IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 6 Ver. III (May. 2016), PP 65-72
www.iosrjournals.org

Clinicoepidemiological Overview of Cervical Cancer and Pre-Cancer with Special Reference to West Bengal

Agniva Misra, Suman Chakraborty, Aurobindo Rautray,
Debdoot Sheet School of Medical Science and Technology, IIT, Kharagpur 721 302, India.

Abstract: *Cervical cancer (CC) is the 2nd most common cause of cancer death among women globally. Worldwide, out of 7.6 million cancer deaths, 3.6% was due to CC in 2008 and out of 12.7 million new cancer cases, 4.2% were CC in 2008 and 84% of it occurs in less developed countries . Cervical cancer was the 3rd largest cause of cancer mortality in India in 2004 and related mortality rate was 15.2/100,000 women in 2008. Amongst different cities, its incidence was highest in Chennai in the year 1982 (41/100,000), 1991(33.4/100,000) and 2005(22/100,000). At different districts of West Bengal, Howrah had the highest CC prevalence rate(4.12%). A study in Barasat during 2002-2012 revealed that in the period of November 2009-October 2010, CC prevalence was highest (21.84%) among the patients attending the OPD. Risk factors for CC are HPV infection, unprotected and multiple sexual activity, multiple full-term pregnancy, long time use of birth control pill, smoking, poor genital hygiene and vaginitis due to infection, immunosuppression, less use of antioxidant-rich food, family history of cervical cancer. Molecular risk factors are activation of nuclear receptor for estrogen, DNA methylation of Zn-finger protein, HPV infection with CD4 count<400 cells/mm3, cytokine genes' dysregulation, polymorphism of Toll-like receptors and miR-124-rs-531564, p-16 and Ki-67 positivity of cells, disturbed expression of HR-HPV E5, E6, E7 oncoprotein .Out of different viral genotypes, HPV-16, 18, 45 are most common to cause cervical cancers. Global and local understanding of CC epidemiology with demographic variations and association with various lifestyle parameters as well as molecular risk factors, especially the HPV infection needs to be understood from an integrated viewpoint in effective prevention and management of such malignancy.*

I. Introduction

Cervical cancer is the 2nd most common cause of cancer death among women worldwide. This is associated with young age at marriage and large number of issues born to these young mothers. Another possible explanation is infection by human papilloma virus or mutation in the p53 tumour suppressor gene. Human papilloma virus is a causative factor in the aetiology of cervical cancer, HPV16 is most prevalent genotype associated with it. Intratype variations in oncogenic E6/E7 and capsid L1 proteins of HPV 16 are of phylogenetic importance and associated with risk of viral persistence and progression. E6 is associated with high risk life cycle & E7 is associated with low risk life cycle of HPV. pRB is converted from active to inactive form with the help of E7 protein. Inactive pRB causes more cell proliferation which is important for carcinogenesis. E6 inhibits the tumour suppressor p53 gene. Molecular risk factors for cervical cancer are cytokine genes'(IL-1α,1β,TNF-α) dysregulation, polymorphism of Toll-like receptors(TLR-2,3,4,9). Globally, 274000 women died due to cervical cancer which is 3.6% of 7.6 million cancer deaths in 2008. Indian mortality rate due to cervical cancer is 15.2/100,000 women in 2008. Diagnosis of cervical cancer is done by checking symptoms(increased vaginal discharge and bleeding, personal and family medical history, pain in the pelvic area, pain during sex), cytology through Pap smear(mainly detects precancerous state), colposcopy, biopsy, endocervical curettage, cone biopsy[Loop electrosurgical procedure(LEEP, LLETZ), cold life cone biopsy], cystoscopy, proctoscopy, examination under anesthesia, chest X-ray, Computed Tomography, IVP, Positron Emission Tomography(to test degree of activity of cancer cells). Epidemiology are of different types-descriptive, analytical, experimental, observational. Indian prevalence of cervical cancer was 1,01,583 in 2002. Nos. of cervical cancer cases were 8396 in west bengal in 2012. So, in this review, literature was searched to understand the clinico-epidemiological status of cervical cancer in India with special reference to west Bengal.(1)

II. Diagnostic measures of cervical cancer

Table 1. Diagnostic measures for cervical cancer :

Diagnostic methods	Role in diagnosis
By checking symptoms(increased vaginal discharge and bleeding,personal and family medical history,pain in pelvic area,pain during sex)	Symptoms are important to know severity of disease
Cytology through pap smear	To detect cancerous cell in cervix
Colposcopy	to see mucosal lining of cervix

Biopsy	to see cellular changes(area,perimeter,major axis length,minor axis length,nucleocytoplasmic ratio) in cancerous cells
Cystoscopy	to see urinary bladder is affected by the cancerous cell/not
Proctoscopy	to see rectum is affected by cancerous cell/not
Examination under Anesthesia	to see severity of disease without biopsy
Endocervical curettage	to collect cells from cervical & vaginal mucosa for staining and imaging
Cone biopsy	to cut a cone-shaped tissue from cervix to detect cancer cells
Chest X-ray	to see for any metastasis in lungs
Computed Tomography	to detect extent of lesion in cervix and in the distant organ
Intravenous Pyelography	to see the urinary system radiologically to check the cancer spread
Positron Emission Tomography	To check metabolic activity of cancerous tissue

III. Overview of epidemiological parameters & Diagnosis of disease

Epidemiology is "the study of the distribution & determinants of disease frequency" in human population. In **epidemiological observations,** the quality of data are commonly described with use of 4 terms (accuracy, validity, precision, reliability). Before a disease to be treated, it is important to detect it. So, case detection is important rather than clinical detection. Studies in which different definitions are used may lead to different conclusions. In principle, the variables that are basis for diagnosis are symptoms, signs, tests. Accuracy of examining the sign is dependent on Inter-observer variation and Intra-observer variation. Epidemiology are of different types-descriptive, analytical, experimental, observational. Descriptive epidemiology describes systematic method for charecterising health problem, provides information used for allocation of resources, enables development of testable hypothesis. Analytical epidemiology is used to identify the cause of disease and it typically involves designing a study to test hypothesis developed using descriptive epidemiology. Experimental epidemiology is where exposure status of a study group is assigned. Observational epidemiology is where exposure status of a study group is not assigned.

Table 2. Quality of data

Terms	**Definitions**
Accuracy	It is the degree to which a measurement represents the true value of the attribute being measured
Validity	It is the extent to which the study measures what it is intended to measure
Precision	It is reproducibility of a study result, that is the degree of resemblance among study results.
Reliability	This is a measure how dependably an observation is exactly the same when repeated, it refers to the measuring procedure rather than to the attribute being measured
Symptoms	Subjective observation by patients
Signs	Subjective observation by examiners
Tests	Objective observations
Inter-observer Variation	Degree of agreement among different examiner
Intra-observer Variation	Degree of agreement between different examinations made by one examiner

Diagnostic criteria can be examined in terms of 4 parameters(sensitivity, specificity, positive predictive value, negative predictive value)

Table 3. Diagnostic criteria:

	Actual Disease status		
Test Results	+ve	-ve	Total
+ve	a	B	a+b
-ve	c	D	c+d
Total	a+c	b+d	a+b+c+d
Parameters		**Definitions**	
Sensitivity		Refers to the probability that the test result is positive, sensitivity=a/(a+c)	
Specificity		Refers to the probability that the test result is negative,specificity=d/(c+d)	
Positive Predictive Value		Refers to the probability that the people who suffer the disease tested will have +ve test result, positive predictive value=a/(a+b)	
Negative Predictive Value		Refers to the probability that the actual disease state is negative, given that the test result is negative, negative predictive value=d/(c+d)	
Prevalence		What proportion of population has the disease in question at specific point of time, prevalence is the total no. of individuals who have a characteristic or disease at a particular point in time divided by the no. who are at risk of having that characteristic or disease at that designated point in time, prevalence depends on both the no. of people who have had the disease or characteristic in the past and the duration of the disease or characteristic,	
Incidence		It describe the frequency of new cases during a time period, incidence is the no. of new cases of a disease in a defined population within a specific time period devided by no. who are at risk of having that disease or characteristic at that designated time-period	

$P=N_d/N_t$, N_d = Nos. of individuals having the ds.at a specific time, N_t=Nos. of individuals in the population at that point in time

3.1 Interrelation among the 3 measures:
P/(1-P)=I*D(I=Incidence, D=Duration of the disease) CI=$1-e^{(-I*t)}$

Table 4. Risks in epidemiology:
RR=[a/(a+b)]/[c/(c+d)], Odds Ratio=ad/bc

		Definitions	
Attributable risk		It is the difference between the incidence of disease in exposed group(Ie) and incidence of disease in unexposed group(Io), AR=Ie-Io	
Relative risk		It indicates the average risk of disease that is due to a given exposure in the exposed group, RR=Ie/Io	
	Disease	**No disease**	
Exposure	a	b	a + b
No exposure	c	d	c + d
	a + c	b + d	a+ b+c+d

IV. Prevalence of cervical cancer

Global scenario of cervical cancer in 2008: Out of 12.7 million new cancer cases, 4.2% are cervical cancer cases. Corresponding cumulative risk is 1.6%, age-standardised incidence rate is 15.2/100,000 person-years (2)
Global Prevalence of cervical cancer: 84% of cervical cancer occurs in less developed countries.
Top 5 countries with highest incidence of cervical cancer are Malawe (75.9/100,000), Mozambique (65.0/100,000), Comoros (61.3/100,000), Zambia (58.0/100,000), Zimbabwe(56.4/100,000).
Global cervical cancer burden: In 2004, cervical cancer was the 5th most common cause of cancer death among women in globally & had 489,000 new cases. In 2002, age-standardised incidence rate of cancer cervix was 16/100,000 women and 268,000 deaths occurred due to cancer cervix .(3)
Indian cervical cancer burden: In 2004, cervical cancer was the 3rd largest cause of cancer mortality in India.In 2002, age-standardised incidence rate of cancer cervix is 30.7/100,000.(4)
Cervical cancer scenario in India: In Bangalore, incidence of CC was 27.2 in 1991, 18.2 in 2001, 17 in 2005(all datas were measured per 100,000 women). In Delhi, incidence was 19.1 new cases/100,000 women in 1998, 18.9 new cases/100,000 women in 2005. In Mumbai, incidence was 12.7 new cases/100,000 women in 2005. In Chennai, incidence was 33.4 cases/100,000 women in 1991, 22 cases/100,000 women in 2005(5)

Table 5:Magnitude of cervical cancer in India in 2009:(6)

Places in India	**Relative incidence of cervical cancer as a proportion of all cancer**	**Crude Rate(CR)(measured/100,000 women**	**Age-Adjusted Incidence Rate(AAR)(measured/100,000 women)**
Silchar	20.6%	10.6	12.1
Ahmedabad	18.6%	6.9	7.9
Chennai	18.5%	20.3	22.3
Bhopal	17.9%	12.0	17.7
Bangalore	15.7%	14.3	18.8
Kolkata	15.7%	13.2	12.3
Delhi	14.9%	12.3	17.4
Mumbai	13.2%	11.5	13.4

V. Age-specific Incidence Rate

In a study conducted in eastern India by Kolkata Cancer Registry showed that 982 cervical cancer cases were present among 5607 cancer cases. Age specific Incidence rate was as follows(7)

Table 6: Age-specific Incidence Rate:

Age(in years)	**0-14**	**15-24**	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75+**	**Crude Incidence Rate(/100,000 women)**	**Age-standardised Incidence Rate(/100,000 women)**
Age-specific Incidence Rate(/100,000 women)	**0.1**	**0.3**	**4.1**	**28.3**	**58.9**	**63.5**	**67.4**	**44.9**	**16.7**	**19.9**

VI. Mortality due to cervical cancer

Global scenario in 2008: Age-specific mortality due to cancer cervix is 7.8/100,000 person-years. In 2008, 274,000 women died due to cancer cervix which is 3.6% of 7.6 million cancer deaths globally.
Indian scenario in 2008: Mortality rate due to cancer cervix is 15.2/100,000 women.(8)

VII. Risk factors for cervical cancer

HPV infection, multiple sexual partners, promiscuous partners, early sexual intercourse, early child bearing(young age at first full-term pregnancy), multiple full-term pregnancy, using birth control pill for long time, cigarette smoking, less age of marriage, poor genital hygiene, reproductive tract infection, heavy bleeding during menstruation , less use of condom, smoking, immunosuppression, chlamydia infection, fatty food, less use of antioxidant-rich food, oral contraceptive pills, use of intrauterine contraceptive device, poverty, diethylstilbestrol, family history of cervical cancer (9)

VIII. Molecular risk factors of cervical cancer

Table 7: Molecular risk factor for cervical cancer :

Molecular Risk Factors	Role in Cervical Cancer
1) Cytokines'(monokine, growth factors) interleukin, chemokine, lymphokine) dysregulation(10)	Used as biomarker for early diagnosis
2) Toll-like receptors'(TLR-2,3,4,9), IL-1α,1β & TNF-α polymorphism(11)	act as genetic risk factor for cervical cancer
3) p-16/Ki-67 +ve cells(12)	Its morphological evaluation may have some benefits in women younger than 30 yrs. Or with L-SIL(low-grade squamous intraepithelial lesion)
4) Trichomonas,Candida,Gardnerella infection(13)	Responsible for 90% of vaginitis and repeated inflammation can lead to cervical cancer
5) miR-124-rs-531564 polymorphism(14)	It plays a role in cancer cervix susceptibility in Chinese Han women & G allele is associated with a decreased risk of cervical cancer
6) Anal Intraepithelial Neoplasia(AIN) among HIV+ve men(15)	This population serve as an important bridge population to women with implications for HPV infection in both men & women
7) HPV-18-E6 oncoprotein(16)	E6 is able to bind & induce mislocalisation of Par-3 protein in PDZ-dependent manner without significant reduction in Par-3 protein levels
8) High-risk(HR) HPV-E5,E6,E7 oncoproteins(17)	These molecules are host genes and/or proteins, cellular microRNAs involved in cell cycle regulation that result from disturbed expression of HR-HPV E5,E6,E7 oncoproteins
9) Trichomonas Vaginalis infection(18)	It is associated with both LR & HR-HPV infection of cervix as well as ASC-US(Atypical Squamous Cell of Undetermined significance) & H-SIL(High-grade squamous Intraepithelial lesion)
10) Non-oncogenic HPV genotypes,TP-53 & MPM-2 genes' polymorphisms in HIV-infected women(19)	HIV-infected women are more susceptible to be infected by low-risk HPV(LR-HPV) genotypes than by high-risk(HR-HPV)
11) C13 or f18 & C1 or f166(MULAN) DNA genes methylation(20)	They are not associated with cervical cancer & precancerous lesions of HPV genotypes in Iranian women
12) Kruppel-like factor(KLF)-5(21)	KLF-5 mRNA overexpression could represent a potential molecular marker for cervical cancer
13) SNP(Single Nucleotide polymorphism)(22)	3 SNPs e.g.rs1112085, rs11102637, rs12030900 in the MAGI-3 gene & 1 SNP(rs-8031627) in the SMAD-3 gene are associated with HR-HPV clearance
14) Viral & Cellular biomarkers(23)	E6 & E7 genes of high risk HPVs bind to and inactivate p53 & pRB oncosuppressors respectively. tumor progression is charecterised by integration of viral DNA into host genome, with disruption of E2 viral genes & host chromosomal loci
15) Reactive Oxygen Species(ROS) & Reactive Nitrogen Species(RNS)(24)	They are generated from inflammatory and epithelial cells, results in oxidative & nitrative DNA damage by 8-oxo-7,8-dihydro-2'-deoxyguanosine(8-oxo dG) and 8-nitroguanine respectively
16) Cervical and Anal HPV infection in women with cervical Intraepithelial Neoplasia(25)	Any frequency and any type of contact with the anus were shown as the most important risk factor for concurrent HPV infection
17) A SNP on 308 position of the promoter region of TNFA gene(26)	308 TNFA AA individuals are at increased risk of invasive cervical cancer development
18) Persistent expression of HPV viral oncoproteins(27)	Expression level of a panel of 4 genes-TOP2A,CTNNB1,PFKM,GSN are able to distinguish between normal tissue and cervical cancer
19) HLA-DRB1 class-2 antigen levelled alleles(28)	Allele frequency of HLA-DRB1*14 was particularly reduced in patientswith cancer when compared with the HPV-persistent group suggesting that this allele is a possible protective factor for the development of cervical cancer
20) Identification of HPV-DNA(GP5+/GP6+,MY09/MY11 and pU1M/2R primers in cervical and urine samples(29)	HPV DNA detection by PCR was positively associated with abnormal cytological findings(ASCUS/SIL-Atypical squamous cells of undetermined significance/Squamous Intraepithelial lesions)

IX. Causes of cervical cancer

9.1. HPV infection: Usually cells infected with the HPV heal on their own.In some cases virus continues to spread and becomes an invasive cancer.HPV type-16,18 are the cause of 75% of cervical cancer globally where 31 and 45 are the cause of another 10%.Of the 150-200 types of HPV known,15 are classified as high-risk types (16,18,31,33,35 ,39,45,51,52,56,58,59,68,73 and 82),3 as probable high –risk(26,53,66) and 12 as low-risk(6,11,40,42,43,44,54,61,70,72,81,CP6108).

9.2. Smoking: Smoking has also been linked to the development of cervical cancer. There are a few different ways that smoking can increase the risk of cervical cancer in women. There are direct and indirect methods of inducing cervical cancer. A female smoker has a higher chance of getting CIN-3. CIN-3 has the potential of forming cervical cancer. Heavy smoking and long term smoking seem to have more of a risk of getting the CIN3 lesions than lighter smoking or not smoking at all. Although smoking has been linked to cervical cancer, it aids in the development of HPV which is the leading cause of this type of cancer.

X. Aetiopathogenesis of cervical cancer

Cause of cervical cancer is associated with sexual activity, HPV infection, venerally transmitted carcinogens. HPVs fall into 2 broad camps- low-risk types, associated with cervical condylomas and CIN-1,high-risk types (mostly 16,18) found in 50-80% of CIN-2,CIN-3 lesions & 90% of cancers. 2 major viral oncogenes,E6 and E7, directly coupled to viral enhancers and promoters, allowing their continued expression after integration. High-risk HPV-E7 proteins bind and inactivate the Rb, whereas E6 proteins bind p53 and direct its rapid degeneration. A range of purgative cofactors has been implicated in progression: HLA type, immunosuppression,sex steroid hormones and smoking.

XI. Signs And Symptoms

Early stages of cervical cancer are free of symptoms. Indicators of presence of malignancy are vaginal bleeding,contact bleeding,vaginal mass etc.Symptoms of advanced cervical cancer are loss of appetite,weight loss,fatigue,pelvic pain,leg pain,swollen legs,heavy bleeding from vagina,bone fractures,leakage of urine or feces from vagina etc.

XII. Clinical Staging

Cervical cancer is staged by the International Federation of Gynecology and Obstetrics (FIGO) staging system,which is based on clinical examination, rather than surgical findings. It allows only the following diagnostic tests to be used in determining the stage: inspection, palpation, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, and X-ray examination of the lungs and skeleton, and cervical conisation.

12.1. Preinvasive carcinoma: Stage-0 means carcinoma-in situ or intraepithelial cancer(cases of stage 0 should not be included in any therapeutic statistics).

12.2. Invasive carcinoma: Stage-1 means carcinoma strictly confined to the cervix(extension to the corpus should be disregarded). Stage-2 means carcinoma extends beyond the cervix but has not extended to the pelvic wall. Stage-3 means carcinoma has extended to the pelvic wall. Stage-4 means carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum.

XIII. Diagnosis

The pap smear can be used as a screening test, but is false negative in up to 50% of cases of cervical cancer.Confirmation of the diagnosis of cervical cancer or pre-cancer requires a biopsy of the cervix. This is done through colposcopy, a magnified visual inspection of the cervix aided by using a dilute acetic acid (e.g. vinegar) solution to highlight abnormal cells on the surface of the cervix. Medical devices used for biopsy of the cervix include punch forceps, SpiraBrush CX, SoftBiopsy or Soft-ECC.

Often before the biopsy, the doctor asks for medical imaging to rule out other causes of woman's symptoms. Imaging modalities including ultrasound, CT scan and MRI have been used to different extent in order to look for alternating disease/spread of tumor/effect on adjacent structures. Typically they appear as heterogeneous mass in the cervix.

XIV. Precancerous Lesions

Histopathologic image (H and E stain) of carcinoma in situ (also called CIN III), stage 0. The normal architecture of stratified squamous epithelium pathologist. For premalignant dysplastic changes, the CIN (cervical intraepithelial neoplasia) grading is used.

The naming and histologic classification of cervical carcinoma precursor lesions has changed many times over the 20th century. The World Health Organization classification system has given description of the lesions, e.g. mild, moderate or severe dysplasia or carcinoma in situ (CIS). The term, Cervical Intraepithelial Neoplasia (CIN) was developed to cover the spectrum of abnormality in these lesions, and to help standardise treatment.It classifies mild dysplasia as CIN1, moderate dysplasia as CIN2, and severe dysplasia and CIS as CIN3. More recently, CIN2 and CIN3 have been combined into CIN2/3. These results are what a pathologist might report from a biopsy.

XV. Cancer Subtypes

Histologic subtypes of invasive cervical carcinoma include the following: Though squamous cell carcinoma is the cervical cancer with the most incidences, the incidence of adenocarcinoma of the cervix has been increasing in recent decades. Different histological types are squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, small cell carcinoma, neuroendocrine tumour, glassy cell carcinoma, villoglandular adenocarcinoma etc. Non-carcinoma malignancies which can rarely occur in the cervix includes melanoma, lymphoma etc.

XVI. Prevention

There are many preventive measures for cervical cancer as follows.

16.1 Screening: Checking the cervix by the Papanicolaou test, or Pap smear, for cervical cancer has been successful with dramatically reducing the number of cases of and mortality from cervical cancer in developed countries.Pap smear screening every 3–5 years with appropriate follow-up can reduce cervical cancer incidence. Abnormal results may suggest the presence of pre-cancerous changes allowing examination and possible preventive treatment. If precancerous disease or cervical cancer is detected early, it can be monitored or treated relatively noninvasively, with little impairment of fertility.Personal invitations encouraging women to get screened are effective. Educational materials increase the likelihood women will go for screening, but they are not as effective as invitations.

According to the 2010 European guidelines, the age at which to start screening ranges between 20–30 years of age, "but preferentially not before age 25 or 30 years", and depends on burden of the disease in the population and the available resources

In the United States it is recommended that screening begin at age 21, regardless of age at which a women began having sex or other risk factors. Pap tests should be done every three years between the ages of 21 and 65. In women over the age of 65, screening may be discontinued if there was no abnormal screening results within the previous 10 years and no history of CIN 2 or higher.HPV vaccination status does not change screening rates. Screening can occur every 5 years between aged 30–65 when a combination of cervical cytology screening and HPV testing is used and this is prefered. However, it is acceptable to screen this age group with a Pap smear alone every 3 years.

Liquid-based cytology is another potential screening method. Although it was probably intended to improve on the accuracy of the Pap test, its main advantage has been to reduce the number of inadequate smears from around 9% to around 1%.

16.2.Vaccination: There are two HPV vaccines (Gardasil and Cervarix) which reduce the risk of cancerous or precancerous changes of the cervix and perineum by about 93% and 62%, respectively.
HPV vaccines are typically given to women age 9 to 26 as the vaccine is only effective if given before infection occurs. The vaccines have been shown to be effective for at least 4 to 6 years, and it is believed they will be effective for longer.

16.3. Condoms: Condoms are thought to offer some protection against cervical cancer. Evidence on whether condoms protect against HPV infection is mixed, but they may protect against genital warts and the precursors to cervical cancer. They also provide protection against other STDs, such as HIV and Chlamydia, which are associated with greater risks of developing cervical cancer.

16.4. Nutrition: Vitamin A , vitamin B12, vitamin C, vitamin E and beta-carotene are associated with a lower risk.

Parameters to be checked to compare Rural & Urban population for clinicoepidemiology of cervical cancer:(30)

1)Occupation, 2) Age, 3) Marital status, 4) Monthly Income, 5) Age of 1st sexual intercourse, 6) Nos. of children, 7) Nos. of abortion, 8) Use of contraceptive measure, 9) Smoking habit, 10) Family h/o cancer, white discharge, 11) Educational Qualification,12) awareness about HPV vaccine, cause,s ign, symptom, prevention, pap test, 13) personal hygiene, 14) Location of residence, 15) status of pregnancy, 16) Time of 1st delivery after marriage, 17) presence /absence of symptoms,18) Pap smear results, 19) Attitudes & beliefs about cervical cancer & Pap test

References

[1]. "Importance of epidemiology to Public Health",gwxy.sysu.edu.cn>Home>Epidemiological Knowledge
[2]. Jacques Ferlay,Hai-Rim Shin,Freddie Bray,David Forman,Colin Mathers,Donald Maxwell Parkin,"Estimates of worldwide Burden of cancer in 2008:GLOBOCAN 2008",International Journal of cancer,Volume-127,Issue-12,pages-2893-2917,15 December-2010,Following a),b),c) are the references of the above article
[3]. Global -2008-reference-Parkin DM-The evolution of the population –based cancer registry-Nat Rev. CA-2006;6;203-12

[4]. WHO-National cancer control programmes-Policies & Managerial guidelines,2nd edition-Geneva-WHO-2002
[5]. Parkin DM,St. jernward J,Muir CS,Estimated of the worldwide frequency of 16 major cancers in 1980,Int. Journal of CA-1988-41;184-97
[6]. Ambika Satiza,"South Asia Centre for Chronic Disease","Cervical Cancer in India",source:WHO,Comprehensive Cervical Cancer Control:a guide to essential practice,Geneva,WHO,2006,Available at http://www.who.int/reproductive health/publications/cancer/9241547006/en/index.html,last accessed November 18,2009
[7]. Imran Ali,Washim A. Wani & Kishwar Saleem,Research Article-"Cancer Scenario In India with Future Perspectives",correspondence: Imran Ali,Dept. of Chemistry,Jamia Milia Islamia Central University,New Delhi-110025,INDIA,available at- www.cancer-therapy.org/CT/v8/A/HTML/9.Ali_et_al, 56-70.htm
[8]. Dr. A Nandakumar,T. Ramnath & Meesha Chaturvedi,"The Magnitude of cancer cervix in India", Indian J Med Res 130,September 2009,pp-219-221,available at :icmr.nic.in/…cancer…/Preliminary_pages_Bhopal_MIC_Report.pdf,Dr. A Nandakumar is Officer-in-charge,National cancer Registry programme(Indian Council of Medical Research),577,7th main,New,B.E.L.Road,Dollars Colony,Bangalore,560094,India,email: ank@ blq.vsnl.net.in
[9]. Jacques Ferlay,Hai-Rim Shin,Freddie Bray,David Forman,Colin Mathers,Donald Maxwell Parkin,"Estimates of worldwide Burden of cancer in 2008:GLOBOCAN 2008",International Journal of cancer,Volume-127,Issue-12,pages-2893-2917,15 December-2010
[10]. Cancer's Global Footprint/Interractive map of cancer,available at global cancermap.com
[11]. American Cancer Society-www.cancer.org/cancer/cervical cancer/detailed guide/cervical cancer risk factors
[12]. Paradkar PH,Joshi JV,Mertia PN,Aquashe SV,Vaidya RA,"Role of Cytokines in genesis,progression & prognosis of cervical cancer",Asian Pac J cancer Prev. 2014;15(9);3851-64,PMID-24935564
[13]. Zidi S,Verdi H,Yilmaz-Yalcin Y,Yazici AC,Gazouani E,Mezlini A,Atac FB,Yacoubi,Loneslatib,"Impact of Toll-Like Receptors 2/3/4/9,IL-1-α/β & TNF-α Polymorphisms in Cancer Susceptibility in Tunisia:Genetic Polymorphisms implicated in the occurance of Cervical Cancer", Pathol Oncol Res.-2014 May 17,PMID-24839201
[14]. Ordi J,Saqasta A,Munmany M,Rodriquez-Carunchio L,Torne A,del Pino M,"Usefulness of p16/Ki67 immunostaining in the triage of women referred to colposcopy",Cancer Cytopathol;2014 Mar,122(3):227-35,PMID-24757722
[15]. Kalantari N,Ghaffari S,Bayani M,"Trichomonas,Candida & Gardnerella in cervical smears of Iranian women for cancer Screening", Aur J Med Sci 2014 Jan;6(1):25-9,doi: 10.4103/1947-2714.125861,PMID-24678473
[16]. Xiong X,Cheng J,Liu X,Tang S,Luo X,"Correlation analysis between miR-124,rs-531564 polymorphisms & susceptibility to Cervical cancer", Nan Fang Yi Ke Da Xue Xue Bao.2014 Feb;34(2):210-3,PMID-24589598
[17]. Melo VH,Guimaraes MD,Rocha GM,Araujo AC,Carmo RA,Grinsztejn B,Pilotto JH,Palefsky JM,"Prevalence & risk factors associated with anal intraepithelial neoplasia among HIV+ve men in Brazil", Low Genit Tract Dis.2014 Apr;18(2):128-35.doi:10.1097/LGT.Ob0113e31829ee855,PMID-24556612
[18]. Facciuto F,Bugnon Valdano M,Marziali F,Massimi P,Banks L,Cavatorter AL,Gardiol D,"Human papillomavirus(HPV-18) E6 protein interferes with the epithelial cell polarity Par3 protein" Mol Oncol.2014 May;8(3):533-43.doi:10.1016/j.molonc 2014.01.002.EPub 2014 Jan14,PMID-24462519
[19]. de Freitas AC,Coimbra EC,Leitao Mda C,"Molecular targets of HPV oncoproteins:potential biomarkers for cervical carcinogenesis", Biochim Biophys Acta 2014 Apr;1845(2):91-103.doi:10-1016/j.bbcan 2013.12.004,EPub-2014 Jan 2,PMID-24388872
[20]. Donders GG,Depuydt CE,Bogers JP,Vereecken AJ,"Association of Trichomonas Vaginalis & Cytological abnormalities of the cervix in low risk women",PLos One.2013 Dec 30;8(12):e86266,doi:10.1371/journal.pone.0086266.eCollection 2013.PMID-24386492
[21]. Entiauspe LG,Seixas FK,Nunes EM,Rodriques FM,Dellaqostin OA,Collares T,da Silveira MF,"Uncommon non-oncogenic HPV genotypes,TP53 & MPM-2 genes polymorphisms in HIV-infected women Southern Brazil",Brazil Journal of Infectious Disease-2014,Aug 30,pii:S1413-8670(14)00170-6,doi:10.1016/j.bjid.2014.07.005,PMID-25181402
[22]. Sohrabi A,Mirab Samiee S,Rahnamaye Farzami M,Rafizadeh M,Akhavan S,Hashemi-Bahremani M, Modarresi MH,"C13 or f18 & C1 or f166 (MULAN) DNA genes methylation are not associated with cervical cancer & Precancerous lesions of HPV genotypes in Iranian women",Asian Pacific Journal of cancer Preview 2014;15(16):6745-8,PMID-25169519
[23]. Marrero-Rodriquez D,Taniquchi-Ponciano K,Jimenez-Vega F,Romeo –Morelos P,Mendoza-Rodriquez M,Mantilla A,Rodriquez-Esquivel M,Hernandez D,Hernandez A,Gomez-Gutierrez G,Munoz-Hernandez N,Ia Cruz HA,Varqus-Requena C,Diaz-Hernandez C,Serna-Reyna L,Meraz-Rios M,Bandala C,Ortiz-Leon J,Salcedo M,"Kruppel-like factor 5 as potential molecular marker in cervical cancer & the KLF family profile expression",Tumor Biology 2014 August 15,PMID-25119587
[24]. Sudenza SL,Wiener HW,King CC,Rompalo AM,Cu-Uvin S,Klein RS,Shah KV,Sobel JD,Jamieson DJ,Shrestha S,"Dense genotyping of immune-related loci identifies variants associated with clearance of HPV among HIV+ve women in the HIV epidemiology research study(HERS)",PLoS One,2014 Jun 11;9(6):e99109.doi:10.1371/journal.pone.0099109.eCollection 2014,PMID-24918582
[25]. Tornesello ML,Beronaquro L,Giorgi-Rossi P,Buonaquro FM,"Viral & Cellular biomarkers in the diagnosis of cervical intraepithelial neoplasia & cancer",Biomed Res Int 2013;2013:519619.doi:10.1155/2013/519619.Epub 2013 Dec 9,PMID-24383054
[26]. Ohnishi S,Ma N,Thanan R,Pinlaor S, Hammam O,Murata M,Kawanishi S,"DNA damage in inflammation-related carcinogenesis & cancer stem cells",Oxid Med Cell Longev.2013;2013:387014.doi:10.1155/2013/387014.Epub 2013 Dec 5,PMID-24382987
[27]. Sehnal B,Dusek L,Cibula D,Zima T,Halaska M,Driak D,Slama J,"The Relationship between the cervical & anal HPV infection in women with cervical intraepithelial neoplasia",J clin virol.2014 Jan;59(1):18-23.doi:10.1016/j.jcv.2013.11.004.Epub 2013 Nov 23,PMID-24315797
[28]. Sousa H,Oliveira S,Santos AM,Catarino R,Moutinho J,Medeiros R,"TNF-α-308 G/A is a risk marker for the progression from highgrade lesions to invasive cervical cancer",Tumour Biol.2014 Mar;35(3):2561-4.doi:10.1007/s13277-013-1337-3.Epub 2013 Nov.7,PMID-24197984
[29]. Mattarocci S,Abbruzzese C,Mivo AM,Carosi M,Pescarmona E,Vico C,Federico A,Vizza E,Corrado G,Arisi I,Felsani A,Paggi MG,"Identification of pivotal cellular factors involved in HPV-induced dysplastic & neoplastic cervical pathologies",J cell physiol.2014 April;229(4):463-70.MG.doi:10.1002/jcp.24465,PMID-24105779
[30]. Bernal silver S,Granados J,Gerodezky C,Alaez C,Flores-Aquilar H,Cerda-Flores RM,Guerrero-Gonzalez G,Valdez-Chapa LD,Morales-Casas J,Gonzalez-Guerrero JF,Barrera-Saklana HIA,"HLA-DRB1 class 2 antigen level alleles are associated with persistent HPV infection in Mexican women;a pilot study",Infect. Agent Cancer.2013 Aug 30;8(1):31.doi 10.1186/1750-9378-8-31,PMID-24000898

[31]. Munoz M,Camargo M, Soto-De Leon SC,Sanehez R,Pineda Pena AC,Perez-Prados A,Patarroyo ME,Patarroyo MA,"Classical Molecular Tests using urine Samples as a potential screening tool for HPV detection in HIV-infected women",J clin Microbiol 2013 Nov;51(11):3688-93.doi:10.1128/JCM.01302-13.Epub 2013 Aug 28,PMID-23985908

[32]. Sreejata Raychaudhuri,Sukanta Mandal,"Socio-Demographic & Behavioural Risk Factors for Cervical Cancer & Knowledge,attitude & Practice in Rural & Urban Areas of North Bengal,India", http://dx.doi.org/10.7314/APJCP.2012.13.4.1093,Asian Pacific J cancer Prev,10,231-234,mariyaamin@aims.amrita.edu,Sheikhzahooahmed@aims.amrita.edu

[33]. Brita Roy,MS,Tricia S Tang,Ph.D,"Cervical Cancer Screening in Kolkata,India:Beliefs & Predictors of Cervical Cancer Among women attending a women's health clinic in Kolkata,India",Jan Yasmeen,Mariya Amin Qurieshi,Najmi Arshad Manzoor,Wali Asiya,Sheikh Zahoor Ahmad,"Community-based screening of Cervical in a Low Prevalence Area of India:A Cross Sectional Study", Journal of Cancer Education,23:253-259,2008,copyright AACE & EACE,ISSN:-0885-8195 print/1543-0154 online,DOI:10.1080/08858190802189105