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### RESEARCH ARTICLE

#### HISTOPATHOLOGICAL CATALOGUE FOR THE PRE-MALIGNANT AND MALIGNANT LESIONS OF UTERINE CERVIX AT A TERTIARY CARE CENTRE OF MAHARASHTRA

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Adenocarcinoma

#### Abstract

**Introduction:** Carcinoma of cervix is the most common cancer in Indian women and is the third largest cause of cancer mortality in India. The transformation zone of the cervix is vulnerable to HPV. A preneoplastic cervical intraepithelial neoplasia can regress, persist or progress towards invasive carcinoma.

**Aims:** To study the prevalence and histopathological spectrum of pre-malignant and malignant lesions of uterine cervix.

**Methods:** This was a retrospective cross-sectional study, carried out at Tertiary Care Hospital, in Department of Pathology, over a period of one-year.

**Results:** Total 14 cases (8%) of total hysterectomy and 156 cases (92%) of cervical biopsy were included, which included 31 cases (18%) pre-malignant lesions (CIN-I, II, III, CIS) and 139 cases (82%) malignant. SCC was found in 73% cases and adenocarcinoma in 8.3%.

**Limitations:** Follow-up was not possible.

**Conclusions:** Awareness programs and educational sessions might help to reduce the burden of carcinoma cervix in India.

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#### Introduction:-

Uterine cervix acts as a "gateway" for various infections, which affects cervix, uterus and upper genital tract.<sup>1</sup> Worldwide, invasive cervical cancer is the second most common female malignancy after breast cancer and the fifth deadliest cancer in women. It affects about 16 per 1,00,000 women per year and kills about 9 per 1,00,000 per year. Carcinoma of cervix is the most common cancer in Indian women and accounts for 20% of all malignant tumors in the females and is the third largest cause of cancer mortality in India after cancers of the mouth, oropharynx and oesophagus.<sup>2</sup> In the urban areas of India, cancer of cervix accounts for 40% of cancer while in rural areas, it accounts for 65% of cancer.<sup>3</sup>

Cervical carcinomas are classified by WHO classification which is widely accepted. Out of the different histopathological types, squamous cell carcinomas account for 75-80% of cervical cancers, adenocarcinoma 15-

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25%, and adenosquamous carcinomas 3-5%. Adenocarcinomas have been rising in incidence since the 1970s; especially in women younger than 35 years of age, may be attributed by an increasing prevalence of high risk Human Papilloma Virus (HPV) infection.<sup>2</sup>

The transformation zone of the cervix, specifically that associated with squamo-columnar junction, is vulnerable to HPV. Also, age at first intercourse has important role to play. A preneoplastic cervical intraepithelial neoplasia can regress, persist or progress towards invasive carcinoma. Thus, the goal of cervical cancer prevention program is to detect and treat all committed cancer precursors before invasion develops.<sup>4</sup>

Carcinoma cervix is more common in the low socioeconomic class, with lack of awareness of risk factors and presenting at an advanced stage,<sup>4</sup> who fail to carry out regular health check-up due to financial insufficiency.<sup>3</sup> There is a need for National cervical screening and education programs for women especially in rural areas. Studies show that histologic assessment is strongly associated with decreased risk of invasive carcinoma compared to repeated cytology in women with low grade squamous abnormalities.<sup>4</sup> Some tumors are clinically in apparent and are diagnosed for the first time during PAP/cervical biopsy/ hysterectomy done for benign pathology. Early detection in preclinical stage ensures 100% survival rate. The ultimate aim of various modalities of diagnosis and treatment is to prevent the development of invasive cervical cancer.<sup>3</sup>

Thus, the present study was carried out with the aim to study the prevalence and histopathological spectrum of pre-malignant and malignant lesions of uterine cervix at a Tertiary Referral Centre with maximum patients coming from a low socioeconomic stratum.

### **Materials and Methods:-**

The present study was a retrospective cross-sectional study, carried out at Tertiary Care Referral Hospital. This study was carried in Department of Pathology, over a period of one-year from June 2018 to June 2019. Among 2862 histopathological specimens received, total 462 were found to be total hysterectomy (abdominal/ vaginal) specimens and 285 were cervical biopsies. All these specimens along with their operative findings were received from Department of Obstetrics and Gynaecology. Clinical history with age, presenting signs & symptoms, possible serum marker assays, radiological and operative findings were studied.

#### **Inclusion criteria:**

All histologically proven premalignant and primary malignant lesions of the uterine cervix

#### **Exclusion criteria:**

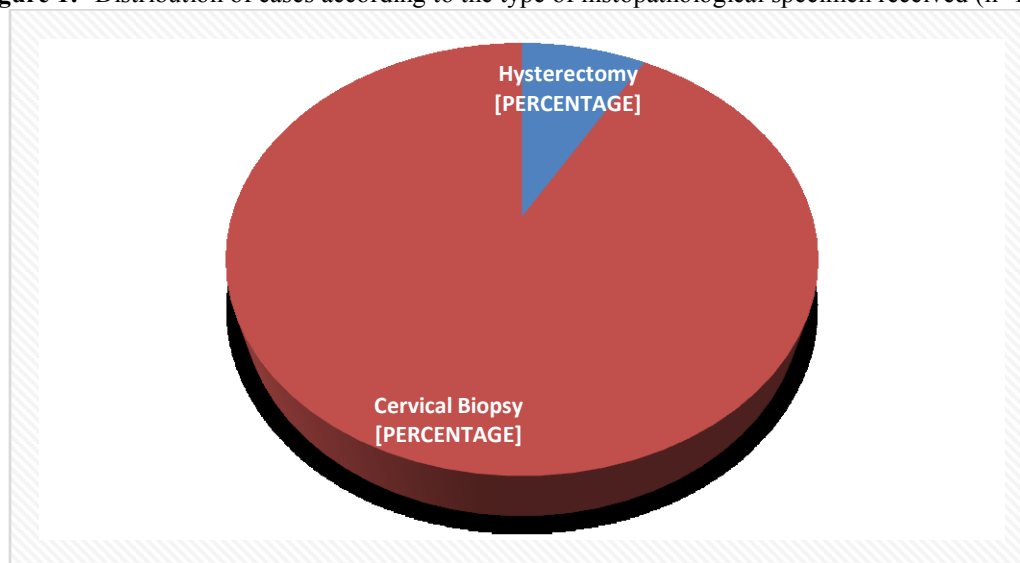
Non neoplastic lesions, benign tumours, secondary tumours involving the cervix, inadequate and autolyzed samples

Gross examination of 10% formalin fixed specimen was done and processed. 1) Cervical biopsies were embedded in toto. Serial sections were also taken wherever needed. 2) In cervix, with no obvious gross abnormality, sections were taken from anterior and posterior lip including the squamo-columnar junction. 3) In hysterectomy specimens with a prior history of cervical Pap smear positive for Low squamous intraepithelial lesion (LSIL) or High Squamous intraepithelial lesion (HSIL), multiple sections were taken along the endocervical canal, in such a way that epithelium including squamo-columnar junction is present in each section.

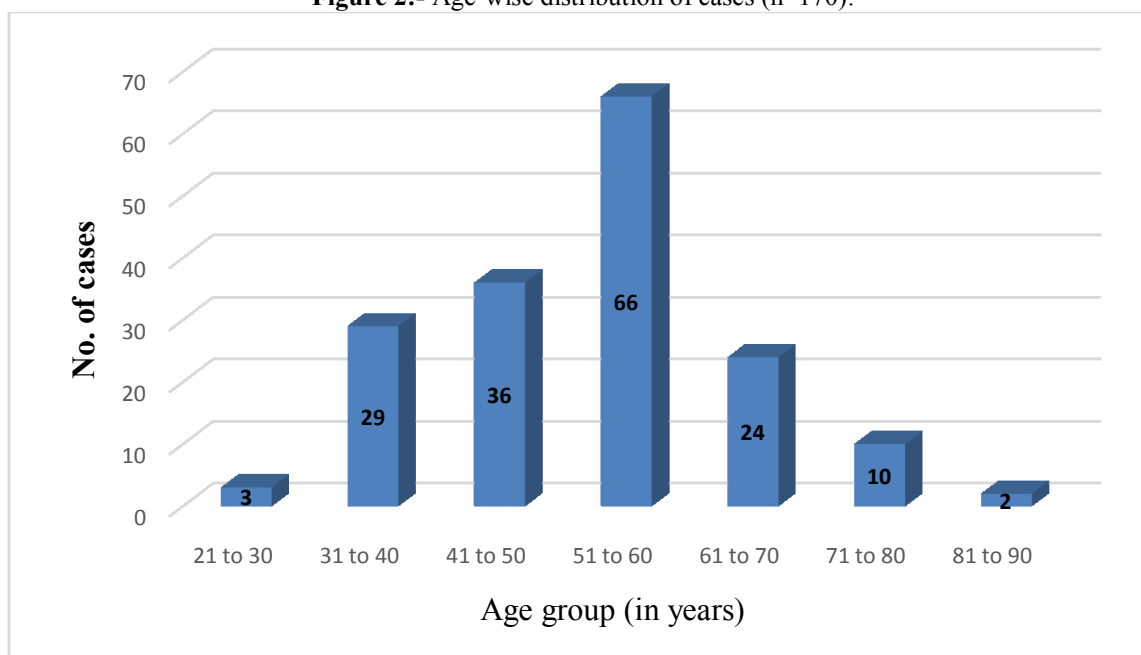
Lesions of the cervix were classified into premalignant and malignant, which were further typed using the World Health Organization histological classification for tumours of the uterine cervix [8]. The histopathologic features analyzed were: Pattern of infiltration, nuclear pleomorphism, character of tumour stromal border or mode and stage of invasion, degree of stromal inflammatory cell infiltrate, presence or absence of lympho-vascular invasion, mitotic index and degree of tumour differentiation.<sup>4,5</sup>

### **Results:-**

Out of the total of 462 total hysterectomy specimen, 14 cases (8%) were included. Out of 285 cervical biopsies, 156 cases (92%) were included in the present study. (Fig 1)

**Figure 1:-** Distribution of cases according to the type of histopathological specimen received (n=170).

In the present study, youngest female of 28-years was diagnosed to have Adenocarcinoma of cervix and the oldest of 83-years to have Squamous Cell Carcinoma (SCC) – spindle cell variant.

**Figure 2:-** Age-wise distribution of cases (n=170).

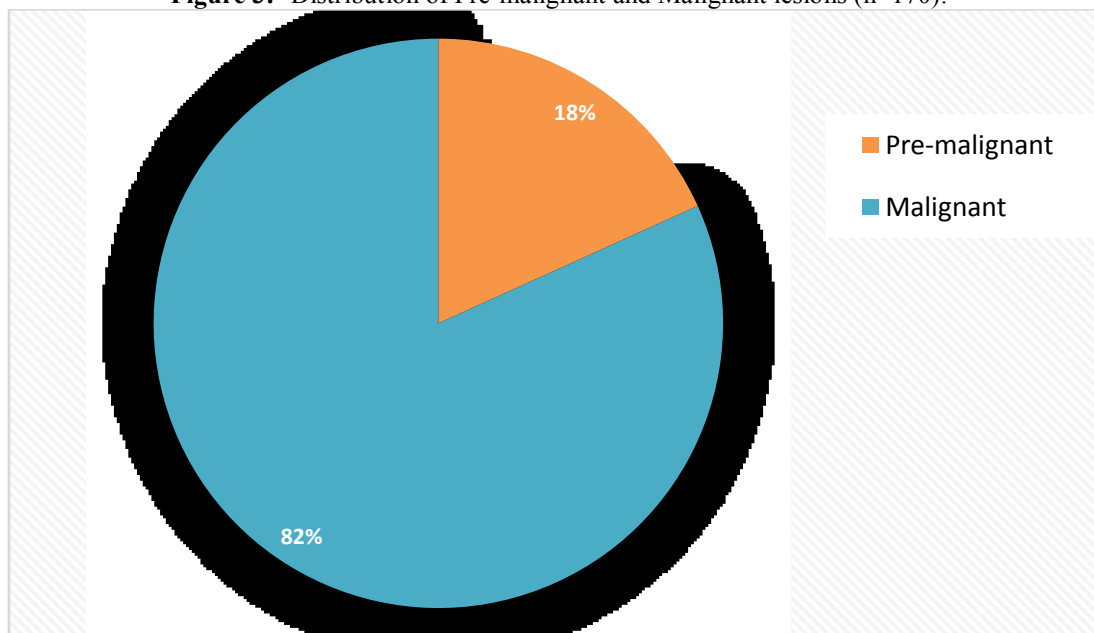
Most common age group to be affected by premalignant and malignant cervical lesions was found to be 51-60 years, followed by 41-50 years. (Fig 2)

Two cases with Cervical Intraepithelial Neoplasm (CIN) -I were found to be in the age group of 21-30 years. While all cases with CIN- II, CIN-III and Carcinoma-in-situ (CIS), fall in 31-40 years of age. Most of the cases diagnosed as SCC were in the age group of 51-60 years and that diagnosed as adenocarcinoma were in 41-50 years of age group.

Most of the females in the present study were multiparous presenting with either blood mixed white discharge or bleeding per vagina (PV). Per speculum (PS) examination of the malignancy suspected females revealed friable growth, which bled on touch.

Present study found 31 cases (18%) as pre-malignant lesions (CIN-I, II, III, CIS) and 139 cases (82%) as malignant. (Fig 3)

**Figure 3:-** Distribution of Pre-malignant and Malignant lesions (n=170).



Most common pre-malignant lesion was CIN-III (7.6%), followed by CIN-I (4.7%). Least common was CIN-II (2.2%). While CIS was found to be 3.5% cases. (Table 1) (Fig 4)

SCC was found to be most common lesion (73%), followed by adenocarcinoma (8.3%). In SCC, keratinizing type outnumbered the series (43.1%), with least of basaloid type (0.6%). (Fig 5)

Whereas, conventional type of adenocarcinoma (3.5%) outnumbered, followed by papillary serous type (1.7%). (Fig 6)

A very rare case of melanoma of cervix was found in a 70-years female, presenting PV-bleed, showing blackish mass blocking the cervical canal on PS-examination. (Table 2)

**Table 1:-** Distribution of Premalignant lesions of cervix (n=31).

| Diagnosis         | No. of cases | Percentage (%) out of total 170 cases |
|-------------------|--------------|---------------------------------------|
| CIN – I           | 08           | 4.7                                   |
| CIN – II          | 04           | 2.2                                   |
| CIN – III         | 13           | 7.6                                   |
| Carcinoma-in-situ | 06           | 3.5                                   |
| <b>Total</b>      | <b>31</b>    | <b>18</b>                             |



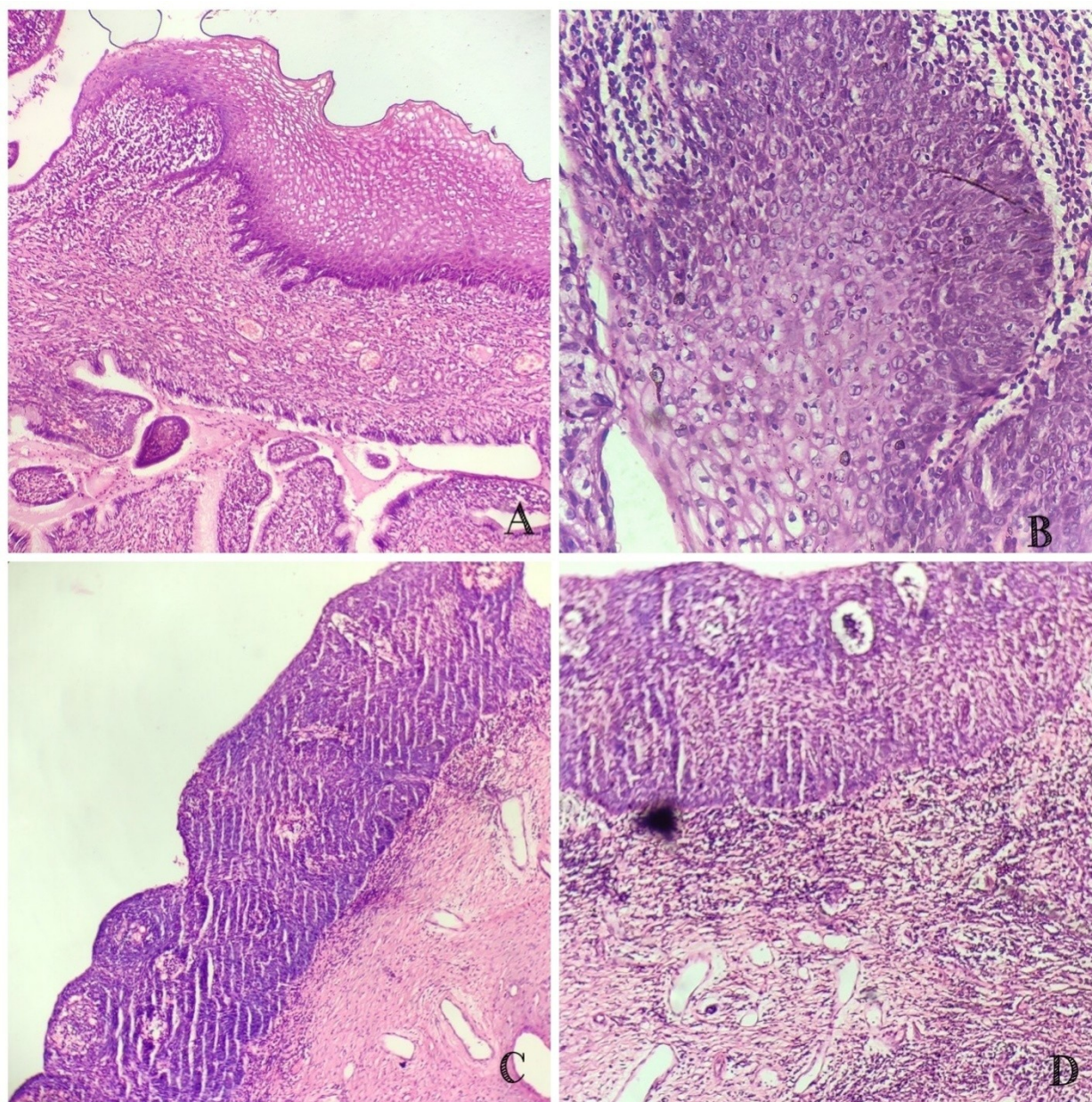
**Figure 4:-** Microphotographs of Pre-malignant lesions of uterine cervix.

Fig A – CIN-I (H&amp;E, 200x)

Fig B – CIN-II (H&amp;E, 400x)

Fig C – CIN-III(H&amp;E, 200x)

Fig D –CIN-III with CIS (H&amp;E, 200x)

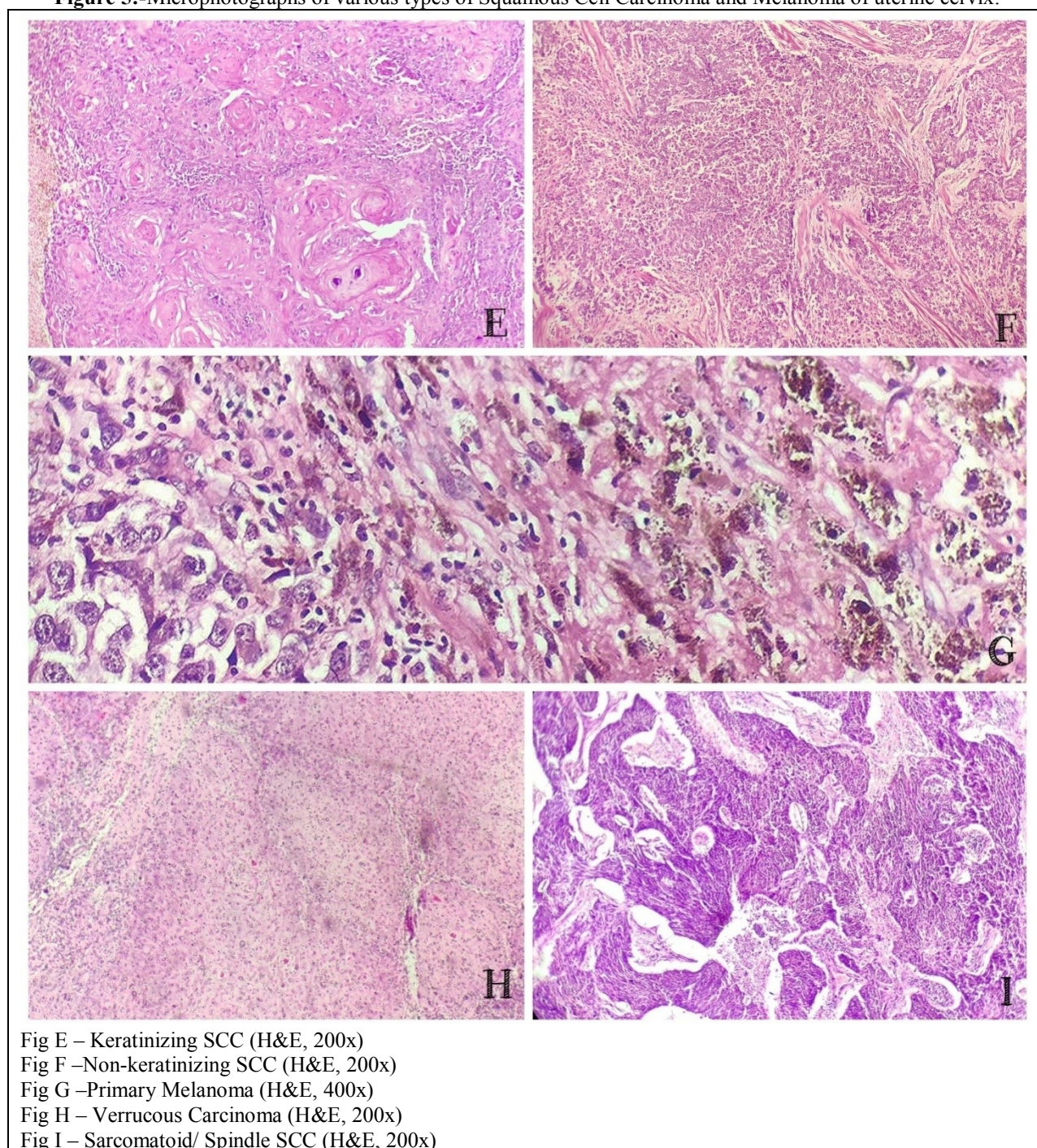
**Table 2:-** Distribution of Malignant lesions of cervix (n=139).

| Diagnosis                                 |                              | No. of cases | Percentage (%) out of total 170 cases |
|-------------------------------------------|------------------------------|--------------|---------------------------------------|
| Squamous Cell Carcinoma (124 cases – 73%) | Keratinizing                 | 58           | 34.1                                  |
|                                           | Non-keratinizing/ Large cell | 46           | 27.0                                  |
|                                           | Spindle/ Sarcomatoid         | 08           | 4.7                                   |
|                                           | Small cell                   | 07           | 4.1                                   |
|                                           | Verrucous Carcinoma          | 04           | 2.3                                   |
|                                           | Basaloid                     | 01           | 0.6                                   |

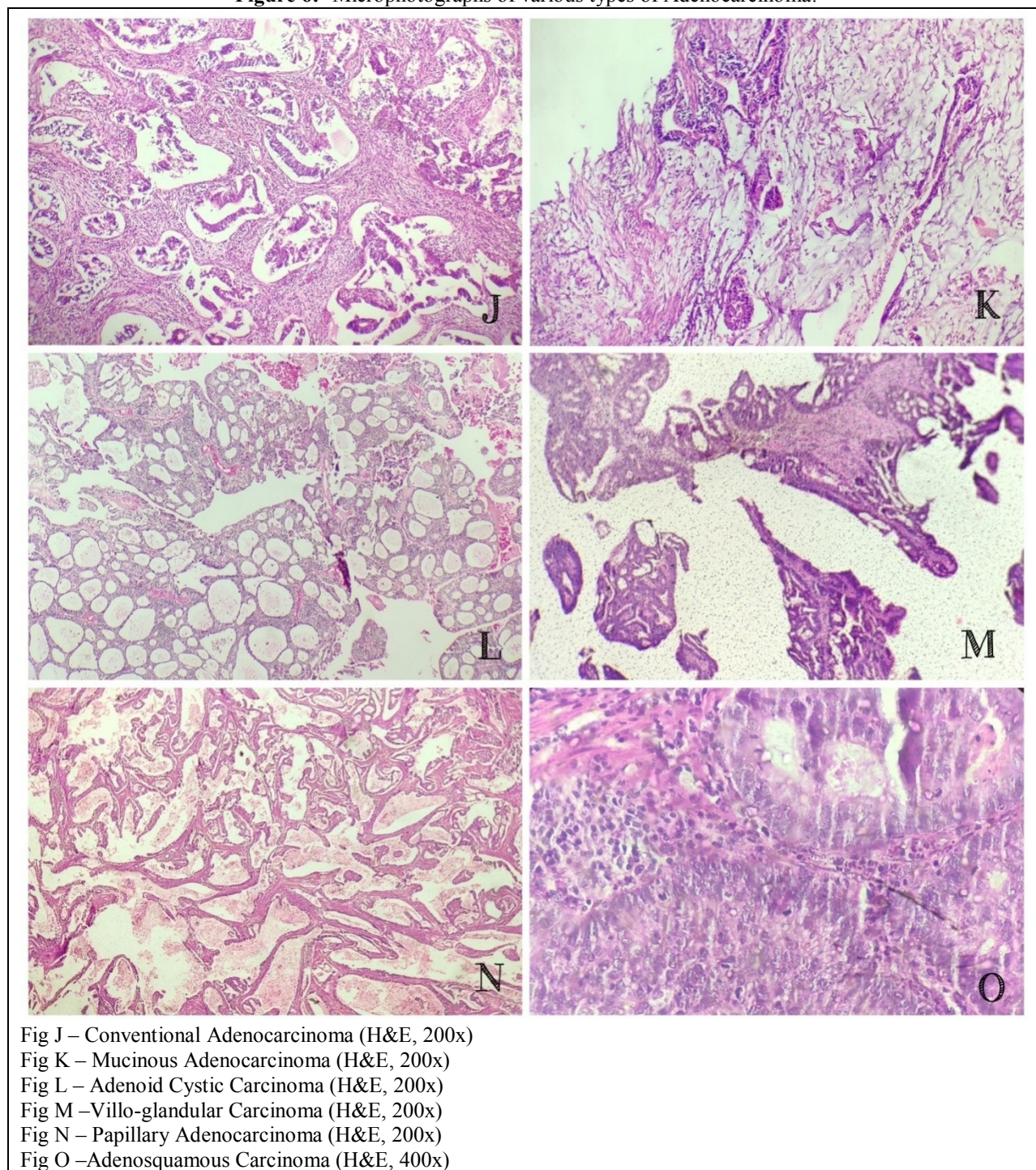


|                                     |                  |            |           |
|-------------------------------------|------------------|------------|-----------|
| Adenocarcinoma<br>(14 cases – 8.3%) | Conventional     | 06         | 3.5       |
|                                     | Papillary serous | 03         | 1.7       |
|                                     | Adenosquamous    | 02         | 1.1       |
|                                     | Adenoma Malignum | 01         | 0.6       |
|                                     | Villo-glandular  | 01         | 0.6       |
|                                     | Adenoid cystic   | 01         | 0.6       |
| Melanoma                            |                  | 01         | 0.6       |
| <b>Total</b>                        |                  | <b>139</b> | <b>82</b> |

**Figure 5:-**Microphotographs of various types of Squamous Cell Carcinoma and Melanoma of uterine cervix.





**Figure 6:-** Microphotographs of various types of Adenocarcinoma.**Discussion:-**

Invasive cancer of cervix is considered to be a preventable condition as it is associated with long preinvasive stage (CIN) making it amenable to screening and treatment. The incidence of cervical cancer can be reduced by 80% if high standards of screening methods and follow up are maintained. Two cases of CIN-I, in present study, were seen in 21-30 years of age and all CIN-II and III with CIS in the age group of 31-40 years. In the study done by Mamta Gupta<sup>4</sup>, mean age of patient of CIN-I was 38.9 years, CIN-II was 41.3 years, CIN-III was 46.4 years and Invasive

carcinoma was 48.5 years. Kaveri SB et al, Bagde S et al, Metha A et al and Bojini K R et al<sup>6,7,8,9</sup> found maximum number of cases of unhealthy cervix in the age group of 31-40 years. These studies substantiate that the disease process starts approximately 10-12 years before the development of invasive carcinoma and holds true for all regions of India.

Cancer that develops in the ectocervix is usually SCC, and around 80- 90% of cervical cancer cases (more than 90% in India) are of this type. Cancer that develops in the endocervix is usually an adenocarcinoma. In addition, small percentages of cervical cancer cases are mixed versions of the above two and are called adenosquamous carcinomas or mixed carcinomas.<sup>2</sup> Present study found SCC of cervix to be the most common (73%), followed by adenocarcinoma (8.3%). This was comparable to study done by Jain A. et al<sup>2</sup>, Gupta M<sup>4</sup>, Haghdel M. et al<sup>10</sup>, Smith HO et al<sup>11</sup> and Ijaiya MA et al<sup>12</sup>.

In recent years it has been suggested that there has been a relative and absolute increase in the incidence of adenocarcinoma of the uterine cervix as shown in studies of Chen J et al., which was done on a large population based database.<sup>13</sup>

In present study, SCC was commonly found in 51-60 years of age and adenocarcinoma in 41-50 years. Jain A. et al<sup>2</sup> found mean age of squamous cell carcinoma as 49.1 years, adenocarcinoma 43.55 years and squamous intraepithelial lesion was 47.7 years. In study done by Dhakal et al<sup>14</sup>, SCC and adenocarcinoma was seen during 5th decade and highest incidence of squamous intraepithelial lesion was during 4th decade. Few authors have reported that adenocarcinomas tend to occur in older population.<sup>15</sup> However, recent study by Alfsen GC et al., have noticed a shift towards younger age.<sup>16</sup>

SCC are classified as – 1) Large cell Non-keratinizing, 2) Keratinizing, 3) Small cell, 4) Verrucous carcinoma, 5) Spindle/ Sarcomatoid, 6) Basaloid, 7) Lymphoepithelioma-like and 8) Transitional Cell Carcinoma. Jain A. et al<sup>2</sup> study showed percentage of large cell non-keratinizing SCC as 42.86% and small cell keratinizing SCC as 19.05% and keratinizing SCC as 38.09%. While present study showed keratinizing SCC to be most common accounting 34.12%, followed by non-keratinizing/ large cell SCC to be 27.03%. (Fig 5) In study done by Abudu EK et al<sup>17</sup> highest occurrence of well differentiated SCC (39%) was noted. Small cell non-keratinizing type and papillary SCC was in one case (1.5%) each in study done by Gupta M.<sup>4</sup> Our observation regarding the predominant cell type of SCC correlates with the study by Lowe D et al<sup>18</sup>. Present study found 4.7% of spindle/ sarcomatoid SCC, 4.11% of small cell SCC and 2.35% of verrucous carcinoma. Sarcomatoid carcinoma is a very rare pathological entity of the female genital tract and even more rare in the cervix. It has been described more frequently in the aero-digestive tracts and skin.<sup>19</sup> Brown et al reported the largest series of 9 cases of sarcomatoid carcinomas of the cervix with a median disease-free interval of 4.9 months.<sup>20</sup>

Uterine cervix is a rare site for Basaloid variant of SCC, usually affecting patients in their 6th and 7th decade of life. Though there are occasional reports mentioning younger patients.<sup>21</sup> Only one case (0.6%) of basaloid SCC was noted in the present study.

Adenosquamous carcinomas previously considered as a subtype of cervical adenocarcinomas is now considered a special and rare histological type accounting for 5-10% of cervical carcinoma and has a poor outcome. In study done by Gupta M<sup>4</sup>, one case with morphological features of adenosquamous carcinoma was reported. Present study found adenosquamous type of adenocarcinoma in 1.18% cases. (Fig 6O)

The significance of an endophytic or exophytic growth pattern, in cases of adenocarcinoma has been debated. Most lesions of adenocarcinoma appearing as endophytic growth may be the manifestation of site of origin of adenocarcinoma within glandular epithelium of endocervix. Whereas, appearance of an exophytic lesions is a result of extension from endocervical glands or its development in a congenital ectropion.<sup>4</sup> Variants of adenocarcinoma are – 1) Conventional, 2) Endometrioid, 3) Papillary serous, 4) Adenoma Malignum, 5) Villoglandular, 6) Adenosquamous, 7) Glassy cell carcinoma, 8) Adenoid cystic carcinoma and 9) Clear cell carcinoma. In present study, conventional type of adenocarcinoma was found to be most common (3.53%), followed by papillary serous type (1.76%). While adenoma malignum, villoglandular and adenoid cystic type of adenocarcinoma was found to be in 0.6% each. (Fig 6) Gupta M<sup>4</sup> and Hurt WG et al<sup>15</sup> found endocervical carcinoma most common subtype, followed by villoglandular and endometrioid type. Rais M. et al<sup>22</sup> reported two cases of adenoid cystic carcinoma of uterine cervix.



A very rare case of melanoma of uterine cervix was seen in present study (0.6%). (Fig 5G) Malignant melanoma accounts for about 0.03% of all newly diagnosed cancers and malignant melanomas of the female genitalia occur very rarely — accounting for approximately 2% of all melanomas. Primary malignant melanoma of the uterine cervix has no early symptoms and the diagnosis is usually delayed; therefore, prognosis is very poor.<sup>23</sup>

Histopathologically, majority of tumours showed few to moderate number of mitotic figures, lymphovascular invasion, lymphoplasmacytic stromal response was moderate to severe. Similar histological findings were observed by Gauthier P et al<sup>24</sup> and van Nagell JR et al.<sup>25</sup> The objective of determining tumour grade (degree of differentiation) is to estimate biologic behaviour and aid inpatient management. Extension of SCC into endometrium and/or myometrium, in hysterectomy specimens, focuses attention on the need for a more complete biopsy procedure and pretreatment workup prior to initiation of therapy.<sup>4</sup>

Bodal VK et al found maximum number of patients were in the fourth decade of life followed by fifth decade.<sup>26</sup> Rathoda GB et al<sup>27</sup> found most patients were in the age group of 41-50 years (42.4%) followed by age group 51-60 years. In present study, maximum patients were seen in the age group of 51-60 years (38.8%), followed by 41-50 years (21.17%).

#### **Limitation:**

The limitation of the present study was that the follow-up was not possible with malignancy cases as they were referred to higher Centre for further management. Also, in cases with CIN, diagnosed on cervical biopsy, we were not able to observe its progression or regression.

#### **Conclusion:-**

Cervical cancer continues to be the most common cancer of females in developing countries like India. One of the most significant advances in the management of cervical neoplasms has been the realization that CIN behave as progressive stages to the development of invasive cancer. Histopathological examination is considered gold standard for diagnosis of CIN and cervical carcinoma. Light microscopy is sufficient for the diagnosis of almost all cases, which minimizes the need for Histochemical stains and Immunohistochemistry in only a few histologic types, particularly in poorly differentiated carcinoma and neuroendocrine tumours. Histologic evaluation of CIN and cervical carcinoma should be attempted at an early stage of disease (since CIN starts at 30-40 years of age) to provide better prognosis, treatment and protection against invasive cervical carcinoma. With recent advancements in molecular techniques more studies comparing different histological features and biomarkers need to be conducted to ensure development of targeted therapy and prevention of invasive carcinomas.

All females with unhealthy cervix should undergo Pap smear or a cervical punch biopsy. Carcinoma cervix is ideal malignancy for screening as it has a long latent period and can be detected at premalignant condition and also prevented from progression to invasive disease. Thus, advantages of screening for carcinoma cervix far outway for cost involved.

Awareness programs and educational sessions might help to reduce the burden of carcinoma cervix in India.

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