43</td>
<td>76,8</td>
</tr>
<tr>
<td></td>
<td>Total</td>
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<td>100</td>
</tr>
<tr>
<td>8</td>
<td>Exclusive breastfeeding</td>
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</tr>
<tr>
<td></td>
<td>a. Yes</td>
<td>25</td>
<td>59,5</td>
</tr>
<tr>
<td></td>
<td>b. No</td>
<td>17</td>
<td>40,5</td>
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<tr>
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<tr>
<td>9</td>
<td>Type of Cancer</td>
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<td>a. Type I Cancer</td>
<td>42</td>
<td>75,0</td>
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<tr>
<td></td>
<td>b. Type II Cancer</td>
<td>14</td>
<td>25,0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>56</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 1 shows that most patients are ≤50 years, have low parity, experience menarche at age ≤12 years, are not obese, do not suffer diabetes mellitus and hypertension and do not have a genetic history. In exclusive breastfeeding variables, nulliparous women were not included in the analysis. In this study, there were 14 patients who did not have children, so only 42 samples could be analyzed for this variable. This study shows that most endometrial cancer patients provide exclusive breastfeeding. Based on the type of endometrial cancer, it was found that most patients had type I endometrial cancer.

The correlation of risk factors with type of endometrial cancer can be seen in table 2.

Based on the Chi-Square test results in table 2, it can be seen that there is a relationship between age of menarche and BMI with the type of endometrial cancer. Age, parity, diabetes mellitus, hypertension, genetic history and exclusive breastfeeding
were not statistically related to the type of endometrial cancer.

To find out the most dominant independent variables affecting the dependent variable logistic regression test was performed. The dominant factors that influence the type of endometrial cancer can be seen in table 3. Table 3 shows that the age, the age of menarche and BMI variables are closely related to the type of endometrial cancer.
Discussion

Characteristics of Age and Its Correlation with Type of Endometrial Cancer

This study showed that most patients with endometrial cancer were \( \leq 50 \) years old. This is in accordance with the study conducted by Effendi, Firdiawati and Rustam in RSUD Arifin Achmad Pekanbaru which found that most patients with endometrial cancer ranged in age from 41-50 years.\(^6\) In Indonesia, age of patients tends to be younger than those in western and European countries, possibly because the use of TSH is still very rare.\(^5\)

Endometrial cancer is divided into type I cancer (estrogen-dependent) and type II cancer (estrogen-independent). Type I endometrial cancer tends to affect younger women and is associated with a history of hyperestrogenism. Type II endometrial cancer usually occurs in older postmenopausal women where estrogen level decreases. This indicates that type II endometrial cancer may not be caused by estrogen excess.\(^12\)

In this study, there was no significant correlation between age and type of endometrial cancer. This is in accordance with the study of Jaishuen, Kunakornporamat, Viriyapak, Benjapibal, Petsuksiri, et al. at Siriraj Hospital which showed no difference in the average age of type I and II endometrial cancer with \( p = 0.86.\)\(^13\)

There was no significant correlation between age and type of endometrial cancer which is also proven by the study of Wan, Gao, Zeng, Yin, Zhao, et al. In the study, it was found that there were no differences in circulating estradiol, progesterone, testosterone, FSH and LH levels between patients with type I and II endometrial cancer in both premenopausal and postmenopausal women.\(^14\) In addition, other studies have shown that type I and II endometrial cancer have same risk factors for each of both and there was also a hypothesis that type II endometrial cancer may not be absolutely estrogen-independent.\(^15\)

In this study, 75\% of cases were type I endometrial cancer and 25\% type II endometrial cancer. With a few number of cases of type II endometrial cancer identified in this study causes this type to be more difficult to learn.\(^13\)

Characteristics of Parity and Its Correlation with Type of Endometrial Cancer

This study shows that most patients with endometrial cancer are parous women. This is in accordance with the study of Dewi and Budiana which showed that 80\% of patients with endometrial cancer are parous women.\(^3\)

Nulliparity increases the risk of developing endometrial cancer by up to four times, while multiparity reduces the risk of endometrial cancer by up to 70\%. This is because parity causes changes in hormonal balance towards increasing progesterone and decreasing estrogen and the release of endometrial tissue during labor which can eliminate precancerous cells.\(^9\)

Based on the study, it was found that there was no significant correlation between parity and endometrial cancer type ( \( p \geq 0.05 \)). This is in accordance with the study of Chen, Tong, Guo, Lau and Zhao which analyzed the correlation of parity with the type of endometrial cancer. In the study, it was found that the majority suffered from type I endometrial cancer (84.8\%) and there was no statistical difference in the proportion of type I and type II endometrial cancer according to parity ( \( p > 0.05 \)).\(^16\)

The results of this study are surprising because a shift in the balance of progesterone and estrogen during pregnancy was considered to have a protective effect on the development of endometrial cancer and type II endometrial cancer was considered independent of estrogen.\(^16\) However, a study
reported that two types of endometrial cancer have common risk factors and the possibility that type II endometrial cancer is not absolutely estrogen-independent.\textsuperscript{15}

**Characteristics of Age of Menarche and Its Correlation with Type of Endometrial Cancer**

This study shows that most endometrial cancer patients experienced menstruation for the first time in ≤12 years old. This is in accordance with the study of Wang, Risch, Lu, Irwin, Mayne, et al. those who found cases of endometrial cancer had a younger age of menarche than controls (p=0.005).\textsuperscript{17}

Menarche in early age is positively associated with some cancers in women such as breast, endometrial and ovarian cancer. This is because early menarche increases the number of menstrual cycles so that the total exposure time for estrogen will be increased. Early menarche increases the risk of endometrial cancer by up to 9 times compared with women who experienced menarche at older age.\textsuperscript{9}

Based on the study, it was found that there was a significant correlation between age of menarche and type of endometrial cancer (p value <0.05). The development of type I endometrium cancer is thought to be stimulated by estrogen and begun with endometrial hyperplasia. Risk factors for type I cancer include conditions with increased exposure to estrogen including menarche at early age.\textsuperscript{8} Unlike type I, type II risk factors are not widely known because there were few cases so it is difficult to study this type separately.\textsuperscript{18}

**Characteristics of BMI and Its Correlation with Type of Endometrial Cancer**

This study shows that most endometrial cancer patients are not obese. Similar results were also found in the study of Pradjatmo and Pahlevi which showed that of 68 endometrial cancer patients, 61.8% had a normal BMI (18.5–24.9).\textsuperscript{19} The relationship of obesity to endometrial cancer is largely due to its effect on estrogen.\textsuperscript{17} Obesity increases estrogen levels in postmenopausal women and reduces progesterone levels in premenopausal women.\textsuperscript{15}

Based on the study, it was found that there was a significant correlation between BMI and endometrial cancer types (p value <0.05). Study by Felix, Weissfeld, Stone, Bowser, Chivukula, et al. showed that 36% of cases of type II endometrial cancer were obese while those of type I were 55%. Felix, Weissfeld, Stone, Bowser, Chivukula, et al. also found an inverse correlation between obesity and type II endometrial cancer.\textsuperscript{20}

The correlation between obesity and endometrial cancer is stronger in cases of type I endometrial cancer (estrogen-dependent). This is in accordance with the study of Felix, Weissfeld, Stone, Bowser, Chivukula, et al. which showed that cases of obesity have an OR value of 2.22 for type I endometrial cancer compared to type II.\textsuperscript{20} Although these findings are consistent with the estrogen hypothesis, there were other findings reported that increased BMI is also a risk factor for type II endometrial cancer. This is proven by the study of Bjorge, Engeland, Tretli and Weiderpass who reported that women with more weight and obesity consecutively had a chance of 1.26 and 1.94 times for the development of type II cancer.\textsuperscript{21} Based on these findings, BMI may have an important role in the development of all cases of endometrial cancer, but the effect seems to be stronger against type I endometrial cancer.\textsuperscript{20}

**Characteristics of Diabetes Mellitus and Its Correlation with Type of Endometrial Cancer**

This study shows that most endometrial cancer patients do not suffer from diabetes...
mellitus. This result is in accordance with the study of Dewi and Budiana at RSUP Sanglah Denpasar which found 11.5% of endometrial cancer patients had diabetes mellitus and 88.5% did not suffer from diabetes mellitus.3

Women with diabetes mellitus have 2 to 3-fold risk of endometrial cancer.11 Friberg Mantzoros and Wolk found that the risk is increased by more than 6-fold when diabetes was associated with obesity and increased by 10-fold when women with diabetes and obesity did not exercise. This reflects the combination of diabetes with obesity and low physical activity associated with an increased risk of endometrial cancer. Interventions to reduce weight and increase physical activity may have important implications in term of preventing endometrial cancer in the future.22

Based on the study, it was found that there was no significant correlation between the history of diabetes mellitus and the type of endometrial cancer. This is in accordance with the study of Setiawan, Yang, Pike, McCann, Yu, et al. who found a correlation between history of diabetes mellitus with both types of endometrial cancer with OR value 1.53 and 1.27.15

Type II endometrial cancer is generally described as estrogen-independent, so it can be anticipated that exposure to estrogen and anti-estrogen will not be associated with risk factors for type II cancer. However, in a study conducted by Setiawan, Yang, Pike, McCann, Yu, et al. identified a correlation between estrogenic and risk factors for type II cancer. This suggests that risk factors related to estrogen proliferation or related mechanisms involving estrogen are also important for type II cancer. For example, the mechanism associated with obesity, hyperinsulinemia which is also a feature of type 2 diabetes mellitus, was found to be associated with type II tumors.15

Characteristics of Hypertension and Its Correlation with Type of Endometrial Cancer

This study shows that most endometrial cancer patients do not have a history of hypertension. This result is in accordance with the study of Dewi and Budiana at RSUP Sanglah Denpasar which found 11.5% of endometrial cancer patients had a history of hypertension and 88.5% had no history of hypertension.3

Based on the study, it was found that there was no significant correlation between hypertension and endometrial cancer type (p value ≥0.05). Malik, Chisti, Aziz and Sheikh also conducted study by comparing risk factors including hypertension between type I and II endometrial cancer and obtained p value of 0.21. In this study, hypertension cannot be considered as a risk factor independently, because it can only be a risk factor if in obese people.18

Characteristics of Genetic History and Its Correlation with Type of Endometrial Cancer

This study shows that most patients with endometrial cancer have no genetic history. Based on the study, it was found that there was no significant correlation between genetic history and type of endometrial cancer (p value ≥0.05). This is in accordance with the study of Malik, Chisti, Aziz and Sheikh that found a history of cancer in family is proportional for both type I and II endometrial cancer (p value =0.20).18

In the study by Wang, Risch, Lu, Irwin, Mayne, et al. it was found that genetic risk was significantly correlated with endometrial cancer without any other factor adjustment. This relationship became insignificant after the BMI and other factors were adjusted in the analysis. This explains that the genetic role in disease risk is relatively weak compared to
environmental and lifestyle exposure.\textsuperscript{17}

**Characteristics of Exclusive Breastfeeding and Its Correlation with Type of Endometrial Cancer**

This study shows that most endometrial cancer patients provide exclusive breast milk. Exclusive breastfeeding generally suppresses ovulation and maternal estrogen level. Decreasing estrogen level reduces endometrial mitosis and hence can reduce the risks of endometrial cancer. However, clear evidence for this association is still lacking.\textsuperscript{23}

The correlation between breastfeeding and the risk of endometrial cancer is biologically plausible because breastfeeding can suppress gonadotropin releasing hormones, inhibit ovarian follicle growth and reduce estradiol level. At this level, the mitosis of endometrial cells is barely occurred.\textsuperscript{23}

Based on the study, it was found that there was no significant correlation between exclusive breastfeeding and the type of endometrial cancer. In the study of Jordan, Na, Johnatty, Wise, Adami, et al. exclusive breastfeeding does not differ substantially based on the type of endometrial cancer. Differences are influenced by race/ethnicity, BMI in early adulthood and the time since the last pregnancy, but the difference is not statistically significant.\textsuperscript{23}

The correlation between breastfeeding and endometrial cancer seems to be influenced by BMI. The body mass index can change that association because obesity lowers level of sex hormone-binding hormones, increasing estrogen and testosterone which are available biologically. Estrone production in adipose tissue in obese women can negate the relative hypo-estrogenic state caused by the breastfeeding effect.\textsuperscript{23}

**Conclusion**

In this study, it can be concluded that there is a correlation between age of menarche and BMI with the type of endometrial cancer. The most dominant factors affecting the type of endometrial cancer are BMI, age and age of menarche.

**Acknowledgement**

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**References**

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