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ORIGINAL ARTICLE

Cervical Cancer Screening: Is the Age Group 30–65 Years Optimum for Screening in Low-Resource Settings?

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Abstract

Background An Operational Framework document for population-wide screening of common cancers in India was launched in 2016. The target age for screening is 30–65 years for cervical, breast and oral cancers. This study was designed to review the frequency and distribution of cervical lesions among women aged 21–29, 30–65 and > 65 years.

Study Design A retrospective review of all satisfactory cervical smears ($n = 79,896$) received over a ten-year period (2010–2019) was conducted. Three age bands were defined: 21–29 years, 30–65 years and > 65 years. The frequency and distribution of the various epithelial cell abnormalities (ECAs) across the three age bands were calculated. Cytohistologic correlation was performed wherever available.

Results Of the 1357 ECAs (1.7% of all smears), about 16.9% were seen in the age band 21–29 years, while 4.5% presented in > 65 years of age. About 80% of the ECAs seen in younger women were low-grade squamous lesions, while 75% of lesions in women > 65 years were high-grade squamous abnormalities. Among the total 512 significant high-grade and malignant (squamous and glandular) lesions, 5.6% presented in women 21–29 years, while 10.1% were seen in > 65 years of age.

Conclusion Majority of the significant cervical lesions would be detected if the screening focuses on the 30–65 years age group. However, about 19% of high-grade squamous preneoplastic lesions (ASC-H/ HSIL) and 13% of preneoplastic glandular lesions (AGC-N) are likely to be missed if women 21–29 years and > 65 years are excluded. The cost of screening incurred by including these age groups has to be weighed against the benefits derived, especially in low-resource settings. In the absence of universal implementation of HPV immunization, there is a felt need to enhance cervical cancer awareness and encourage screening, more so in high-risk category and symptomatic females beyond the selected age group.

Keywords Cervical cancer · Screening · High-grade lesions · Age · Low-resource settings

Introduction

According to Globocan 2020, cervical cancer is the second leading cancer among women in India with an incidence of 18.3%. With around 123,000 new cases detected annually, India contributes to 20.5% of the global incidence of cervical cancer. Similarly, around 22.6% of global mortality due to cervical cancer is attributed to India [1].

Despite being amenable to prevention, many developing countries have so far not been able to reduce the burden of cervical cancer significantly. This has largely been attributed to several factors such as the absence of organized screening programs, inadequate infrastructure and manpower and lack of political will. Hence, the current strategy in such countries relies on opportunistic screening for cervical cancer in healthcare settings. However, the low levels of cancer awareness and poor health-seeking behavior especially of females in India lead to neglect of screening for cancer when there are no apparently significant symptoms. To address this void, the Government of India has recently formulated the Operational Framework for systematic, population-wide screening and management of three prevalent cancers in our

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country, viz. the cancers of oral cavity, breast and uterine cervix [2]. This program is in the process of being rolled out in various districts of the country. For the sake of feasibility as well as programmatic and operational purposes, the age group of the beneficiaries for screening of all three cancers is recommended as 30–65 years and the screening frequency as once in 5 years. The screening coverage is estimated to reach 80% in the target age group by the third year of successful rollout of the program.

Though cervical carcinoma in women younger than 30 years is rare, few reports from the western countries have shown a rising trend in the incidence of cervical cancer in women aged 20–29 years [3]. In addition, there have been conflicting reports on the prognosis of these cancers in young women with some authors describing poorer prognosis than older patients and others not finding so [4, 5]. A proportion of cervical cancers present in age later than 65 years also. Hence, we attempted to assess from our data as to what fraction of cases of cervical cancers/precancers are detected in women less than 30 years and those more than 65 years of age, which may be missed if the population-wide cancer screening focuses on the '30–65 years' age group.

Material and Methods

This was a retrospective review of all cervical smears received over a ten-year period (2010–2019). Our laboratory receives approximately 8000 to 10,000 cervical smears annually as a part of opportunistic cervical cancer screening undertaken at the Health Promotion Clinic (HPC) at our cancer research institute as well as nearby hospitals. The smears were conventional cervical smears that had been processed using the standard Papanicolaou procedure followed in our laboratory. The smears had been screened by cytoscreeners and reported by experienced cytopathologists according to The Bethesda System 2010/2014, as applicable [6, 7].

Follow-up data and histologic diagnosis, wherever available, were collected and correlated. Cervical biopsy and endocervical curettage, wherever required, were performed within six months to one year after the cervical smear in majority of the cases. In a few cases, the cervical smear and biopsy were done in the same visit for women with positive result on visual inspection with acetic acid (VIA) or with unhealthy cervix on speculum evaluation in order to minimize the loss to follow-up. Cervical biopsies were reported as per the CIN classification [8].

Statistical Analysis

The data were analyzed using OpenEpi software [9]. Three age bands were defined for analysis: 21–29 years, 30–65 years and > 65 years at the time of cancer screening. The frequency of ECA in all the three age bands was calculated. Further sub-classification of the ECA into squamous and glandular lesions as well as low-grade and high-grade lesions was also done and comparative analysis performed in three age bands.

Results

A total of 81,361 cervical smears were received in our laboratory over the study period (2010–2019). The age of women ranged from 21 to 95 years (median age 38 years). Majority (95.03%) of the women were either asymptomatic or reported minor symptoms like abdominal pain, backache or vaginal discharge. Only a few women (4.97%) presented with history of postcoital or intermenstrual or post-menopausal bleeding. None of the women had ever had a cervical smear done previously. Speculum examination showed a normal cervix in majority of the women (90.03%), while 4.9% cases showed hypertrophied cervix, 3% showed cervical ectopy, and 1.9% women had an unhealthy cervix or a frank growth at presentation.

Of the 81,361 smears received, 79,896 (98.2%) were considered satisfactory for evaluation on cytology. Majority (78,539, 98.3%) of the satisfactory smears were reported as negative for intraepithelial lesion or malignancy (NILM). Epithelial cell abnormalities (ECA) were detected in 1357 (1.67% of satisfactory smears). Of all the ECAs, the squamous ECA comprised 80.98% (1099), while glandular abnormalities were 19.02% (258) of all ECA. The distribution of overall ECAs into squamous and glandular lesions and as per the three age bands is tabulated in Table 1. The screen-detected lesions on cytology were followed up/managed as per standard protocols.

Age Band 21–29 Years

Of all the ECAs detected in the study period, 229 (16.9%) were seen in this age group. Squamous lesions were the most frequent (209, 91.2% of ECAs in this age band), while glandular lesions were seen in 8.8% of cases.

Among squamous abnormalities, low-grade lesions (ASC-US and LSIL) comprised 181 [79.0% of all ECAs in this age group]. High-grade squamous abnormalities, i.e., ASC-H, HSIL and SCC, were detected in 28 women in this age band, comprising 13.4% of squamous abnormalities in this group and 2.1% of total ECA in all age groups. Of note, 28.2% (181/640) of all low-grade lesions (ASC-US and LSIL) presented in this age group and 13.1% (25/191) all high-grade precancerous lesions (ASC-H & HSIL) presented in this age group (Table 2, Fig. 1). Only a small fraction (1.1%, 03/268) of SCCs were detected in

Table 1 Distribution of epithelial cell abnormalities among the three age bands in the present study

	Total number	21–29 years, *N* (% of total, 95% CI)	30–65 years, *N* (%, 95% CI)	> 65 years, *N* (%, 95% CI)
No. of satisfactory smears	79,896	25,327	52,971	1598
Epithelial cell abnormalities	1357	229 (16.9, 14.9–18.9)	1067 (78.6, 76.3–80.7)	61 (4.5, 3.5–5.7)
Squamous ECA	1099	209 (19.0, 16.8–21.4)	839 (76.3, 73.7–78.7)	51 (4.6, 3.5–6.1)
ASC-US	275	74 (26.9, 22.0–32.4)	199 (72.4, 66.8–77.3)	02 (0.7, 0.2–1.6)
LSIL	365	107 (29.3, 24.8–34.2)	255 (69.8, 64.9–74.3)	03 (0.8, 0.2–2.4)
ASC-H/HSIL	191	25 (13.1, 9.0–18.6)	155 (81.1, 75.0–86.1)	11 (5.7, 3.2–10.0)
SCC	268	3 (1.1, 0.4–3.2)	230 (85.8, 81.1–89.5)	35 (13.1, 9.5–17.6)
Glandular ECA	258	20 (7.7, 5.1–11.)	228 (88.4, 83.9–91.7)	10 (3.8, 2.1–6.9)
AGC-NOS	205	19 (9.3, 6.0–14.0)	182 (88.7, 83.7–92.4)	04 (1.9, 0.7–4.9)
AGC-N	45	1 (2.2, 0.4–11.5)	39 (86.7, 73.8–93.7)	05 (11.1, 4.8–23.5)
Adenocarcinoma	08	0	07 (87.5, 52.9–97.7)	01 (12.5, 2.2–47.1)

ECA epithelial cell abnormality *ASC-US* atypical squamous cells—undetermined significance *LSIL* low-grade squamous intraepithelial lesion *ASC-H* atypical squamous cells—cannot exclude HSIL *HSIL* high-grade squamous intraepithelial lesion *SCC* squamous cell carcinoma *AGC-NOS* atypical glandular cells—not otherwise specified *AGC-N* atypical glandular cells—neoplastic

Table 2 Proportion of squamous and glandular epithelial cell abnormalities detected in the different age bands in the present study

Age group (years)	Squamous epithelial cell abnormalities			Glandular epithelial cell abnormalities		
	Low-grade squamous lesions (ASC-US & LSIL) (%)	High-grade squamous lesions (ASC-H & HSIL) (%)	SCC (%)	AGC-NOS (%)	AGC-N (%)	Adenocarcinoma (%)
21–29	28.2	13.1	1.1	9.3	2.2	–
30–65	70.9	81.2	85.8	89.8	86.7	87.5
> 65	0.78	5.8	13.1	1.95	11.1	1.3

ASC-US atypical squamous cells—undetermined significance *LSIL* low-grade squamous intraepithelial lesion *ASC-H* atypical squamous cells—cannot exclude HSIL *HSIL* high-grade squamous intraepithelial lesion *SCC* squamous cell carcinoma *AGC-NOS* atypical glandular cells—not otherwise specified *AGC-N* atypical glandular cells—neoplastic

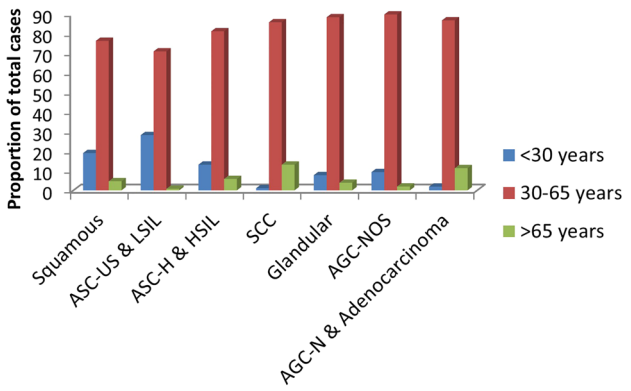

Fig. 1 Graphical representation of the distribution of various cervical epithelial lesions among the three age bands: < 30 years, 30–65 years and > 65 years (squamous: cervical squamous lesions (total); ASC-US: atypical squamous cells—undetermined significance; LSIL: low-grade squamous intraepithelial lesion; ASC-H: atypical squamous cells—cannot exclude HSIL; HSIL: high-grade squamous intraepithelial lesion; SCC: squamous cell carcinoma; glandular: cervical glandular lesions (total); AGC-NOS: atypical glandular cells—not otherwise specified; AGC-N: atypical glandular cells—neoplastic)

this age group. The median age varied from 25 years for ASC-US, LSIL and HSIL to 26 years for SCC.

Among the glandular lesions, AGC-NOS comprised 95% (19/20) of all glandular lesions in this group and 1.4% of all ECA detected across all age groups. AGC-N was reported in one woman (5% of glandular lesions in this age group). There was no case of adenocarcinoma in this group. Hence, 7.8% (20/258) of all glandular lesions presented in this age group. About one-tenth (9.3%, 19/205) of AGC-NOS and 2.2% (1/45) of AGC-N cases were detected in this age group. AGC-NOS was detected at a median age of 26 years while AGC-N at 25 years of age.

Histologic correlation was available in 87 cases of ECA (37.9%) in the age group of less than 30 years (Table 3). CIN 2–3 lesions were seen in 28 cases, while three cases of SCC were confirmed on cervical biopsy. Hence, CIN2 + lesions were detected histologically in 31 cases (35.6% of cases with histologic follow-up; 13.5% of all ECAs in this age group).

Table 3 Histologic outcome of cervical biopsies in the present study

	Histologic diagnosis (n= 87)			
	Chronic cervicitis	CIN 1	CIN 2-3	Malignant
Age 21–29 years				
Cytologic diagnosis				
ASC-US (12)	6	5	1	0
LSIL (38)	7	26	5	0
ASC-H/HSIL (25)	2	4	19	0
SCC (3)	0	0	0	3
AGC-NOS (8)	2	4	2	0
AGC-N (1)	0	0	1	0
Age 30–65 Years ($N = 241$)				
Cytologic diagnosis				
ASC-US (25)	19	5	1	0
LSIL (36)	9	24	3	0
ASC-H/HSIL (52)	6	7	39	0
SCC (84)	0	0	5	79
AGC-NOS (25)	6	10	9	0
AGC-N (12)	0	2	8	2
Adenocarcinoma (7)	0	0	0	7
Age > 65 years ($n = 34$)				
Cytologic diagnosis				
LSIL (01)	0	1	0	0
ASC-H/HSIL (10)	0	2	8	0
SCC (18)	0	0	0	18
AGC-NOS (01)	0	1	0	0
AGC-N (03)	0	1	2	0
Adenocarcinoma (1)	0	0	0	1

ASC-US atypical squamous cells—undetermined significance *LSIL* low-grade squamous intraepithelial lesion *ASC-H* atypical squamous cells—cannot exclude HSIL *HSIL* high-grade squamous intraepithelial lesion *SCC* squamous cell carcinoma *AGC-NOS* atypical glandular cells—not otherwise specified *AGC-N* atypical glandular cells—neoplastic *CIN* cervical intraepithelial neoplasia

Age Band 30–65 Years

Majority of all ECAs were detected in this age band (78.6%, 1067/1357). Squamous ECAs were most frequent (839, 78.6%), while 228 (21.4%) were glandular lesions.

Among squamous abnormalities, low-grade lesions (ASC-US and LSIL) comprised 454 [42.5% of all ECAs in this age group; 33.5% of total ECA in all age groups]. The significant squamous abnormalities, i.e., ASC-H, HSIL and SCC, were detected in 385 women, comprising 45.9% of squamous abnormalities in this age group. High-grade squamous precancerous lesions (ASC-H and HSIL) were detected in 155 cases (18.4% of total squamous lesions across all age groups). This age group accounted for 70.9% (454/640) of all low-grade lesions (ASC-US and LSIL) and 81.2% (155/191) all high-grade precursor lesions (ASC-H & HSIL). Majority (85.8%, 230/268) of SCC also presented in this age group, as depicted in Table 2 and Fig. 1. The median age at presentation for various squamous lesions was: 40 years for ASC-US, 46 for LSIL, 42 for HSIL and 51 years for SCC.

Among the glandular lesions in this age group, AGC-NOS comprised 79.8% (182/228) of all glandular lesions and 16.8% of all ECA detected across all age groups. AGC-N and adenocarcinoma were reported in 46 smears (20.2%) of glandular lesions in this age group. Majority (88.3%, 228/258) of all glandular lesions, both AGC-NOS (89.8% (182/205)), AGC-N (86.7% (39/45)) and adenocarcinomas (87.5% (7/8)), presented in this age group. AGC-NOS presented at a median age of 42 years, while AGC-N and adenocarcinoma had median age of 49 years in this age group.

Cervical biopsy information was available for 241 cases (Table 3). Of these, CIN2 + lesions were seen in 153 women (63.5% of cases with histology available; 14.3% of all ECA in this age group).

Age Band > 65 Years

This age band accounted for 61 ECA detected during the study period. Of these, 51 (83.6%) were squamous ECA, while 10 (16.4%) were glandular lesions.

Among squamous abnormalities, low-grade lesions (ASC-US and LSIL) comprised 05 [8.2% of all ECA in this age group]. The significant squamous abnormalities, i.e., ASC-H, HSIL and SCC, were detected in 46 women, comprising 90.2% (46/51) of squamous abnormalities in this age group. For squamous ECAs, 0.78% of all low-grade lesions (ASC-US and LSIL), 5.8% of all high-grade precancerous lesions (ASC-H & HSIL), and 13.1% of SCC presented in this age group. The median age at diagnosis of HSIL and SCC was 73 and 72 years, respectively.

Among the glandular lesions detected in 10 women, AGC-NOS comprised 40% (4/10) of all glandular lesions. AGC-N and adenocarcinoma were reported in one woman each (5% of glandular lesions in this age group). Hence, 3.9% of all glandular lesions, 1.95% of AGC-NOS, 11.1% of AGC-N and 1.3% of adenocarcinomas were detected in this age group (Table 2, Fig. 1). The median age at diagnosis of glandular lesions was 70 years.

Of the 61 women with ECA, 34 underwent cervical biopsy either concurrently or subsequently. CIN2 + lesions were seen in 29 cases (85.3% of women with histologic information; 47.5% of all ECA in this age group).

Discussion

Cervical cancer is the second most common cancer among women in India and is a major public health problem both in terms of incidence and mortality [1]. Till recently, there

was no organized screening program or national guidelines for cervical cancer screening in our country. The age at initiation of screening, frequency of screening and age at exit from screening were not clearly defined and different institutions followed their own guidelines lacking uniformity and consistency in implementation. The ASCCP guidelines recommend screening to be initiated at 21 years of age [10], while WHO recommends 30 years as age of initiation and focuses on 30–49 years for low-resource settings like ours [11]. The Indian professional gynecological societies or bodies also advocated variable guidelines with regard to cervical cancer screening, whereas ISSCP-recommended age for initiating screening is 21 years and frequency of screening is every 3 years [12]; FOGSI recommends target age group for screening to be 25–65 years for settings with good resources and 30–65 years for settings with limited resources [13]. The frequency of screening for good-resource settings has been kept at 5 years if primary HPV testing or co-testing (cytology + HPV) is being used, while it is 3 years if cytology alone is used. For limited resource settings, the frequency of screening is kept at every 5 years (at least 1 to 3 times in life time) [13]. To remove these ambiguities in the initiation age of cancer screening, the Government of India launched the Operational Framework for screening and management of common cancers. For operational and logistic reasons, the age of screening for all three cancers has been decided as 30-65 years [2]. Since the population-wide cancer screening as per this document is being rolled out in different districts of India, we reviewed our data for the proportion of cervical cytologic abnormalities detected in the age bands 21–29 years, 30–65 years and > 65 years. The intent of this exercise was to assess whether we are likely to miss significant numbers of precancers and cancers of cervix if only the age group 30–65 years is focused for screening. Although in the operational guidelines, the recommended method of cervical screening is visual inspection with acetic acid (VIA) and not cytology, the test characteristics of the two modalities are more or less comparable [14], except in post-menopausal women. Hence, it can be presumed that the present analysis of cytology-based cervical cancer screening would provide substantially reliable data that can be extrapolated to screening by VIA by trained medical workers.

We detected a total of 1.7% epithelial cell abnormalities in around 80,000 cervical smears screened over a 10-year period. Majority of these (80.98%) were squamous abnormalities, while glandular lesions were detected in 19.02% of the women across all age groups. When the results were stratified into three age bands, i.e., < 30 years, 30–65 years and > 65 years, we found that almost 80% of high-grade squamous intraepithelial lesions and more than 85% of AGC-N presented in age bracket 30–65 years which is intended to be screened as per the Operational Framework document. Also 85% of squamous cell carcinomas and 87% of adenocarcinomas were detected in this age band. About three-fourths of low-grade squamous lesions and 90% of AGC-NOS were also picked up in this age group. Hence, it is anticipated that screening this age group for cervical cancer shall be able to detect majority of the cervical precancerous lesions and appropriate management at such times would avoid their progression to frank cancer. These findings are in consonance with the recommended age group for screening in the Operation Framework document [2].

However, noteworthy in the present study is that 13% of high-grade precancerous squamous lesions and a few (1.8%) of glandular lesions (AGC-N) were detected in women less than 30 years of age. This early presentation of high-grade intraepithelial lesions is worrisome since they may progress to malignancy if not detected and managed. A large cohort study of histologic outcome of cervical intraepithelial neoplasia showed that in the age group of 25–30 years, 34.6% of women had persistence and 13.1% had progression of their lesion during the follow-up period. The same authors, in a meta-analysis of published studies, observed similar rates of persistence and progression in women < 30 years of age [15]. Data from the Surveillance, Epidemiology and End Results (SEER) database of the USA showed that only a small fraction of cervical cancers were diagnosed in women in the age group of 20–29 years during the period 1999–2008, amounting to 1.4 per 100,000 females in the age group of 20–24 years and 5.94 per 100,000 females in the 25–29 year group [16]. Hence, invasive cervical carcinomas are rare in young women. However, recent data suggest an increasing trend in the incidence of cervical cancer in young women with higher likelihood of adenocarcinomas [17]. Studies from various parts of India have demonstrated an appreciable fraction of low-grade lesions in women younger than 30 years [18], similar to the present study. Since majority of these low-grade lesions regress on their own in young females, follow-up of these lesions is mandatory to detect the few women who progress to high-grade intraepithelial lesions. A study of cervical biopsies from south India reported that 13.2% of CIN2 + lesions (including adenocarcinoma) were seen in women in the age group of 21–30 years [19]. These data, along with ours, suggest that high-grade cervical precancerous lesions do occur in younger females, and hence, symptomatic patients in this age group should be included in the cervical cancer screening activities for timely detection and appropriate management of these lesions. In addition, females younger than 30 years of age should be provided with cervical cancer screening information and encouraged to enter the routine screening program at the appropriate age to improve the overall coverage of the screening activities. Moreover, the median age at first birth in India is 20 years, as per the World Bank data [20]. Hence, women in the age group of 20–30 years are likely to approach the health facilities for antenatal check-ups,

delivery and vaccination of their children. This opportunity should be amply utilized for creating awareness and screening them for common cancers since this could be the only occasion many women utilize the health services in their lifetime. Similarly, in the age band of women more than 65 years at the time of screening, about 6% of the high-grade squamous intraepithelial lesions, 13% of all SCCs and 11% of the AGC-N were detected. Our results are in consonance with those reported by Arco et al. in their study of distribution of cervical lesions in women younger than 30 years and older than 65 years [21].

Though the number of lesions detected in the two age bands (21–29 years and > 65 years) may appear small, adding them up highlights that about 19% of high-grade squamous intraepithelial lesions, 13% of AGC-N and about 14% of SCC are likely to be missed if the cervical cancer screening focuses on screening in the age bracket of 30–65 years. However, at the same time, the benefits of screening these age groups and number of extra lives saved have to be weighed against the additional cost of screening the women in these age brackets, especially in resource-limited settings like ours. Since the inclusion of HPV vaccination in our national immunization program is not likely in the near future, efforts should be directed at enhancing cancer awareness among women of all age groups, preferably starting at high school or college level. The women should be encouraged to attend the screening clinics if they have any warning signs, irrespective of their age. At the same time, the healthcare workers need to be sensitized to the need of being inclusive during the cancer screening activities regardless of the age of the individual presenting oneself for the same. Women in high-risk categories like HIV-positive, women with other STIs and those with immunocompromised status should ideally be screened across all age groups as the frequency of detection of precancerous lesions is high in these categories. These results may be useful for other low-resource countries with an intent to implement nation-wide cervical cancer screening.

Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Ethical statement The study was approved by the Institutional Ethics Committee.

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