

ORIGINAL RESEARCH

Age and Body Mass Index in Type I Endometrial Cancer Grade

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ABSTRACT

Background: The increase in obesity and life expectancy has contributed to type I endometrial cancer cases worldwide. Increased risk factors play a role in the increase of these cases. **Objective:** To determine the relationship between age and BMI with the cancer grade. **Material and Method:** This research was a cross-sectional study. The data were obtained from the patient's medical records. The sampling technique was total sampling. The analysis used was Spearman Rho correlation test for the relationship between age and BMI with cancer grade. **Result:** This study recorded 54 patients with type I endometrial cancer in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from 2019 to 2020. The patients were from the age group 56-65 years 25 patients (46.30%), 46-55 years 17 patients (31.48%), 36-45 years 8 patients (14.81%), 26-35 years 2 patients (3.7%), and >65 years 2 patients (3.7%). For BMI, the patients were overweight (23-24.9 kg/m²) 21 patients (38.89%), normal (18.5-22.9 kg/m²) 14 patients (25.93%), obesity (25-29.9 kg/m²) 12 patients (22.22%), and obesity II (≥ 30 kg/m²) 7 patients (12.96%). For grade, grade III were 22 patients (40.75%), grade II 20 patients (37.04%), and grade I 12 patients (22.22%). There was a weak, insignificant positive correlation between age with grade ($\rho=0.116$, $0.405 > \alpha=0.05$) and a weak, insignificant negative correlation between BMI with grade ($\rho=-0.206$, $0.135 > \alpha=0.05$). **Conclusion:** A total of 54 patients with type I endometrial cancer at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from 2019-2020 aged 56-65 years and overweight (23-24.9 kg/m²) with grade III cancer. The patient's age and BMI did not correlate with the patient's grade.

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BACKGROUND

According to data from the [World Cancer Research Fund International \(2020\)](#), there were more than 380,000 new patients with endometrial cancer in 2018. This cancer showed an increase in new cases as evidenced by data from The Global Cancer Observatory (GCO) in 2012, which recorded 6,475 new cases, and in 2020 recorded 7,773 new cases of endometrial cancer in Indonesia ([International Agency for Research on Cancer, 2020](#)). Confirming these data, The Global Burden of Disease study in 2017 stated that an increase in endometrial cancer cases occurred from 1990 to 2017 at global, regional, and national levels throughout the world ([Zhang, et al., 2019](#)). Recording of endometrial cancer is not carried out precisely and routinely in Indonesia because there is no data collection system for this cancer. Still, several descriptive studies in major hospitals in Indonesia show epidemiological data on endometrial cancer.

Most endometrial cancers are those of type I which is an estrogen-dependent endometrial cancer ([Wilczyński, et al., 2016](#)). Type I endometrial cancer often presents symptoms at an early stage, so this cancer generally has a good prognosis and is characterized by high five-year survival rates ([Stubert & Gerber, 2016](#)). The exact cause of this cancer is unknown, but the risk factors are well known. This increase in cancer cannot be separated from the increase in risk factors in the community. Two major risk factors that play a significant role today are age and obesity ([Khazaei, et al., 2018](#)).

Old age is the age group that most often develops cancer, including type I endometrial cancer. The increase in life expectancy worldwide has contributed to this cancer. From 2010 to 2020, an increase in life expectancy occurred in Indonesian women from 71.83 to 73.46 years ([Statistics Indonesia, 2021](#)). This increase means that many Indonesian women can reach the age at which most type I endometrial cancers are diagnosed.

From 1975 to 2016, obesity in the world has almost tripled, and about 650 million adults (≥ 18 years) are obese ([World Health Organization, 2021](#)). Based on Basic Health Research (Riskesdas) 2018, overweight and obesity among Indonesian women are more common among those who are aged 40-44, with junior high school education, working as civil servants, and living in urban areas. Then, based on Riskesdas 2013-2018 for the East Java area, obesity increased from 8.4% to 22.37% in adult population ([The Ministry of Health, Republic of Indonesia, 2018b](#)).

Other studies also support that Indonesian women (≥ 18 years old) have a greater chance of being overweight than Indonesian men in this decade. Several factors related to obesity in women are marital status, having a high standard of living (indicating a high income), or being in the highest socioeconomic group, low daily physical activity, unhealthy eating habits, and living in an urban area ([Rachmi, Li & Alison Baur, 2017](#)).

The increase in obesity cannot be separated from the widespread consumption of unhealthy food and passive activities, which are very common today ([The Ministry of Health, Republic of Indonesia, 2018a](#)). One of the most frequently described mechanisms is obesity. They are increasing the active estrogen through peripheral conversion by fat tissue. The higher the fat tissue content, the higher the estrogen level ([Onstad, et al., 2016](#)).

Type I endometrial cancer's grade, or degree of differentiation is generally low-grade (grade 1 or 2). The grade is one indicator to determine the prognosis of these cancer patients so that many of the patients with lower grades have a better prognosis ([Soslow, et al., 2019](#)). Type I endometrial cancer is a multifactorial disease, so various risk factors influence the development of this cancer. Stronger or bigger risk factors are thought to affect the appearance of the cancer in this grade.

Previous studies describing endometrial cancer in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, did not precisely separate the two types of endometrial cancer, so it had not been clearly described. This study tried to update the data based on these facts, and because there is no national registration system yet, it must be updated continuously ([Sofyan, et al., 2020](#)).

This study compared age and BMI with grade I endometrial cancer for preoperative indicators that can help manage type I endometrial cancer therapy. In most cases, treatment for endometrial cancer is generally surgery. However, many controversies regarding therapeutic management still require further investigation ([Dinkelspiel, et al., 2013](#)). An example is surgery in managing endometrial cancer, such as bilateral salpingo-oophorectomy and lymphadenectomy, which are not routinely performed for all cases of endometrial cancer. This is not routinely done because if surgery is performed on early-stage patients and young patients can have some complications. FIGO recommends complete surgical therapy

only if the patient's prognostic factors are identified. As a result, other preoperative indicators are needed to assess the presence of metastases in the adnexa and lymph nodes as a prognostic factor (Askandar & Saputra, 2021).

Then low-grade endometrioid cancer, one of the endometrial cancer types I, is the most common and controversial surgical therapy. Many studies recommend lymphadenectomy for all grades, but it is not routinely performed (Rahestyningtyas, et al., 2019).

Preoperative indicators that can potentially be used for therapeutic management are major risk factors for endometrial cancer, namely nutritional status and age. These two are the factors that can interfere the differentiation of endometrial cells that affect the grade as a prognostic factor. In summary, excess adipose tissue causes dysregulation of adipose tissue signaling, resulting in extra reactive oxygen species (ROS) formation and increased proinflammatory or immune signaling (Reho & Rahmouni, 2017). Similarly, aging is associated with the production of antiproliferative molecules (He & Sharpless, 2017). Therefore, in addition to the descriptions of patient characteristics based on age, BMI, and grade, this study also aimed to determine whether there was a relationship between age and BMI with type I endometrial cancer grade.

OBJECTIVE

To determine the relationship between age and BMI with type I endometrial cancer grade.

MATERIAL AND METHOD

This was a cross-sectional study with the population comprising patients diagnosed with type I endometrial cancer and treated at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from 2019-2020. Data of the patients were taken from the medical records that met the inclusion criteria that contained all information related to the variables to be studied, ie. the patient's age, body mass index, diagnosis, and cancer degree. The medical records were excluded if one of those data was missing. From 54 medical records obtained, all of them met the inclusion criteria. Then the data was processed and analyzed by SPSS. The analysis carried out was descriptive and correlative analysis with the Spearman Rho test.

RESULT

Of the 54 subjects, the majority had a diagnosis age of 56-65 years (46.30%), had a body mass index (BMI) of overweight (38.89%), and had grade III of cancer (40.75%).

Table 1. Frequency distribution based on patient's age of diagnosis

Age (Years)	Quantity (People)	Percentage
Early adulthood (≤ 35)	2	3.70%
Late adulthood (36-45)	8	14.81%
Early elderly (46-55)	17	31.48%
Late elderly (56-65)	25	46.30%
Seniors (> 65)	2	3.70%
Total of patients	54	100%

Table 2. Frequency distribution based on patient's body mass index

Body mass index (kg/m ²)	Quantity (People)	Percentage
Underweight (< 18.5)	0	0%
Normal (18.5-22.9)	14	25.93%
Overweight (23-24.9)	21	38.89%
Obesity (25-29.9)	12	22.22%
Obesity II (≥ 30)	7	12.96%
Total of patients	54	100%

Table 3. Frequency distribution based on patient’s cancer grade

Grade	Quantity (People)	Percentage
I	12	22.22%
II	20	37.04%
III	22	40.75%
Total of patients	54	100%

The results of this study stated that the mean age of diagnosis of the patients was 53.28 years (SD±8.97), and the median age of diagnosis was 55.5 years. Then the mean BMI of the patients was 25.86 kg/m² (SD±4,38), and the median BMI of the patients was 25.16 kg/m².

Table 4. Descriptive statistics on age and body mass index

Variables	N	Mean±SD	Median	Min-Max
Age	54	53.28±8.97	55.50	33-70
Body mass index	54	25.86±4.38	25.16	19.53-41.01

The results of the Shapiro-Wilk normality test on this research variable can be seen in Table 5. The grade and BMI variables showed a significance of less than 0.05, so the two variables were not normally distributed, while the age variable showed a significance of more than 0.05 and it was normally distributed. Because there were data that were not normally distributed, the correlation test used was the Spearman Rho test.

Tabel 5. Shapiro-Wilk test results of each variable

Variable	Statistic	df	Sig.
Age	0.971	54	0.209
BMI	0.901	54	0.000
Grade	0.791	54	0.000

The results of the Spearman Rho test for age and BMI for a grade can be seen in Table 6. Based on these results, the correlation coefficient (ρ) between age and grade was 0.116, indicating a weak positive correlation between age and patient grade. The significance was 0.405 (>0.05), indicating a weak or insignificant positive correlation between age and patient grade. Furthermore, from the test results, BMI and grade showed -0.206, showing a weak negative correlation between BMI and patient grade. The significance was 0.13 (>0.05). This showed a weak or insignificant negative correlation between BMI and patient grade.

Table 6. Spearman Rho test result of age and BMI on grade

Variables	Correlation coefficient (ρ)	Significance (Sig.)
Age – Grade	0.116	0.405
BMI – Grade	-0.206	0.135

DISCUSSION

Age

The results of this study indicated that the age range was relatively the same as in other studies, which was between 56-65 years. According to SEER, the most diagnosed age range for type I endometrial cancer is 55-64 years (National Cancer Institute, 2022). However, although many studies have similarities in the age range of diagnosis, there are differences between the mean and median age of this cancer diagnosis. This cancer was diagnosed at a mean age of 61.9 years in America, 55 years in China, 53.37 years in a hospital Jakarta, Indonesia, and 53.28 years in this study (Nevadunsky, et al., 2014; Gao, et al., 2016; Nuryanto & Fransiska, 2019).

Several factors may have caused differences in the mean age of diagnosis. The first was the difference in the number of data samples. The study on American and Chinese women used a much larger sample than the study in Jakarta, Indonesia. The study conducted in America involved 592 types I endometrial cancer patients (Nevadunsky, et al., 2014). Then a study in China with samples from all major hospitals in China with a sample of 1127 patients (Gao, et al., 2016). While the study in Jakarta had an average age of diagnosis that was relatively close to this study, using only 82 samples (Nuryanto & Fransiska, 2019).

Larger number of samples allowed higher number of older women to be diagnosed, so there were more older women included in calculating the average age of diagnosis. The mean age of diagnosis is the ratio between the total age and the amount of data. As a result, higher number of samples may result in an older mean age of diagnosis.

The second reason was the role of other unobserved risk factors. In this study, the median age of diagnosis was 55.5 years, while other studies still showed an older age. A New York study with 39 patients showed the median age of diagnosis was 61 years, then a study at Royal Cornwall Hospital Truro with 688 patients showed a median age of diagnosis of 66 years (Khoury et al., 2019; Donkers et al., 2020).

The difference between the mean age and median age of the diagnosis was not statistically significant. Differences in age of diagnosis can be based on the nature of type I endometrial cancer, which has many risk factors that may be different for each person, and the development of cancer in each person can be faster or slower depending on the risk factors.

Until now, Indonesia does not yet have a registration system for type I endometrial cancer, so it must continually be updated so that there is continuous data for epidemiological studies and a better understanding of this cancer.

Body Mass Index

Body mass index is one of the risk factors for endometrial cancer, with every increase of 5 kg/m² increasing the risk of 50% of endometrial cancer (Onstad, et al, 2016). However, this study showed that higher BMI did not indicate more endometrial cancer sufferers. This is because overweight people are statistically in larger number than those with obesity. Individuals with higher BMI are not necessarily affected with endometrial cancer. Therefore, obese people with endometrial cancer are rarely found than those with overweight. Such condition may also result from delayed examination. Cancer is one factor of weight loss, which, in more extreme condition, it may lead to cachexia. When the cancer has developed and resulted in weight loss, but the patient had not been examined, the body weight at the time of diagnosis may relatively lower than before. This shows that body weight data of the patient before being ill is also important (Baracos, et al., 2018).

In this study, the nutritional status group with the most diagnosed type I endometrial cancer was relatively similar to a study conducted in China involving 872 types I endometrial cancer patients from a major hospital. In that study, the group most frequently diagnosed was the overweight group, with 395 patients (46.2%). However, the mean BMI of patients in that study was lower than in this study, which was 23.19 kg/m², while in this study, it was 25.86 kg/m² (Gao, et al., 2018).

If looking at the median BMI in the Chinese study previously described, the median BMI was not far from the statistical average BMI. The median BMI in that study was 24.01 kg/m² for stage I, 23.44 kg/m² for stage II, 23.43 kg/m² for stage III, and 22.61 kg/m² for stage IV. The study also showed that in more progressive cancer, the patient's BMI tends to decrease but is still in the overweight category, except for stage IV in the normal category (Gao, et al., 2018).

The median BMI of patients in this study was 25.16 kg/m². This figure is also not far from the patient's average BMI statistically and shows that most type I endometrial cancer patients have an overweight BMI. This finding aligns with the statement that being overweight increases the risk of type I endometrial cancer (Pokharna, 2017).

Grade

The most frequently encountered grade in this study was grade III. According to the theory, type I endometrial cancer usually occurs in lower grades (grades I and II) (Pokharna, 2017). Based on the binary system, the results of this study were that most of the patients (32 patients) had a low grade. However, based on the FIGO system, most of the patients in this study had grade III as many as 22 patients. In this study, patients with higher grade of cancer were found in higher number than those with lower grade, while theoretically, it was the patients with lower grade of cancer who should have been in higher number. Research conducted at Ciptomangunkusumo Hospital, Jakarta involving 82 patients showed that most patients had low-grade endometrial cancer, namely 31 grade I patients, 33 grade II patients, 13 grade III patients, and 5 of whom were unknown (Nuryanto & Fransiska, 2019).

This difference may have resulted from shortcomings in grade determination. For example, methodology, and specimens used by the examiner are different. The difference is also affected by the variation between examiners in assessing the results of the examination due to unclear classification. For example, a microacinar which appears as a small lumen can be judged by the examiner as solid growth (no lumen). Finally, the growth rate is higher than expected and it is also possible that the grade is categorized as a higher grade than it should be because dense growth is an aspect of this cancer classification. There are no special rules regarding this in the FIGO or binary system, which also causes variations between examiners (Soslow, et al., 2019).

Other causes could be unobserved risk factors that may affect grade appearance. Further research is needed on this variable because the findings differ from previous studies to confirm whether this phenomenon happens by chance or other influencing factors.

Relationship between age and grade

The degree of differentiation or grade of cancer is based upon genetic expression. Aging affects the expression of genes. This study did not find significant relationship between the samples. There had been no other studies observing relationship between age and endometrial cancer type I. However, such relationship in other cancers had been examined, for instance: relationship between age and grade in breast cancer, but no association was found. A study at the Central General Hospital Adam Malik Medan on breast cancer, which also has estrogen-dependent properties, did not show an association between age and grade (Mardiah, et al., 2021).

The TCGA classification divides endometrial cancer into four groups and can explain the appearance of grades based on their genetic profile (Travaglino, et al., 2020). The older the age, the higher the possibility of cells experiencing mutations. Mutations that occur can affect endometrial tissue cells in gene expression. However, mutations in DNA in aging are unpredictable and can occur randomly (Lodato & Walsh, 2019). As a result, it is possible that age does not seem to be related to the grade of this cancer.

Then, other risk factors can influence the relationship between age and grade. Although there was a positive relationship between age and cancer grade in this study, the relationship between age and grade of cancer can be very complex. If there is only the effect of age, the single effect of age is not sufficient to cause a significant change in cancer grade, but when age with other risk factors are present, it can cause a significant change in cancer grade due to the effect from age and other risk factors are mutual. Therefore, further studies with larger samples and other risk factors are needed to determine better relationship between age and cancer grade.

Relationship between BMI and grade

Factors that influence cell differentiation include signaling, environment, and developmental level of the organism. These will determine the gene expression of the cell. Fat cells in fat tissue play a role in cell signaling that can regulate gene expression in other body parts. One of the molecules that play a role in this signaling is leptin, an adipocytokine that plays a role in storing long-term energy reserves (Flak & Myers, 2016). Fat tissue also affects the balance of estrogen. Excess fat tissue will cause higher

estrogen levels in the body and interfere with cell differentiation in the endometrium (Rodriguez, et al., 2019). These two molecules are thought to play a role in developing type I endometrial cancer (Boroń, et al., 2021).

In this study, the sample was also unable to show the relationship between BMI and grade. This result also means that this study did not find a relationship between BMI and grade. Other studies examining relationship between BMI and grade for type I endometrial cancer were not available. However, relationship between BMI and grade of breast cancer had been examining in a study, which also found no relationship between BMI and grade. A study at Central General Hospital Adam Malik Medan on breast cancer involving 103 patients showed a weak correlation between BMI and cancer grade ($p=0.018$, $r=0.018$ (0.233)) (Mardiah, et al., 2021). This study found that the correlation was negative, which means that the higher the BMI, the lower the grade. This fact needs to be a concern because, in addition to being found in many grade III patients, this correlation shows a different direction from similar estrogen-dependent cancers.

CONCLUSION

Most of the 54 endometrial cancer type I patients at Dr. Soetomo General Hospital in 2019-2020 had a were between 56-65 years, a body mass index of overweight, and had grade III cancer. There was a weak insignificant correlations between age and grade and between BMI and grade.

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Conflict of Interest

All authors have no conflict of interest.

Ethics Consideration

This research has passed the ethical clearance test from the Dr. Soetomo Hospital Health Research Ethics Committee with a number (0604/104/4/III/2021).

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The authors declare that we have no relevant or material financial interests that relate to the research described in this paper.

Author Contribution

All authors whose names appear on the submission have contributed to all processes in this research, including preparation, data gathering, and analysis, drafting, and approval for publication of this manuscript.

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