



e-Newsletter

ISCCP

Member International Federation of Cervical Pathology and Colposcopy

Newsletter of Indian Society of Colposcopy & Cervical Pathology (Reg.)

www.isccp.in

From the Editor's Pen

Greetings from ISCCP and a Healthy life to all,

The rapidly expanding COVID-19 pandemic has impacted all areas of daily life, including medical care. The primary intervention to slow the disease are physical distancing, hand hygiene, use of mask for respiratory hygiene, and staying home as much as possible. These interventions are affecting the psychosocial health in general population and affecting the recovery of already ill patients as well. Appropriate care to cancer patients during this pandemic is challenging and the of death from cancer versus death or serious complications from SARS-CoV-2, and the likely higher lethality of COVID-19 in immunocompromised hosts is to be carefully balanced. Other challenges which we all are facing comprise of cancellations of in-hospital visits; delays in routine cancer screening leading to significant declines in the number of patients with newly identified cancers during the pandemic and surgery postponements or cancellations. There is no "one size fits all" approach to delivering cancer care during the COVID-19 pandemic, and no international guidelines.

Treatment decisions must be made on a case-by-case basis. Although in the current scenario, all the cancer patients in need of surgery must be undertaken whenever necessary and surgery if can be postponed in favour of chemotherapy and radiotherapy, should be done. American college of surgeons guidelines on resuming elective surgeries states

1. SARS-CoV-2 infection rates should be on a downward trend for at least two weeks at the facility's geographic location.
2. Resource utilization, including ICU bed and personal protective equipment, must be carefully calibrated.
3. Testing of patients and employees must be strongly considered.
4. Prioritization and scheduling of cases must be managed carefully by all key stakeholders.

The article on "Role of Vaginal Microbiota in the Development of Cervical Cancer" in this issue looks into the present knowledge of microbiota, their interactions and the possible interventions possible in future with relation to use of Probiotics. It is well known that the cervix and vagina are colonised by a whole unique set of organisms consisting of bacteria, fungi, archaea and other eukaryotes called the Cervicobaginal Microbiome. It has been seen that it is a complex dynamic state of specific microbiomes, called Community State Types which may protect or predispose to dysbiosis and HPV infections. CST I,II,III,V are Lactobacilli dominant while CST IV lack it thus predisposing to an altered microbiome. CST III predisposes

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Abstract Submission

Open till

28th February, 2021

to HPV while CST IV may increase the progression to cervical intraepithelial tumours or cervical cancer.

This issue also contains 'Journal Scan' and 'News from around the world' sections.

I, once again, request all the ISCCP members to contribute in the Newsletter in the form of review articles/original articles/ viewpoint/case reports/images.

Stay Home and Stay Healthy

Chief Editor

Prof Aruna Nigam

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Role of Vaginal Microbiota in the Development of Cervical Cancer

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Introduction

Microbiota are the communities of all microorganisms-pathological, commensal and symbiotic organisms found in all specific environments in all multicellular organisms. They may include bacteria, fungi, viruses etc and are unique in the different body environments like skin, gut and vagina. It is well known that HPV infection is causative for cervical cancer. In the last two decades there has been more evidence of certain cervicovaginal microbiota (CVM) and infections to be more commonly associated with cervical cancer. This review will look into the present knowledge of different cervicovaginal microbiota, their associations with different infections and the progression to cervical cancer and to look for any practical interventional strategies.

Relation of Microbiota to Health

There is a lot of research linking different microbiota to different states of health and disease. In other body parts like gut, oral cavity or skin, diversity indicates a healthy state, in contrast low diversity and predominance of Lactobacillus in the CVM indicate health. Studies have been conducted to classify the CVM into groups depending on the prevalent bacterial species.

The human microbiota comprise almost 50% of the human body cells. The detection methods improved over time from insensitive culture methods to bacterial RNA fragment detection. Till recently most studies used detection of rRNA 16s fragments which primarily detect bacterial genetic fragments, with a sensitivity of 49% of the 'Next Generation Sequencing (NGS) Analysis techniques. To analyse genetic fragments of a wider spectrum of the microbiome, NGS is better.¹

Normal Cervico-Vaginal Microbiota (CVM)

The vaginal flora of a normal, asymptomatic reproductive-aged woman includes multiple aerobic (Lactobacillus spp., Diphtheroids, Staph. aureus, Staph. epidermidis, E.coli, Klebsiella spp. etc.) as well as obligate anaerobic species (Peptostreptococcus spp., Clostridium spp., Propionibacterium, Eubacterium, etc.). These bacteria exist in symbiotic relationship with the host and are alterable, depending on the microenvironment. They localize where their survival needs are met and have exemption from the infection-preventing destructive capacity of the human host. With this vaginal ecosystem, some microorganisms (predominantly Lactobacilli) produce substances such as lactic acid and other organic acids, bacteriocidins and hydrogen peroxide that maintain a pH of 4-4.5. This inhibits nonindigenous organisms.² They prevent colonization of high amine-producing bacterial species, mop up these potentially carcinogenic amine derivatives, providing an additional layer of biosurfactants and thus contribute substantially to an anticarcinogenic protection. Treatment with broad-spectrum antibiotic may result in eradication of the normal vaginal flora and leads to symptoms attributed to inflammation from Candida species or other anaerobes.

Normal Microbiota - Community state types (CST)

Using NGS, Rovel et al has broadly classified the CVMs into 7 CST (Community State Types) on the basis of NGS. This classification has been widely used for many subsequent studies.³ These Community State types differ in their prevalence and pathogenicity. Lactobacillus crispatus, L.gasseri, L.iners, L.jensenii were

found to predominate CST I, II, III and V. In contrast, CST IV lacks Lactobacillus and has more anaerobes. The CVM is dynamic and changes from one type to another. This change depends on multiple factors like age, phase of menstrual cycle, hygiene, lifestyle and sexual practices.⁴ In this dynamism CST III is more commonly seen to change to CST IV, implying that L.ineri is not inhibit growth of anaerobes like Gardenella, Mobiluncus and Pevotella thus increasing the susceptibility to Bacterial Vaginosis (BV).^{5,6}

Ethnicity is another important factor which decides the CST. Caucasians and Asians have a higher prevalence of Lactobacillus in the microbiota compared to Hispanic or black women. This is due to genetic variations which influence the mucosal metabolic and immunity pathways. This could be associated with a higher prevalence of HPV infections and cervical cancer.

The age or phase of menstruation decides the cyclical rise (or fall) of estrogen-progesterone which increases (or decreases) the amount of glycogen in the squames, which further increase (or decrease) the population of Lactobacillus. This explains the lack of Lactobacilli in the postpartum and postmenopausal period. A metaanalysis has shown that hormones like COCs can reduce the prevalence of recurrent BV by almost 30% by maintaining the glycogen in the squamous cells.⁷ However other factors like smoking, intercourse, vaginal douching and other sexual practices reduce the presence of L.crispatus and increases the biodiversity, thus increasing the chances of HPV persistence and further progression to cervical cancer.

Role of Cervicovaginal Microbiota in HPV/HIV and Cervical Cancer

Immune-microenvironment in infections: Altered microbiota, also called Dysbiosis results in increased production of inflammatory mediators like IL-1, IL-6, TNF- α , IFN- γ etc. Chronic expression of these cytokines leads to higher genetic instability and reduced tumour suppressor protein functions in the infected cells. These conditions increase the chances of cervical cancer.⁸

HPV plays a major role in the development of cervical cancers. Of the 200 genotypes only 45 infect the anogenital tract. There are low risk and high risk strains for cervical cancer. Unlike low risk serotypes, oncogenic HPV serotypes can integrate into human genome. Globally HPV-16 and HPV-18 are most commonly associated with invasive cancers and are thought to cause approximately 65-75% of cases. There have been some studies which give evidence of the impact of HPV infections on the cervicovaginal microbiome. CST II, dominated by L.gasseri was associated with a faster

clearance of HPV infection. It has also been seen that CST III and IV are likely to be HPV positive.⁶ It is yet to be seen whether this is just an association or a causal factor.

CIN: A higher diversity in the vaginal flora and lack of Lactobacilli was seen to be associated with increasing severity of CIN. The prevalence of CST IV was 2-4 times more prevalent in women with LSIL, HSIL and microinvasive carcinomas.^{3,9}

The complex relationship between HPV and cervical cancer can be further examined in Sub-Saharan Africa. It has been seen that oncogenic potential of HPV-16 (one of the primary oncogenic strains) has an inverse relation to the prevalence of HPV-16 infection in the population. Sub-Saharan Africa has the lowest prevalence of HPV-16 in normal women, but most of the oncogenic strains are contributed by non HPV-16 strains like 52, 58, 33 & 45. This is in contrast to the observation elsewhere. Another very interesting observation is that elsewhere in the world, infection with multiple HPV strains was more common in normal women. However in Sub Saharan Africa infection with multiple strains was more commonly associated with progression to cervical cancer. Scientists are trying to find the reason for such opposite behaviour. All these may be a result of the variations in the microbiota and further research will throw light on such complex interactions between HPV and the microbiota.⁸

HIV: HIV decreases the body immunity. This increases the susceptibility to multiple HPV infections and a reduced clearance potential. This leads to a higher oncogenic potential.

Role of Probiotics

Probiotics have an established role in improving the gut flora after antibiotics and other illnesses.¹⁰ Probiotics have been used with metronidazole and clindamycin in treatment of BV. Oral preparations containing certain exogenous Lactobacilli were used in studies which successfully increased Lactobacilli dominant microbiota, however the predominant species in the CVM was found to be L.ineri, which maynot be a very good replacement.¹¹ So more research is required to explore better probiotic options. That will not only reduce the prevalence of HPV, but will also bring down the incidence of bacterial vaginosis (BV). Reduction in BV will further help in reduction of other morbidities like preterm labour pains or PPRM.

Conclusion

The cervical and vaginal microbiota has a very important functional role in the protection of vaginal

health or to susceptibility to infections, persistence of HPV and progression to cervical carcinomas.¹² The normal cervicovaginal microbiota (CVM) is commonly classified as different Community State Types (CST) varies according to age, phase of menstrual cycle, medications and dysbiosis. The presence of *L.crispatus* has been associated with lower dysbiosis and HPV infections and have better resistance compared to those containing *L.iners* have more chances of infections. Dysbiosis triggers cytokines like IL-1, IL-6 etc which increase genetic mutations and reduce the synthesis of tumour suppressor factors, subsequently increasing the chances of cancers.

More research is required to understand the complex interaction of different microbiomes with different actions. Research should also find more options of Probiotics, which can replenish the normal microbiota in the female reproductive tract and

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Journal scan

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Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, Sundström K, Dillner J, Sparén P.

HPV Vaccination and The Risk of Invasive Cervical Cancer

N Engl J Med. 2020 Oct 1; 383(14): 1340-1348.

Authors used nationwide Swedish demographic and health registers to follow an open population of 1,672,983 girls and women who were 10 to 30 years of age from 2006 through 2017. The subjects were evaluated for cervical cancer until their 31st birthday.

They assessed the association between HPV vaccination and the risk of invasive cervical cancer, controlling for age at follow-up, calendar year, county of residence, and parental characteristics, including education, household income, mother's country of birth, and maternal disease history.

Result

Cervical cancer was diagnosed in 19 women who had received the quadrivalent HPV vaccine and in 538 women who had not received the vaccine.

The cumulative incidence of cervical cancer was 47 cases per 100,000 persons among women who had been vaccinated and 94 cases per 100,000 persons among those who had not been vaccinated.

After adjustment for age at follow-up, the incidence rate ratio for the comparison of the vaccinated population with the unvaccinated population was 0.51 (95% confidence interval [CI], 0.32 to 0.82).

After additional adjustment for other covariates, the incidence rate ratio was 0.37 (95% CI, 0.21 to 0.57). After adjustment for all covariates, the incidence rate ratio was 0.12 (95% CI, 0.00 to 0.34) among women who had been vaccinated before the age of 17 years and 0.47

(95% CI, 0.27 to 0.75) among women who had been vaccinated at the age of 17 to 30 years.

The authors concluded that among Swedish girls and women 10 to 30 years old, quadrivalent HPV vaccination was associated with a substantially reduced risk of invasive cervical cancer at the population level.

Ikeda S, Ueda Y, Hara M, Yagi A, Kitamura T, Kitamura Y, Konishi H, Kakizoe T, Sekine M, Enomoto T, Sobue T.

Human Papillomavirus Vaccine to Prevent Cervical Intraepithelial Neoplasia in Japan: A nationwide case-control study

Cancer Sci. 2020 Oct 10. doi: 10.1111/cas.14682.

This nationwide case-control Japanese study from April 2013 to March 2017 targeted women aged 20-24 years old at cervical screening. Authors compared HPV vaccination exposure between those with abnormal and normal cytology.

Abnormal cytology was classified based on the results of histological test. Authors calculated the odds ratio (OR) and 95% confidence interval (CI) of the above endpoints and vaccination exposure using the conditional logistic regression model and estimated vaccine effectiveness using the formula $(1 - OR) \times 100$.

Result

A total of 2,483 cases and 12,296 controls (one-to-five matching) were eligible in 30 municipalities in Japan.

The distribution of histological abnormalities among cases was 797 CIN1 (including dysplasia) (32.1%), 165 CIN2 (6.7%), 44 CIN3 (1.8%), and 8 squamous cell carcinoma (SCC) (0.3%).

The ORs of HPV vaccination compared with no vaccination for abnormal cytology, CIN1+, CIN2+, and CIN3+ versus controls was 0.42 (95% CI, 0.34-0.50), 0.42 (95% CI, 0.31-0.58), 0.25 (95% CI, 0.12-0.54), and 0.19 (95% CI, 0.03-1.15), respectively, equating to a vaccine effectiveness of 58.5%, 57.9%, 74.8%, and 80.9%, respectively. None of the 8 patients with SCC were vaccinated.

This nationwide case-control study from Japan demonstrated a substantial risk reduction in abnormal cytology and CIN among women who did versus those who did not receive HPV vaccination.

Preti M, Rosso S, Micheletti L, Libero C, Sobrato I, Giordano L, Busso P, Gallio N, Cosma S, Bevilacqua F, Benedetto C.

Risk of HPV-related extra-cervical cancers in women treated for cervical intraepithelial neoplasia.

BMC Cancer. 2020 Oct 7; 20(1): 972. doi: 10.1186/s12885-020-07452-6.

The aim of this Italian study was to estimate the risk of subsequent extra-cervical Human Papillomavirus (HPV) related cancer in patients surgically treated for high-grade cervical intraepithelial neoplasia (CIN 2-3).

3184 patients surgically treated for CIN2-3 since 1992 at the Department of Surgical Sciences of University of Torino were considered.

The risk of HPV-related cancer was calculated as Standardized Incidence Ratio (SIR), using as expected values tumour age specific incidence of resident population.

Result

173-second primary cancer (SCPs) were identified.

SIR to develop cancer after treatment for CIN2-3 was 2.2 (CI 95% 1.89-2.50).

Among these occurrences, 10 were in HPV related sites: 1 anus (SIR = 1.8; 0.04-10.0), 3 vagina (SIR = 12.4; 2.56-36.3), 1 vulva (SIR = 1.7; 0.04-9.59), 5 oropharynx (SIR = 8.5; 2.76-19.8).

Significant risk was also recorded for pulmonary (SIR = 3.1; 0.70-5.27) and bladder (SIR = 4.05; 1.10-10.56), with smoking as possible cofactor.

Authors also found increased risk for breast (SIR = 2.4; 2.07-2.84) and ovarian cancers (SIR = 2.1; 1.13-3.49), probably due to an higher adherence to spontaneous and programmed screening programs.

The study supports the hypothesis of an increased risk of HPV-related tumors for CIN treated patients, mostly for CIN3. It is conceivable the need of early diagnosis for these cancers in this higher-risk populations.

Cervical Cancer News from Around The World

Roopa Hariprasad

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(Under Ministry of Health and Family Welfare, Govt. of India)
Co-Editor, Indian Society of Colposcopy & Cervical Pathology
Course Director & Convenor, NICPR-ECHO Online Cancer Screening Program

New Guidance for Testing of Minimal Abnormalities Detected in Cervical Cancer Screening

Cancernetwork.com: 18 October 2020

Following the new ASCCP-led national consensus guidelines for managing abnormal cervical cancer screening tests, these new guidelines estimate risk based on an individual's risk factors, thus allowing for more personalized care. New guidance for managing further testing for patients with minimal abnormalities detected during cervical cancer screenings have been published in *JAMA Insights*.

Following the new ASCCP-led national consensus guidelines for managing abnormal cervical cancer screening tests, these new guidelines estimate risk based on an individual's risk factors, thus allowing for more personalized care management.

To read more: <https://www.cancernetwork.com/view/new-guidance-for-testing-of-minimal-abnormalities-detected-in-cervical-cancer-screening>

Cancer Screenings Plummeted During Height of COVID-19

The Times: October 19, 2020



During the height of the COVID-19 shelter-in-place orders, there were only three lung cancer screenings across three Northeast Georgia Health System hospitals that are accustomed to running 70-80 tests per month.

Medical professionals in the cancer field are concerned about a drop in screenings due to COVID-19, because people are nervous about being at medical facilities during the outbreak

Angie Caton, the assistant nurse manager for oncology services at NGHS, said there is a concern among health care providers about people delaying essential cancer screening out of fear of going to health care facilities earlier this year.

<https://www.gainesvilletimes.com/news/health-care/cancer-screenings-plummeted-during-height-covid-19/>

Importance of Breast and Cervical Cancer Screenings During COVID-19

Pennsylvania Department of Health: Oct 03, 2020

Secretary of Health Dr. Rachel Levine emphasized the importance of continuing breast and cervical cancer screenings during the COVID-19 pandemic. The state has seen many women and transgender individuals postpone these essential screenings due to COVID-19.

Regular screening for certain types of cancer, including breast and cervical cancer, are essential to good health and can save lives. Although breast cancer screening cannot prevent breast cancer, it can help find breast cancer early when it is easier to treat. It is imperative that all women talk with their health care provider about cancer screening tests to find which one is best, and when they should have them.

The Pennsylvania Breast and Cervical Cancer Early Detection Program (PA-BCCEDP) is a free breast and cervical cancer early detection program funded by the department through a grant from the Centers for Disease Control and Prevention (CDC). Free services, like mammograms, MRIs, pap and HPV tests, and follow-up diagnostic tests for abnormal screening results are available for those who are eligible.

Read more: <https://www.bctv.org/2020/10/03/department-of-health-emphasizes-importance-of-breast-and-cervical-cancer-screenings-during-covid-19/>

Returnee Invents AI Robot to Help Diagnose Cervical Cancer

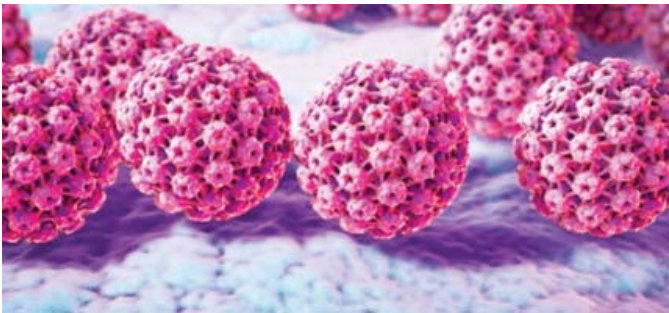
med-technews: October 15, 2020

The latest award will provide funding to a Cervical Patch Sampling Device that screens for HPV (Human Papillomavirus) which can cause cervical cancer. The new device has been developed to improve detection results by enabling non-invasive evaluation of all the cells at the cervical surface while preserving their orientation.

Developed by a team of researchers based at Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge, this latest grant means that, since its inception in 2016, Medtech Accelerator has now fully committed £1.7 million of funding to 14 technologies.

While HPV screening has led to a significant reduction in cervical cancer occurrence, current approaches have a low positive-predictive value meaning many women would be referred for secondary testing and possible treatment unnecessarily. By allowing women to be diagnosed in the community in one test, it is hoped this novel sampling approach will help reduce further testing referrals and unnecessary possible treatment, saving critical NHS time and money.

Read more: <https://www.med-technews.com/news/cervical-screening-device-awarded-125k-grant/>



ISCCP Activities

Professor Nisha Singh

Department of Obstetrics and Gynaecology, King George's Medical University, Lucknow

Online Comprehensive Cervical Cancer Prevention Module (20th April 2020 to 3rd May 2020). The module was planned daily for 2 weeks between 3-4 pm. The knowledge partner was Periwinkle Technologies –Smart Scope. The webinar was attended by 250+ delegates from all over the country.



Partha Basu MD, DNB, PhD

DESIGNATION: HEAD, SCREENING GROUP

AFFILIATIONS: INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (WHO), LYON, FRANCE

AWARDS:

- COMMONWEALTH FELLOWSHIP
- UICC YY MEMORIAL INTERNATIONAL CANCER STUDY FELLOWSHIP
- UICC ICRETT FELLOWSHIP
- CSIR INDIA TECHNOLOGY EXCELLENCE AWARD
- SILVER MEDAL & HONORS IN SURGERY, CALCUTTA UNIVERSITY

RESEARCH INTERESTS:

- HPV VACCINE – ALTERNATE SCHEDULES; NEW VACCINES; SURVEILLANCE
- CERVICAL CANCER SCREENING & TREATMENT- ALTERNATIVE STRATEGIES
- EVALUATING CANCER SCREENING PROGRAMS IN DIFFERENT COUNTRIES
- IMPROVING CANCER CONTROL & REDUCING INEQUITIES IN LMICS

PUBLICATIONS: MORE THAN 120 PEER REVIEWED JOURNALS, BOOKS AND WHO PUBLICATIONS

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International Agency for Research on Cancer
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Slide also features a portrait of Partha Basu and a vertical list of participant thumbnails on the right side, including Partha Basu, SARITHA SHAMSUNDER, Anita Singh, and Veena Mokta, along with logos for Periwinkle Technologies and DR V Singh.

ISCCP & FOGSI Oncology Committee in Association with Oncology Committee of AOGD Sunday webinar Series (June-July 2020)

Online workshop was organized for Updating Skills in Cervical Cancer Prevention which was supported by Genworks India. Six weekly sessions were attended by about 400 delegates.

