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Original Article

Risk Factors of Cervical Carcinoma and the Association of Age with Histopathological Diagnosis

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ABSTRACT

Introduction: *Within the high-risk group, HPV16 is the most oncogenic type, being responsible for approximately 50% of all worldwide cervical cancers. This study aimed to analyze the risk factors of cervical cancer and the association of age with histopathological diagnosis.* ***Methods and materials:*** *This cross-sectional study was carried out in the Pathology department of Sir Salimullah Medical College and Mitford Hospital Dhaka, from July 2017 to June 2019 with a total of 60 adult female patients with cervical cancer diagnosed histopathologically.* ***Results:*** *The mean age of the patients having cervical cancer was 57.75±8.96 years. 63.3% of patients belonged were over 11 years of age and 60.0% of patients were postmenopausal. The mean marital age was 16.48±2.22 years. Most (81.7%) of the patients underwent a hysterectomy. 48.33% of the patients had moderately differentiated squamous cell carcinoma and 26.7% well differentiates squamous cell carcinoma. The average age of different histopathological entity was also found 60 years. However, when the age was compared with different histopathological types of carcinoma (WHO-2014) it was found statistically insignificant (p=0.714).* ***Conclusion:*** *This study concluded that late menarcheal age was inversely associated with cervical cancer. Marriage at an early age, high parity, and irregular menstrual cycle are also important risk factors for cervical carcinoma.*

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Menopausal status is a well-known risk factor for cervical cancer and most cases occur after menopause. Most of the tumor belongs to moderately differentiated and their age range were mostly between 50-59 years.

***Keywords**: Cervical carcinoma, Histopathology, HPV, Menarche, Menopause*

INTRODUCTION

Cancer of the cervix uteri is the 4th most common cancer among women worldwide, and 7th overall [1]. Bangladesh has the highest level of incidence and mortality rates due to cervical cancer among women. The prevalence of cervical cancer in Bangladeshi women has been reported to be 25 to 30 per 100000 [2]. It is common in lower socio-economic groups, in women with sexual activity at an early age or multiple sex partners, and in smokers and alcoholics [3]. Infections with HPV are common and transmitted by direct contact. Although the great majority (90%) of infections resolve within 2 years but sexually transmitted HPV genotypes mainly HPV 16 cause cervical cancer if not controlled immunologically or by screening [4]. The main histological subtypes of cervical cancer are squamous cell carcinoma (80%) followed by adenocarcinoma (15%), and adenosquamous and neuroendocrine tumors account for the remaining (5%) [5]. In Bangladesh, cervical cancer remains the 2nd most leading cause of female cancers, mostly among women aged 15 to 44 years. About 11,956 new cervical cancer cases are diagnosed annually in Bangladesh [6]. In our community early age of marriage and conception, multiple pregnancies as well as other factors play important roles in cervical carcinogenesis. Several risk factors are linked with exposure to the Human Papilloma Virus. It tends to occur in mid-life and is most frequently diagnosed at the age of 35 to 44 [7]. Cervical cancer remains the second most common cancer and the leading cause of cancer deaths among women living in low to middle-income countries and for that matter Ghana [8]. Again, a weak immune system due to a lack of Langerhans cells can lead to poor viral clearance, which can result in the persistence of viral-infected cervical cells in smokers [9]. Poor nutrition among women who may be subsequently infected with HR HPV develops cervical cancer as compared with infected women taking good nutrition. Most of these women with cervical cancer may have had their first sexual debut at an early age with the risk increasing with the number of lifetime partners as stated by Akosua et al [10]. As confirmed by research, high parity increases a women's chance of developing cervical cancer; the greater the number of children the higher the risk of developing cervical cancer with age at first birth been important [11]. Other important risk factors are infrequent screening for cervical cancer and tobacco use. Overall lack of knowledge regarding cervical cancer is an underestimated risk factor for cervical cancer [10,12].

OBJECTIVES

General Objective

- To analyze the risk factors of cervical cancer and the association of age with histopathological diagnosis.

Specific Objectives

- To see the age distribution among the respondents
- To know the distribution of the study patients by age of menarche and marriage
- To know the menstrual status and parity of the study subjects
- To know the history of exposure

METHODS AND MATERIALS

This cross-sectional study was carried out at the department of pathology, Sir Salimullah Medical College, and Mitford Hospital Dhaka. The study was conducted over two years starting from 1st July 2017 to 30th June 2019. A total of 60 cervical biopsies and hysterectomies specimens with histologically confirmed carcinoma of the cervix were selected purposively. For histopathological diagnosis, the surgical specimens were fixed in 10% formalin, processed, embedded in paraffin, and stained with Hematoxylin–Eosin. All data were collected from the patients by a pre-designed questionnaire and data analysis was conducted by descriptive and analytical techniques including mean, SD, frequency distribution, computation of percentage, etc. Associations among qualitative and quantitative variables of various factors were studied by using the chi-square test and t-test where appropriate. A p-value < 0.05 was considered to be significant. Statistical Package for Social Science (SPSS) version 21 for windows was used to analyze the data.

Inclusion Criteria

- Adult female patients.
- Patients who had given consent to participate in the study.

Exclusion Criteria

- Patients with coexistent pathology of any other organ like the uterus and ovary etc. in addition to the cervix.
- Tissue blocks with extensive necrosis or hemorrhage
- Patients who did not give consent to participate in the study.

RESULTS

It was observed that the majority of the patients 29 (48.4%) were between 50-59 years. Out of them, more than two third of the patients belonged to age 50-69 years. The mean age was 57.75±8.96 years with ages ranging from 40 to 90 years (**Table-I**).

Table I: Age distribution of the study patients (N=60)

Age (in years)	N	%
40-49	9	15.0
50-59	29	48.4
60-69	17	28.3
≥70	5	8.3
Mean±SD	57.75±8.96	
Range(min-max)	40-90	

Regarding the distribution of the patients according to the age of menarche, it was observed that more than half (63.3%) of patients belonged to the age of menarche between 11 - 14 years. The mean age of menarche was found 11.92±1.28 years.

The age of menarche ranges from 9-15 years (**Table II**).

Table II: Distribution of the study patients by age of menarche (N=60)

Age of Menarche	N	%
9-11	22	36.7
>11	38	63.3
Mean±SD	11.92±1.28	
Range(min-max)	9-15	

It was observed that 38 (63.4%) patients were married between 15-18 years, 11 (18.3%) patients were married at 15 years and 38 (18.3%) patients got married over the age of 18 years. The mean marital age was 16.48±2.22 years. The range of age at marriage was between 12-21 years (**Table III)**.

Table III: Distribution of the study patients by age of marriage (N=60)

Age of Marriage	N	%
<15	11	18.3
15-18	38	63.4
>18	11	18.3
Mean±SD	16.48±2.22	
Range(min-max)	12-21	

Regarding the menstrual status of the patients, more than two-thirds (60%) of patients were postmenopausal and 24 (40%) are pre-menopausal (**Figure 1**).

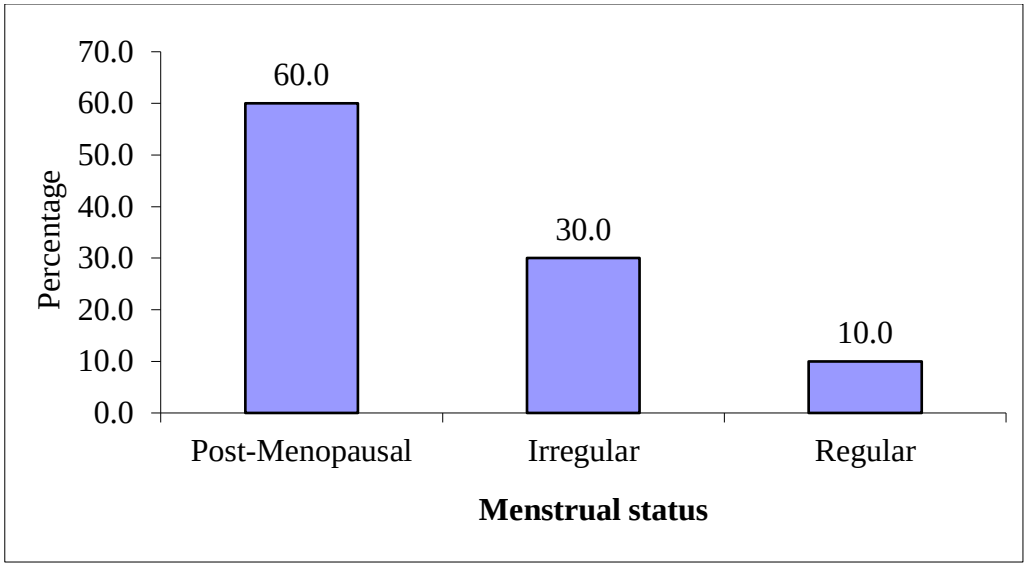

Figure 1: Bar diagram showing the menstrual status of the study patients [N=60]

Regarding the parity of the patients, it was observed that most of the patients were multiparous and each having 3 children or more (63.3%) (**Table IV**).

Table IV: Distribution of the study patients by parity (N=60)

Parity	N	%
0	3	5
2	16	26.7
3	17	28.3
4	14	23.3
5	7	11.7
6	3	5
Mean±SD	3.2±1.36	
Range (min-max)	0-6	

It was observed that only 10 (16.67%) patients disclose their exposure history and patients (13.3%) did not answer the question (**Table V)**.

Table V: Distribution of the study patients by the history of exposure (N=60)

History of Exposure	N	%
Yes	10	16.67
No	42	70
Not Answered	8	13.3

Regarding the type of specimen, it shows that most of the patients underwent 49 (81.7%) hysterectomies and 11(18.3%) underwent biopsies (**Figure 2**).

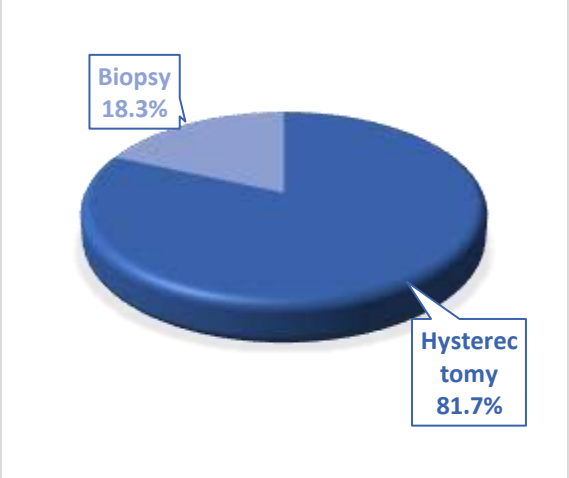

Figure 2: Pie chart showing the type of specimen of the study patients (N=60)

Histopathological diagnosis was done according to WHO (2014) classification system. It was observed that among 60 cases of cervical cancer, most of the patients had squamous cell carcinoma, 55 (91.67%) cases. Among the SCC 29 (48.33%) were moderately differentiated squamous cell carcinoma, followed by 16 (26.7%) well-differentiated squamous cell carcinoma, and 5(8.33%) were poorly differentiated carcinoma. Among the rest of the patients, 5 patients had adenocarcinoma with 8.3% and only 1 had (1.7) adenosquamous carcinoma. CIS (Carcinoma in situ) was found in 4 (6.7%) cases only (**Table VI)**.

Table VI: **Distribution of the study patients by histopathological diagnosis (N=60)**

Histopathological Diagnosis	N	%
Moderately differentiated SCC	29	48.3
Well differentiated SCC	16	26.7
Poorly differentiated SCC	5	8.3
Carcinoma in situ	4	6.7
Adenocarcinoma	5	8.3
Adenosquamous carcinoma	1	1.7

When the age of the patient was compared with a histopathological diagnosis it was found that most of the tumors belonged to moderately differentiated SCC and their age range was mostly between 50-59 years. The age of poorly differentiated tumors was mostly above 60 years of age. The average age of different histopathological entity was also found 60 years. However, when the age was compared with different histopathological types of carcinoma (WHO-2014) it was found statistically insignificant (**Table VII**).

Table VII: Association of age with histopathological diagnosis (N=60)

Age (in years)	Histopathological Diagnosis						
	WD SCC	**Moderately differentiated SCC**	**Poorly differentiated SCC**	**CIS**	**ADCA**	**AdSqca**	**Total**
40-49	4	3	2	0	0	0	9
50-59	9	14	2	2	2	0	29
60-69	1	7	4	2	2	1	17
≥70	2	1	1	0	1	0	5
Total	16	25	9	4	5	1	60

P-value-0.018 s. | p-Value- Significant. | the p-value is reached from the ANOVA test.

When the association between mean ages with different types of carcinoma was compared it was found that the mean age of well-differentiated SCC was found to be 56.69±11.82, moderately differentiated SCC was 57.12±6.73 and poorly differentiated SCC was found 58.33±11 years. Adenocarcinoma was 63±8.49 years and adenosquamous carcinoma was 65±0 years (**Table VIII**).

Table VIII: Association of mean age with the histopathological diagnosis (N=60)

Histopathological Diagnosis	Age		P value
	Mean±SD	Min-max	
Moderately differentiated SCC	57.12±6.73	42-74	0.714^{ns}
Well differentiated SCC	56.69±11.82	40-90	
Poorly differentiated SCC	58.33±11	40-72	
CIS	56.25±4.79	50-60	
ADCA	63±8.49	53-75	
Adenosquamous	65±0	65-65	

ns = not significant | p-value reached from the ANOVA test

DISCUSSION

In this current study, it was observed that 48.4% were between 50-59 years and more than two third of the patients belong to age 50-59 years. The mean age of the patients having cervical cancer was 57.75±8.96 years with ages ranging from 40 to 90 years Different investigators from Bangladesh such as Nasreen (2013) and et al (2017) stated similar findings from their study [13],[14]. A similar age range was also observed by Munhoz et al. (2009), where they found age range varied from 22 to 90 years, which supports the present study. The median age of women in the Munhoz et al. (2009) study was 45.74 years, ranging from 22 to 90 years [15]. Gong et al. (2015) obtained in their study that late menarcheal age is inversely associated with cancer of the female reproductive organs risk and there was a 4.0% reduction in risk per 2-year delay in menarcheal age. it was observed that 63.3% of patients belong to the age of menarche more than 11 years [16]. The mean age of menarche was found 11.92±1.28 years varying from 9 to 15 years. The previous study by Gong et al. (2013) found a statistically significant inverse association between later menarcheal age and ovarian cancer risk [17]. The increased risk of cervical cancer is also associated with early menarcheal age and has been attributed to a longer lifetime exposure to endogenous estrogen and progesterone deficiency associated with anovulatory cycles [18]. A recent (BBS) survey titled "Bangladesh Sample Vital Statistics 2016" also found that rural women got married at an average age of 18.3 years and urban women at 19.9 years [19]. In this current study, it was observed that 63.4% of patients were married between 15-18 years, 18.3% at 15 years, and 18.3% over the age of 18 years. Globally, the majority of cervical cancer is most commonly diagnosed after menopause between the ages of 60 to 64 years, with a typical age of 63 years at diagnosis (Shen et al. 2017) [20]. In this current study, it was observed that most of the patients were multiparous and had a child 3 or more (28.3%) and the average parity was 3.2±1.36. High parity is biologically plausible as a higher frequency of unprotected sex results in greater exposure to HPV and an increased risk of developing cervical cancer (Bucchi et al. 2016) [21]. Cervical cancer is more

common among those with polygamy (Sine Bayo et al 2002) [22]. In this present study, according to WHO (2014) out of 60 cases of cervical cancer most (48.33%) of the patients had moderately differentiated squamous cell carcinoma, followed by 26.7% well differentiates squamous cell carcinoma, 8.33% poorly differentiated carcinoma. 8.3% of patients had adenocarcinoma and only 1 (1.7%) had adenosquamous carcinoma. Similarly, Ancuta et al. (2009) found 49.2% of patients had moderate differentiated, 6.6% patients had Adenocarcinoma, Invasive squamous cervical carcinoma 68.9%, carcinoma in situ 16.4%, Adenosquamous cervical carcinoma 4.9% and micro-invasive carcinoma 3.3% [23]. The average age of different histopathological entity was also found above 60 years. Similarly, the higher mean age of adenosquamous carcinoma was 65±0 years followed by ADC was 63±8.49 years, poorly differentiated SCC was found 58.33±11 years, moderately differentiated SCC was found 57.12±6.73 and well-differentiated SCC was 56.69±11.82 years.Chan et al. (2010) study showed that the commonest age group with adenocarcinoma was 41-45 years [24]. The peak age of cervical cancer worldwide is 45 years [25].

Limitations of the Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSION

This study concluded that late menarcheal age was inversely associated with cervical cancer. Marriage at an early age, high parity, and irregular menstrual cycle are also important risk factors for cervical carcinoma. Menopausal status is also a well-known risk factor for cervical cancer and most cases occur after menopause.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

RECOMMENDATION

Proper diagnosis and early treatment are imperative to stop the progression of cancer. There is a need to make the general population aware of the risk factors of cervical cancer, and proper screening should be done to prevent the development of cervical cancer.

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