Relationship between Age and Histopathological Type and Grade of Cervical Cancer Incidence

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Abstract
Cervical cancer is the fourth most common gynecologic cancer worldwide, mostly caused by Human Papillomavirus (HPV) infection. HPV infects squamous epithelial cells at the squamocolumnar junction in young women, where many lesions can disappear within 6-12 months thanks to the immune system. However, some lesions can persist and develop into cancer, especially squamous cell carcinoma and adenocarcinoma. As age increases, the decline in the immune system worsens the prognosis, and the type and grade of histopathology detected tend to be more severe in old age. Methods: This study was an observational analytic with a retrospective approach with a cross-sectional study design. Data were obtained from medical records of cervical cancer patients for age categories. Then, 26 histopathological slides of cervical cancer patients were observed under a microscope to see the type and grade of histopathology of cervical cancer. Results: Based on age with histopathological type, adenocarcinoma was found in <50 years of age 9 samples and squamous cell carcinoma in> 50 years of age 12 samples. In age with histopathological grade, mild-moderate grade occurs in <50 years or >50 years with 18 samples and severe grade occurs in >50 years with 6 samples. The results of the Fisher Exact Chi-square test obtained p = 0.003 and p = 0.395. Conclusion: There is a relationship between age and histopathology and there is no relationship between age and histopathological grade of cervical cancer patients.

Keyword:
Cervical cancer grade, histopathological type , cervical cancer, age

1. INTRODUCTION

Cervical cancer is the fourth most common gynecological cancer in women worldwide. In 2020, an estimated 604,000 new cases and 342,000 deaths were recorded, with 90% of new cases and deaths worldwide occurring in low- and middle-income countries. In Indonesia, cervical cancer is the second most common cancer after breast cancer. According to GLOBOCAN (Global Cancer Observatory) data, the incidence of cervical cancer in Indonesia in 2018 was around 32,469 cases (17.2%) with a mortality rate of 18,279 (8.8%). According to the International Academy of Pathology reported that in 13 hospitals in Indonesia, cervical cancer reached the highest number with a percentage of 17.25% which was then followed by breast cancer at 12.2%. Most patients are in the productive age of life. This disease is a major problem both in terms of economy and health in Indonesia. Most cervical cancers are caused by persistent Human Papillomavirus (HPV) infection. The International Agency for Research on Cancer has determined 12 types of HPV as carcinogenic from 200 other types of HPV, where the presentation of HPV16 accounts for 50% and HPV18 accounts for 10% playing a role in the occurrence of cervical cancer cases. Human Papillomavirus is categorized into low-risk or high-risk strains depending on its oncogenic potential. This virus can be transmitted through sexual contact which will cause squamous intraepithelial lesions. HPV will infect immature squamous epithelial cells at the squamocolumnar junction in young children. Most of these lesions can disappear after 6-12 months due to intervention from the immunological system. However, a small portion of these lesions can persist and will eventually cause cancer. The incidence of cervical cancer has decreased in developed countries due to increased screening and HPV vaccination . However, a study conducted by Li et al (2021) reported that the incidence of cervical cancer in China shows an increasing trend and is found at a younger age in recent years. Several studies have found that cervical cancer is found

at the age of 27 years with a peak seen at the age of 41-60 years. The average age found was 48.6 years and in Indonesia itself, cancer patients were found to be dominated by the age of 41-60 with an average age of 48 years which was conducted in Surabaya from March to August 2016.

The most common histological types of cervical cancer after HPV infection are squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma has various subtypes including keratinizing and non-keratinizing squamous cell carcinoma and basaloid type. From the research that has been done, the histopathological picture of keratinizing and non-keratinizing squamous cell carcinoma has a peak age of 41-50 years. While the average age of adenocarcinoma picture in the study was the age group of 41-55 years. In another study, it was reported that the histopathological results of squamous cells with a presentation of 55% at the age of> 50 years, and the histopathological picture of adenosquamous was most often found> 50 years with a presentation of 58%. The next type is adenosquamous carcinoma which is most common at the age of 35-50 with a presentation of 31%. There are risk factors that affect the incidence of cervical cancer, including low socioeconomic status, having sex at an early age, namely under 18 years of age, many sexual partners, multiple pregnancies, a history of sexually transmitted diseases and long-term use of oral contraceptives for more than 5 years and smoking because it can destroy Deoxyribonucleic Acid (DNA) cells in the cervix which contributes to the development of cervical cancer. Another factor that plays a role is age. During puberty, the endocervical epithelium is replaced by immature squamous epithelium until it matures. This is known as the transformation zone which is the most common site for the development of cervical cancer. In 94% of women under the age of 25 years, the transformation zone is located in the ectocervix. As age increases, the proportion decreases to less than 2% after the age of 64 years. If the transformation zone is located in the ectocervix, there is a 1.8 times higher chance of finding dysplastic lesions. As age increases, the immune system decreases, so the prognosis will be worse where the type and grade of histopathology detected are also worse in old age. Research that has been conducted by several researchers shows that disease-free survival is longer in cases with squamous cell carcinoma (1.53 years) compared to histopathological images of adenocarcinoma type (1.51 years). Patients with adenocarcinoma have worse survival compared to patients with squamous cell carcinoma, especially in patients with advanced stages and show a strong impact of adenocarcinoma compared to squamous cell carcinoma. Until now, research related to age with the incidence of cervical cancer has not been conducted at the location to be studied. By conducting this research, researchers expect to find the incidence of cervical cancer and analyze the types and degrees of histopathology that most often occur at a predetermined age. Based on the description above, researchers want to know the relationship between age with the type and degree of histopathology of cervical cancer incidence

2. RESEARCH METHODOLOGY

This study is an observational analytical study with a retrospective approach with a cross-sectional research design. The study was conducted by collecting medical record data and slides from patients with cervical cancer. This study was conducted from July to December 2022. The research location was at the Anatomical Pathology Laboratory, Faculty of Medicine, Muhammadiyah University of North Sumatra. Medical records and histopathological preparations of cervical cancer patients were taken from Medan General Hospital and Prof. Najib Dahlan Lubis Laboratory, Sp.PA (K). The sampling technique used was the total sampling technique due to the minimal sample. The samples obtained were 26 samples. The collected slides will be re-observed to determine the type and histopathological grade of cervical cancer.

3. RESULT AND DISCUSSION

The research has received approval from the Health Research Ethics Commission (KEPK) of the Faculty of Medicine, Muhammadiyah University of North Sumatra with No: 932/KEPK/FKUMSU/2022. The samples obtained with cervical cancer were 14 slides and from a private Anatomical Pathology laboratory were 12 slides. Data collection in this study was carried out using primary data, namely by directly examining histopathology slides and secondary data obtained.

Table 1. Distribution of Age Groups in Cervical Cancer Disease

Age	Frequency	%	Cumulative Percent
<50 years	11	42.3	42.3
>50 years	15	57.7	100.0

Amount	26	100.0

Based on the results Table 1 above shows that cervical cancer sufferers are more often diagnosed at the age of >50 years with a sample size of 15 people (53.8%).

Table 2. Frequency Distribution of Cervical Cancer Patients Based on Histopathology Type

Histopathology Type	Frequency	%	Cumulative Percent
Squamous cell carcinoma	14	53.8	53.8
Adenocarcinoma	12	46.2	100.0
Amount	26	100.0	

Based on **Table 2** above, it shows that the majority of samples (53.8%) of cervical cancer patients had a histopathological type of squamous cell carcinoma

Table 3. frequency Distribution of Cervical Cancer Patients Based on Histopathology Grade

Degrees	Frequency	%	Cumulative Percent
Light - Medium	18	69.2	69.2
Heavy	8	30.8	100.0
Amount	26	100.0	

Table 3 shows that the above shows that cervical cancer sufferers are mostly diagnosed with mild-moderate degrees.

Table 4 Relationship between Age and Histopathology Type of Cervical Cancer Patients

Histopathology Type	Age				Amount	Value
	<50 years	%	>50 years	%		
Squamous Carcinoma	2	14.3%	12	85%	14	0.003
Adenocarcinoma	9	75%	3	25%	12	
Amount	11	89.3%	15	110%	26	

Based on Table 4, the chi square test above obtained the Fisher's Test Exact Sig. (2-sided) value of 0.003 (P <0.05) which means there is a relationship between the two variables. Table 4.4 above shows the histopathology type of squamous cell carcinoma, most of the 12 samples were diagnosed with cervical cancer at the age of >50 years, some 2 samples were diagnosed with cervical cancer at the age of <50 years. While in the histopathology type of adenocarcinoma, most of the 9 samples were diagnosed with cervical cancer at the age of <50 years, some 3 samples were diagnosed with cervical cancer at the age of >50 years

Table 5. Relationship Between Age and Histopathology Grade of Cervical Cancer Patients

Histopathology Grade	Age				Amount	Value
	<50 years	%	>50 years	%		
Light - Medium	9	50%	9	50%	18	0.395
Heavy	2	25%	6	75%	8	
Amount	11	75%	15	125%	26	

Based on Table 5, the chi square test above obtained the Fisher's Test Exact Sig. (2-sided) value of 0.395 (P>0.05) which means there is no relationship between the two variables. The table above shows that mild-moderate degrees mostly occur in <50 years or >50 years. So it can be concluded that there is no relationship between age and histopathological degree at the time of diagnosis. HPV infection is the leading cause of cervical cancer, the fourth leading cause of gynecologic cancer in women worldwide. This virus can cause squamous intraepithelial lesions to develop through sexual contact. Lesions caused by the virus can

disappear due to intervention from our own immune system, but some of these lesions can also persist and develop into cancer. From this study in table 4.1 it was found that most cases of cervical cancer were diagnosed at the age of >50 years as many as 15 samples (57.7%). The results of this analysis are in line with Soeparjoo Azmel's article which found that the average age of cervical cancer was at the age of >50 and found a factor of ADAM9-positive expression. Where the results are in accordance with the theory according to the American Cancer Society which states that cervical cancer is most often diagnosed with an average age of 50 years when diagnosed. Many older women are not aware that the risk of developing cervical cancer increases with age. Because in the early stages of cervical cancer, patients will not find symptoms until abnormal cervical cells begin to attack the surrounding tissue. In table 4.2, it is found that the type of cell carcinoma is more often found in cervical cancer patients with a sample size of 14 (53.8%). Where this result is in line with the journal from Indan J Med which states that squamous cell carcinoma is the most common type of carcinoma found in female genitalia. (6) Generally occurs due to the location of the cell itself which is located in the ectocervix. There are several things to help find out about its invasion by looking at stromal inflammation, groups of single or small epithelial cells, elongated rete ridges and loss or absence of nuclear polarity in cells.

In the adenocarcinoma type itself, it is very rarely detected because the anatomical location of the cervix makes it difficult for ectocervical tissue to be taken for a pap smear test. Based on table 4.3, it was found that mild-moderate cervical cancer was diagnosed more with 18 samples (69.2%). Where the results of the study are in line with the study conducted by Rahmani et al who obtained mild-moderate results of 47 samples more than severe grades of 18 samples. According to the theory that the degree of severity is based on nuclear plemorphism, nucleolus size, mitosis activity and necrosis. The results of the statistical analysis that have been explained in table 4.4, the results obtained a p-value = 0.003, which means that there is a relationship between age and the histopathological type of cervical cancer. This explains that cervical cancer patients who have undergone histopathological examination, found differences in types at different age ranges. In this study, the results were that squamous cell carcinoma was mostly found at the age of >50 years in 12 samples. The results of this study are in line with the research conducted by Anggray Pupasari (2021), where out of 300 research samples, 122 (55%) women were diagnosed with squamous cell carcinoma at the age of >50 years. Likewise, Qin Liu's research found that most types of squamous cell carcinoma were found in women who were >50 years old. Godstime It et al conducted a study that was not in line with this study, the results found that the squamous cell carcinoma type was often found in those aged <50 years with a sample size of 151 samples from the total samples studied. This seems to be proven by the literature that states that squamous cell carcinoma develops from ectocervical cells found on the outside which have a higher risk of being exposed to and infected with HPV, especially with the risk of early intercourse where there is still a transformation zone consisting of immature cells.

However, for the adenocarcinoma type, it was mostly found at the age of <50 years in 9 samples. This study is in line with the study of Godstime I et al which produced data with the adenocarcinoma type at the age of <50 in 3 samples. The results of this study are also in line with Kemin Li (2017) who had an average age of adenocarcinoma occurrence at the age of <50 years as much as 86 (3.72%). However, on the one hand, this study is not in line with Lei Zhang who found that adenocarcinoma was mostly diagnosed at the age of> 50 years as much as approximately 50% of the total adenocarcinoma samples studied. Where the literature states that adenocarcinoma is reported more at a young age, often occurs in white skin, and is often diagnosed at an early stage. According to A Berington De Gonzales, the diagnosis of adenocarcinoma type is related to other risk factors such as parity, use of oral contraceptives and others. This is also a limitation of this study where factors related to earlier diagnosis of adenocarcinoma type could not be identified. In table 4.5 there are data showing that mild degrees can mostly occur at the age of <50 years or >50 years. Where there is no relationship between age and histopathology degree. Likewise with the research of Kyeong A So where the results of the study found that mild-moderate and severe degrees were most common at the age of <30 years. While in the study of Qin Liu, the severity was found to be significantly higher at the age of 25-39 compared to the age group of 40-65. Based on this study, Kyeong A So and Qin Liu can conclude that the degree of cervical cancer can occur at varying ages. This has proven that there is no relationship between age and the occurrence of the degree of histopathology of cervical cancer patients.

The main limitation of the study is the use of cross-sectional as a research design, where the collection of medical records alone cannot assess the cause of adenocarcinoma in those aged <50 years and vice versa in the type of squamous cell carcinoma in those aged >50 years.There was no relationship between age and

degree because this study was not a case control study, so we cannot assess or see the degree of severity that occurs only from the age of first diagnosis. According to literature written by Pualina R Evriati in 2019, cervical cancer takes about 5-10 years after the first infection to develop into invasive cancer. Therefore, in women who have reached an older age, it takes longer so that exposure suppresses the immune system and can develop into cervical cancer. Persistent Human Papilloma Virus will make the lesion extensive and invasive, so it can delete the E2 coding gene that has an impact on blocking the cell cycle and inactivating tumor suppressor proteins, namely p53 and pRb. Over time, the work of natural killer (NK) will be disrupted and experience a decrease in receptor regulation so that it cannot attach to and eliminate cancer cells. With the decline in NK function, it can trigger the failure of the apoptosis mechanism and fail to control cell division which leads to the formation of cancer. The process of cancer formation takes a long time to infect so that it changes the shape of the cell and eventually develops into cancer. However, it does not rule out the possibility of developing faster, especially in women who have low immunity.

4. CONCLUSION

The number of cervical cancer patient samples found was 26 samples. With the age of patients >50 years totaling 11 people and <50 as many as 15 people. In the examination of histopathology slides of cervical cancer patients, squamous cell carcinoma was found in 14 samples and adenocarcinoma was found in 12 other samples. In the examination of the degree, 18 samples found mild to moderate degrees and 8 samples found severe degrees. There is a significant relationship between age and histopathological type in cervical cancer patients. There is no relationship between age and histopathological grade in cervical cancer patients.

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