10.5005/jp-journals-10032-1095

ORIGINAL ARTICLE

Review of Cervical Carcinoma Screening Program in Tamil Nadu – Current Trend and Recommendations from a Histopathologist's Viewpoint

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ABSTRACT

Objectives: Cervical carcinoma, the commonest carcinoma affecting Indian females, is caused by human papilloma virus (HPV) infection. Primordial prevention and primary prevention with HPV vaccine and cancer screening respectively, can go a long way in preventing this carcinoma. The health system project in Tamil Nadu has done a commendable job in reducing the disease burden by introducing screening programs for cervical carcinoma at the grassroots level, way back in 2005. This study was done to evaluate the cervical biopsy specimens received as a part of this program to compute its incidence, compare the incidence among various districts, and suggest future directions based on our observations.

Materials and methods: From visual inspection with acetic acid/visual inspection with Lugol's iodine positive cervical biopsy specimens, 506 were chosen randomly from various districts. Based on histopathological examination, incidence of individual lesions and district-wise incidence were calculated. Predictive factors that determine the progression of these lesions were analyzed based on the literature.

Results: Out of the 506 cervical biopsy specimens, 34 were unsatisfactory. The incidence of high-grade dysplasia peaked around 31 to 40 years, and squamous cell carcinoma peaked among 51 to 60 years. Madurai ranked high in the incidence of both high-grade dysplasia and carcinoma.

Conclusion: Incidence of dysplasia and carcinoma in our study was comparable to those seen in the literature. Integration of HPV deoxyribonucleic acid studies into the program can increase the detection rate, detect the progressors, help to identify the HPV species prevalent in an area, and aid in formulating cost-effective HPV vaccine cocktail.

Keywords: Acetowhite, Dysplasia, Human papilloma virus, Vaccine.

How to cite this article: Ibrahim SS, Kesavaraj K, Arun M, Ameen SAM, Sankar R. Review of Cervical Carcinoma Screening Program in Tamil Nadu – Current Trend and Recommendations from a Histopathologist's Viewpoint. J South Asian Feder Menopause Soc 2017;5(1):1-7.

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Source of support: Nil

Conflict of interest: None

Date of submission: 05 February 2017

Date of acceptance: 07 April 2017

Date of publication: June 2017

INTRODUCTION

Cervical carcinoma is the first common carcinoma affecting the female population in India, with an incidence of 134,420 new cases per year, bearing one-fifth of the world burden.[1] It is seen among 15- to 44-year-old females; 80% of the cases with cervical carcinoma are concentrated in the rural areas.[2,3] About 87.8 to 96.67% of the invasive carcinoma was associated with human papilloma virus (HPV) infection.[4] Cofactors that help in the progression from HPV infection to carcinoma include tobacco smoking, poor local hygiene, early coitus, multiple sexual partners, sexually transmitted disease, high parity, long-term use of contraceptives, and infection with human immunodeficiency virus. To contain this preventable carcinoma, Tamil Nadu government had started cervical cancer screening program in the year 2005 as a pilot project in two districts, which is now scaled up to include all the districts of urban and rural population.

Being a referral center, our department receives cervical biopsy specimens from camps organized in the nearby districts, district headquarters hospital, and from the hospital attached to our college. This study was undertaken to histopathologically analyze the specimens to find out the incidence of cervical dysplasia and carcinoma, its incidence among the districts from which we received the specimens, to analyze the progression factors in low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL) cases, and to formulate future goals in its control.

MATERIALS AND METHODS

Tamil Nadu health system project had devised a method to screen the females for cervical cancer. It included visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI), followed by cervical biopsy if VIA/VILI is positive. Both ectocervix and endocervical

biopsies were sent. When the squamocolumnar junction is not made out, then endocervical biopsies were sent. The cervical biopsy specimen thus obtained from the camps organized by the Tamil Nadu government to prevent noncommunicable diseases from clinics attached to the district hospitals and from those who attended our college-attached gynecology outpatient department were received in our department.

We had received 4,117 gynecological specimens per year. Out of that, 506 cervical biopsy specimens were randomly chosen from the different districts, processed routinely, and examined by a team of expert pathologists. Based on histopathological examination, the specimens were categorized whether they were satisfactory or not. When the lining epithelium was absent or when there were only mucinous material, it was labeled as unsatisfactory. Those slides on which lining epithelium were seen, further screening was done to know whether the biopsy included squamous epithelium, columnar epithelium, endocervical glands, and stroma. When only endocervical glands and endocervical lining were seen, then it was sorted as endocervicitis (EC). If both the linings were present, then normal epithelium/cervicitis/cervical dysplasia – LSIL and HSIL and various types of carcinomas were diagnosed, categorized, and graded based on World Health Organization grading system. The incidences of various pathologies were tabulated. The incidences of these pathologies identified in different districts were categorized to find the region-wise variance in the incidence of these pathologies. Predictive factors that influence the progression of the diseases were also analyzed based on the literature.

RESULTS

Out of the 506 cervical biopsy specimens, 34 were unsatisfactory (6.7%), and hence, were excluded from our study. Out of the remaining 472 specimens, 75% of the cases were diagnosed as chronic cervicitis (CC). The incidence of LSIL was 1.69%; 5.08% of the cases had HSIL and 6.4% of the cases had squamous cell carcinoma (SCC) – grade II. Our study group comprised females of age groups 21 to 90 years. The mean age at which the biopsy was taken, was 41.46 years. The incidence of high-grade dysplasia peaked around 31 to 40 years, whereas the incidence of SCC peaked among 51 to 60 years. Adenocarcinoma (AC) was seen in only 0.2% of the cases (Table 1).

More number of cervical biopsies was received from Madurai district (65%). The incidence of high-grade dysplasia and SCC was also high in this district (13%) followed by Sivagangai district (11%). In the rest of the districts, only inflammatory pathologies were identified (Table 2).

DISCUSSION

Squamous cell carcinoma and its precursor lesions – low-grade intraepithelial neoplasm and high-grade intraepithelial neoplasm – are associated with HPV infection. Almost 80% of the females in their second decade harbor this infection and it declines to about 5% as they reach their fifth decade due to innate immunity. HPV 16, 18, 31, 33, 35, 39, 45 and HPV 6, 11, 40, 42, 43 come under high- and low-risk categories respectively.[5,6] Human papilloma virus resides on the surface of the epithelium and for an infection or viral deoxyribonucleic acid (DNA) integration, this should reach the mitotically active basal layer which requires microabrasion. After integration, HPV infection progresses to either low-grade or high-grade dysplasia or wanes due to innate immunity. Later, low-grade or high-grade dysplasia may regress or progress to carcinoma.

Our study group included women aged between 21 and 90 years with a mean of 41.46 years. Half of the women screened in our study groups belonged to both 31 to 40 years category and 41 to 50 years. In correlation with our study, in the study conducted by Poli et al,[7] most of the women belonged to 31 to 40 years and it was 30 to

Table 1: Age-wise stratification

Age (years)	*21–30*	*31–40*	*41–50*	*51–60*	*61–70*	*71–80*	*81–90*	*Total*
CC	65	136	85	36	8	23	–	353
EC	7	28	12	2	–	2	–	51
LSIL	–	3	4	–	–	–	1	8
HSIL	4	8	3	6	2	1	–	24
SCC I	–	–	1	1	–	–	–	2
SCC II	1	3	11	7	6	2	–	30
AC	–	–	–	1	–	–	–	1
PC	–	–	1	1	1	–	–	3
US	3	12	12	6	1	–	–	34
Total	80	190	129	60	18	28	1	506

PC: Poorly differentiated carcinoma; US: Unsatisfactory

Table 2: District-wise distribution of the cases

Districts	*Madurai district*				*Dindigul district*			*Sivagangai district*			*Ramnad district*	*Virudhunagar district*		
Town	*Madurai*	*Usilampatti*	*Melur*	*Sholavandhaan*	*Nilakottai*	*Dindigul*	*Natham*	*Sivagangai*	*Karaikudi*	*Devakottai*	*Ramnad*	*Virudhunagar*	*Kariapatti*	*Aruppukottai*
CC	192	17	10	1	4	5	7	1	57		22	1	15	19
EC	35	1	–	–	–	1	1	–	3	–	6	–	–	4
LSIL	4	–	–	–	–	–	–	–	5	–	–	–	–	–
HSIL	14	–	–	–	–	–	–	–	7	1	–	–	–	2
SCC I	2	–	–	–	–	–	–	–	–	–	–	–	–	–
SCC II	28	–	–	–	–	–	–	–	2	–	–	–	–	–
AC	1	–	–	–	–	–	–	–	–	–	–	–	–	–
PC	3	–	–	–	–	–	–	–	–	–	1	–	–	–
US	20	2	1	–	1	–	–	1	5	1	3	–	1	–
Total	331				19			82			32	42		

PC: Poorly differentiated carcinoma; US: Unsatisfactory

39 years in Sankaranarayanan et al[8] study group. In Ghosh et al[9] study group, the mean age of the patients were 34.1 ± 9.2 years, which was in correlation with our study.

Low-grade intraepithelial lesion is usually asymptomatic; 85% of the cases are associated with high-risk HPV. Grossly, they may be flat, present as squamous papilloma, or as condyloma accuminata.[10] Flat lesions are identified by acetowhitening and colposcopic examination of the cervix or by cytological screening as grossly no change is identifiable. Low-grade squamous intraepithelial lesion is classified histologically into mature and immature type. Mature type of LSIL consists of proliferating basal and parabasal cells involving one-third of the epithelium, representing a delay in the maturity of the cells with koilocytic atypia of the superficial layers.[11,12] Sometimes, binucelation and multinucleation will be the only findings. In the immature LSIL type, there will be minimal atypia in the superficial layers and increase nuclear density throughout the epithelium (Fig. 1). Flat lesions are diffusely positive for p16, whereas papillary lesions show patchy p16 positivity denoting association with low-risk HPV infection. The incidence of LSIL was 1.69% in our study. It was 0.28% in Poli et al[7] study, which was very less compared with the incidence observed in our study; 50% of the cases diagnosed as LSIL were less than 50 years, which was comparable with Poli et al study.[7] In Luthra et al[13] and Bhaskaran et al[14] studies, the mean age at which LSIL was seen was 33.8 and 31.4 years respectively, which was comparable to our study. The LSILs usually regress spontaneously, hence, regular follow-up is mandatory with cytology smears or HPV DNA testing every 6 to 12 months.[15]

Like LSIL, flat HSIL is also not visible grossly and is asymptomatic. It is identified by acetowhitening or Lugol's iodine but confirmed only by histopathology.

Fig. 1: Increase in nuclear density of all the layers with minimal atypia in the superficial layers – LSIL, immature type (hematoxylin and eosin, 40×)

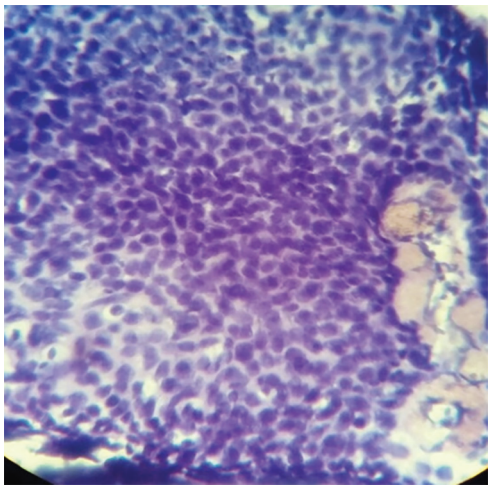

Fig. 2: Marked atypia of all the layers with intact basement membrane – HSIL (hematoxylin and eosin, 40×)

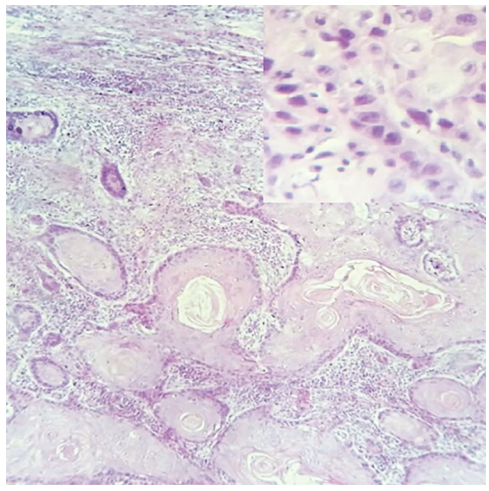

Fig. 3: Atypical squamous cells invading the stroma with inflammatory stromal reaction (hematoxylin and eosin, 10×). Inset shows pleomorphic squamous cells – SCC – grade I (hematoxylin and eosin, 40×)

These lesions exhibit atypia in all layers of the epithelium, anisokaryosis, coarse nuclear chromatin, and abnormal mitotic figures (Fig. 2). Variants include keratinizing and papillary lesions. The incidence of HSIL was 5.08% in our study, which was comparable to other studies (1.05–27.4%).[7,16,17] Peak incidence of HSIL was seen in the 31 to 40 year group, which was similar to Sankaranarayanan et al study group.[8] The mean age at which cervical intraepithelial neoplasia (CIN) II and III were detected was 35.2 and 40.2 years in Luthra et al[13] study and 34.3 years in Bhaskaran et al[14] study, which was similar to our study. The ratio of detection of LSIL to HSIL in our study group was 0.3:1, which was also observed in the study conducted in England and Australia, and it was higher in Sankaranarayanan et al study group (8.1:1).[8,18,19] Treatment of HSIL includes cone biopsy, cryotherapy, or loop electrosurgical excision procedure.

Both LSIL and HSIL have a chance of regression. According to Nasiell et al,[20] 62% of the cases with LSIL will regress and 50% of CIN II cases regress according to another study by Nasiell et al,[21] and it progresses to high-grade lesions or carcinoma in 16% of the cases and 35% respectively. In India, HPV prevalence is common among 26- to 35-year-old females, and carcinoma occurs around 45 to 59 years old.[22] Effective intervention in this 20-year window period can prevent the progression of this carcinoma. The cytological and histopathological regression along with spontaneous HPV DNA negativity is possible in 95% of the cases.[23] Only those with persistent HPV infection often progress to the next stage. Histopathological predictors of progression to squamous carcinoma include extensive involvement of surface epithelium and deep endocervical crypts by HSIL, luminal necrosis, intraepithelial squamous maturation, papillary architecture, mucin differentiation, and fibroblastic proliferation of the stroma.[24] According to Koeneman et al[25] study, nonsmokers, prebiopsy Pap 3a, and a concomitant LSIL in the biopsy and not more than one biopsy containing CIN II were predictors of spontaneous regression. Several markers are on trial to predict the progression. Sirtulin 1 (SIRT1) and p16 are the immunohistochemical markers helpful to assess the disease progression.[26]

Grossly, SCC presents as a friable exophytic or an ulcerated lesion. Histopathologically, the tumor is composed of sheets of cells with nuclear irregularity and prominent nucleoli and shows brisk mitosis and invasion into the stroma (Fig. 3). The variants include keratinizing type, nonkeratinizing type, small cell, basaloid squamous, verrucous, warty, squamotransitional, and lymphoepithelioma-like carcinoma. The incidence of SCC in our study group peaked around 51 to 60 years, which was also observed in Sankaranarayanan et al study group.[8] In Bhaskaran et al[14] study, the age group affected with carcinoma *in situ* was 34.7 years and with invasive carcinoma 42.2 years, which was comparable to our study.

Adenocarcinoma of the cervix arises from an *in situ* lesion. Most AC is associated with HPV types 16 and 18. Grossly, the tumor is either exophytic or ulcerated. Histopathologically, the tumor is composed of confluent cribriform glands, apical mucin depletion, and pseudostratification (Fig. 4). Variants include mucinous, villoglandular, endometrioid, clear cell, serous, adenoid basal, adenoid cystic, and mesonephric carcinoma. The incidence of AC of the cervix has increased in the developed countries as SCC incidence is declining due to effective cervical screening program. Major hindrance in the detection of the precursor lesions of AC is inaccessible columnar epithelium by cytology and colposcopy. Relatively, it is easier to detect precursor squamous carcinoma lesions as the squamous lining is well exposed to

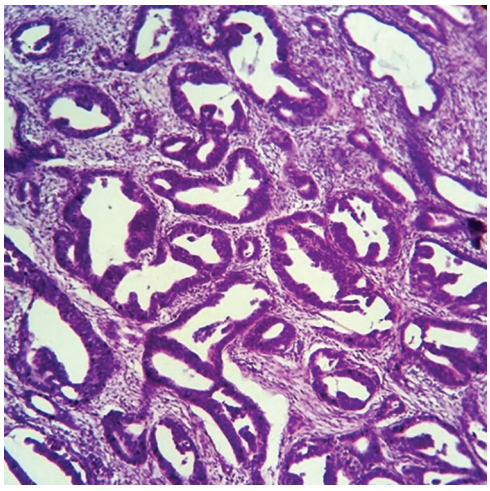

Fig. 4: Tumor cells arranged in glandular pattern with loss of mucin and showing nuclear stratification – AC (hematoxylin and eosin, 40×)

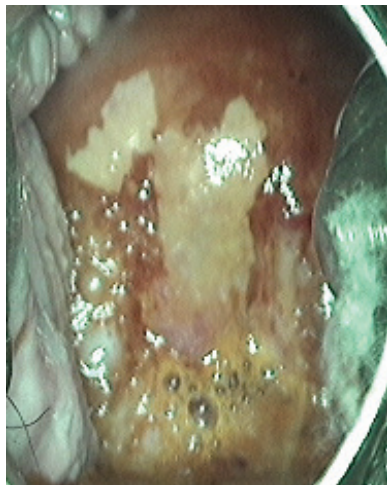

Fig. 5: An opaque circumscribed patch in the cervix – positive VIA

screening. The incidence of AC was 14% of all carcinomas of the cervix according to Greer et al, whereas in our study the incidence was 0.2%.[27] Treatment of both SCC and AC of the cervix includes radical hysterectomy, lymphadenectomy with or without chemoradiation depending upon the stage of the tumor.

Cervical carcinoma can be prevented by early screening methods. Most cases of cervical carcinoma were diagnosed after opportunistic screening, i.e., after the patient develops symptoms. To prevent the occurrence of cervical carcinoma among high-risk females and thereby prevent cervical cancer-related deaths, the Government of Tamil Nadu had initiated a project to screen all sexually active females from both the urban and rural background.[28] Protocols were devised by experts under the guidance of Tata Memorial Hospital, Mumbai, and Adyar Cancer Institute, Chennai, and approved by the World Bank. Awareness programs were organized to mobilize the population, and to accept the program.

The project includes magnified visual inspection with 3 to 5% acetic acid and Lugol's iodine if positive followed by histological sampling. A well-demarcated opaque lesion due to increased intracellular protein content located in the transformation zone close to the squamocolumnar junction is taken as VIA test positive (Fig. 5). When there is no whitening, faint or dot-like positivity, endocervical polyps, nabothian cysts, or a prominent squamocolumnar junction, they are taken as negative VIA. Iodine nonuptake areas or if the cervix is densely yellow, it is taken as VILI positive (Fig. 6). The transformation zone in the cervix represents the squamous metaplastic zone where the resting reserve cells in response to injury proliferate and form immature squamous cells. These cells do not form glycogen, hence, does not stain with iodine. This is identified by the iodine test. These metaplastic cells are prone for HPV infection and

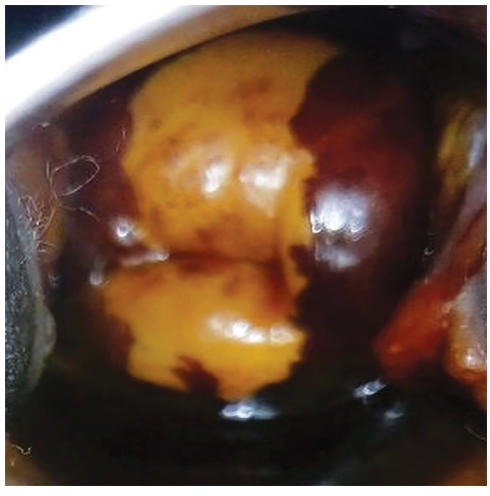

Fig. 6: Yellow area in the cervix – positive VILI

hence, progress to form dysplastic cells and carcinoma. The sensitivity of VIA/VILI to detect HSIL was 66 to 96% and the specificity was 64 to 98%. The sensitivity of VIA/VILI was found to be similar to that of cytology, whereas its specificity was more and hence, it was implemented in the place of cytological screening.

Recently, HPV DNA tests were introduced along with cervical screening in the developed countries. This can identify those who might develop intraepithelial lesions. But because of its high cost, implementing it in the developing countries is not possible now. Stoler et al[29] in their study had analyzed the diagnostic interpretation of the biopsy cervix of both community pathologists and an expert panel and had concluded that incorporation of HPV and immunohistochemical markers like p16 can improve the diagnosis and hence, can appropriately guide the treating physicians. As follow-up of patients with LSIL and HSIL is difficult in our setup, as it needs more community motivation, implementation of HPV tests and ancillary prognostic

tests are needed as it mitigates the need for follow-up and it can be cost-effective if done with dedication and refined implementation methodologies.

Higher turnover and higher incidence of dysplasia was seen in Madurai district. Because Madurai is the epicenter of this district, it might have received maximum number of cases and our hospital being a referral center the higher incidence might be due to pooling of cases from the nearby areas. There was a region-wise variability in the prevalence of HPV. According to Bhatla et al[30] study, HPV 45 was more prevalent in the southern states compared with northern states. Such variation might also exist among various districts, thereby leading to the increased prevalence of carcinoma in certain districts, which might be the second reason for higher incidence in Madurai district. This could be ascertained with certainty only if HPV DNA assay is integrated in our program. This, though increasing the cost of screening, in the long run can help in identifying the areas where high-risk HPV is prevalent and hence, concentrated approach can be given to that area. This can also help us to formulate individual area-wise HPV strain vaccine cocktails to prevent such infections.

CONCLUSION

In our study, the incidence of HSIL peaked around 31 to 40 years and SCC peaked around 51 to 60 years. This implicates that HPV infection in those before 30 years wane and these 20-year window period populations are more likely to develop carcinoma. This population can be targeted for HPV screening, analyze the type of HPV prevalent in them, persistence of HPV infection in them, percentage of progressors, and the type of HPV more likely to cause carcinoma, which is more cost-effective than screening the entire population with HPV DNA in addition to histopathological examination. This can guide us to formulate the vaccine cocktail specific to a particular district based on the HPV strains prevalent in that district. The benefit is more compared with cost in this methodology.

ACKNOWLEDGMENT

The authors acknowledge the support given by their Professor and Head, Department of Pathology, Dr T Geetha, and they also thank all the technical staffs and the workers in their department for giving them a helping hand.

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