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Cervical Cancer And Its Primary Screening In China, India And Nepal

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Abstract:
Cervical cancer the preventive cancer which is the most common cancers among women in developing countries, it lies as the fourth most common killer of women worldwide. As in developed country systemic screening programs have reduced the morbidity and mortality but it still stays challenging in developing countries especially in rural areas where the resources are not adequate to screen maximum women who are at high risk. This study is to understand the prevalence of cervical cancer and human papillomavirus (HPV) in china, India and Nepal and policies for the screening focused for the women of rural settings where resources are difficult to provide. Invasive cervical cancer (ICC) remains an important health problem in all those countries. However, the major burden is observed in rural settings. National screening policy had been made in all those countries but the implementation of nationwide programs for cervical cancer screening still doesn't exist and majority of women have never been screened. However, governmental and non-governmental organizations have been collaborating to establish demonstration centers in both high and low – resource settings to provide screening and obtain geographic specific data. Till now no any HPV vaccines programs for the prevention of HPV have been licensed as it infections accounts for more than 80% in cancers in China, India and Nepal. In this review we also focus on the assessment of simpler screening methods and it is believed that creativity, flexibility and well-focused use of resources can reduce the inequitable burden of cervical cancer in poor settings.

Keywords: Cervical cancer, screening, morbidity, mortality, HPV

Introduction:

Cervical cancer refers to a class of disease in which a cell or group of cells divide and replicate uncontrollably and intrude into adjacent cells and tissue and ultimately spread to other parts of the body that the location at which they arose. Before turn into cancer it first gradually develops pre-cancerous changes then turn into cancer that is describes as CIN (cervical intraepithelial neoplasia), SIL (squamous intraepithelial lesion) and dysplasia [1].

As cervical cancer the fourth most common cancers among women and the only gynecological cancer that can be early detected and having maximum chances of cure but still 7.5% of all cancer death is due to cervical cancer. 87% death occurs in the less developed region of the WHO estimated 528000 new cases in 2012 with death of 266000 from cervical cancer among which Asia Pacific region accounts for more than half of the world's burden and hope to reach 62% by the year 2025 [2, 3].

Cancer of cervix actually develops in women aged 35-49 years [4] with the peak age for incidence varying with population, although it can develop in women of all ages who are at the risk as persistent infection of cervix with Human Papillomavirus (HPV), high parity, multiple sexual partners, young age of first sexual intercourse, low socio-economic status, history of smoking and long term use of contraceptives pills [5]. Among all the risk factors HPV alone appears to be involved in more than 90% of cases for invasive cervical cancer world with in which HPV16 and 18

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have the highest prevalence (>70%), Many people who have had HPV infections however do not develop cancer of cervix [6, 7]. Asia pacific region contains more than half of the world population and manifests wide geographic diversity in prevalence of infection with HPV and of incidence rate of cervical cancer [8].

As cervical cancer has a long preinvasive state and screening is available so it can be detected before cancerous changes and treated for the detected preinvasive lesion, and we can reduce the incidence of morbidity and mortality from cervical cancer. It has been well known that most of the developed countries with well-organized screening by cytology have substantially reduced the incidence of morbidity and mortality from cancer of cervix [9].

Screening:

The procedure of testing for any precancerous or cancerous changes is known as screening. For the screening of cervical cancer conventional cytology, liquid based monolayer cytology, HPV testing, visual inspection.

Visual inspection to detect pre-cancer or cancer:

It is the procedure in which acetic acid (white vinegar) VIA or lugol's iodine VILI is used to highlight precancerous lesion, which can be viewed with the naked eye and shifts the identification of precancerous changes from laboratory to the clinic. It is the procedure, which eliminates laboratories evaluation and transport of specimens, it require very little equipment and provide with immediate test results and further plan of treatment if abnormalities found. To perform visual inspection effectively need to arrange medical professional-doctors, nurses or professional midwives with adequate training and supervision.

VIA as screening test with trained physician and mid-level providers may perform as or better than cervical cytology in accurately identifying precancerous lesion (45% and 79% of women at high risk of developing cervical cancer) [10, 11]. VIA can offer significant advantages over Pap smear in low-resource setting, particularly in terms of increased screening coverage, improved follow-ups care and overall program quality due to the need of fewer specialized personnel and less infrastructure, training and equipment, with VIA public health system can offer cervical cancer screening in more remote health care settings and can achieve higher coverage and VIA with cryotherapy is a relatively simple and inexpensive method of treating lesion of cervix that can be performed by primary care physician and mid-level providers [12].

As in several cross-sectional studies VIA compared with cytology shows that VIA has low specificity and a high rate of false negative such as inflammation, cervical condyloma and leukopastia which can give false positive results of VIA test and it is ineffective in detecting lesions located in the cervical canal of uterus [13-16].

In few other studies reported sensitivity of VIA for CIN II+ vary from 41.4% to 80% and specificity 49% to 92%. Table 1

Author, year of publication	Sensitivity (95% CI)	Specificity (95% CI)
JHPIEGO, 1999 [17]	76.7% (70.3-82.3)	64.1% (61.0-66.2)
Denny et al, 2000 [18]	67% (56-77)	84% (82-85)
Belinson et al, 2001 [19]	71% (60-80)	74% (71-76)
Denny et al, 2002 [20]	70% (59-79)	79% (77-81)
Cronje et al, 2003 [21]	79% (69-87)	49% (45-52)
Sankaranarayanan et al, 2004 [22]	76.8% (74.2-79.4)	85.5% (85.2-85.8)
Vuyst et al, 2005 [23]	73.3% (61.8-84.9)	80% (76.6-83.4)
Arbyn M et al, 2008 [24]	79% (73-85)	85% (81-89)
Sauvaget et al, 2011 [25]	80% (79-82)	92% (91-92)
Qiao et al, 2015 [26]	73.2% (66.5-80.0)	86.7% (82.9-90.4)
Mustafa et al, 2015 [27]	69% (54-81)	87% (79-92)

As VIA provides the immediate results and allowing diagnostic investigation and treatment at the same screening appointment it has the major advantages on other screenings however the low specificity of these tests means that a large number of women will undergo investigation, although most of them could be negative for neoplasia or may not have any significant lesion.

VIAM: It is the investigation of acetowhite changes after applying acid under low-level magnification(2-4X). magnification might increase the sensitivity of acetowhite lesions located close to SCJ by magnification but the accuracy of both VIA and VIAM are nearly same [28].

VILI: visual inspection using lugol's iodine solution that stains glycogen stored in cervical epithelial cells which is seen as mustard-yellow. Among the ACCP studies of 10 cross-sectional studies involving 49,080 women were evaluated for the accuracy of VILI where sensitivity vary from 77.8-98.0% and specificity 73.0-91.3% [22]. This data indicated that VILI also have nearly similar sensitive test than VIA.

One of the most important concerns in assuring good-quality screening with VIA or VILI is adequate preparation of the examiners [29].

Conventional cytology/Pap test:

Dr. Papanicolaus in 1933 discovered that cells in the cervix change in appearance before they become cancerous and Pap smear was named after him. It is a simple procedure in which cells are collected from cervix and placed in to slide

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and sent to laboratory for any unusual changes, which might be cancer. In some studies the accuracy of conventional reported 72% sensitivity and 94% specificity [30]. In three meta-analysis of the accuracy of cervical cytology, the sensitivity of test in detecting CIN 2-3 range from 47-60% and specificity ranged from 60-95% [31-33]. A study published in 2007 suggested that the act of performing a Pap smear produces an inflammatory cytokine response, which may initiate immunological clearance of HPV, and reducing the risk of cervical cancer [34]. For more information on Pap test accuracy for cervical intra-epithelial neoplasia CIN II+ lesions are mentioned in table 2 where the sensitivity lies between 44%-78% and specificity 91%-99%.

Author, year of publication	Sensitivity (95% CI)	Specificity (95% CI)
University of Zimbabwe, 1999 [17]	44% (37-51%)	91% (89-92%)
Denny et al 2000 [35]	78% (67-87%)	95% (94-96%)
Wright et al 2000 [36]	61% (46-74%)	96% (94-97%)
Denny et al 2002 [20]	57% (46-67%)	96% (95-97%)
Cronje et al 2003 [21]	48% (38-60%)	96% (94-97%)
Sankaranarayanan et al 2004 [37]	61% (56-66%)	95% (94-95%)
Coste J et al 2003 [38]	51% (36-67%)	99% (99-100%)
Naucler et al 2009 [39]	71.3% (60.6-80.5%)	98.6% (98.3-98.9)
Ronco et al 2006 [40]	74% (62.4-83.6%)	94.8% (94.4-95.0%)

In developing countries conventional cytological screening programs have been introduced but due to suboptimal performance of cytology, lack of quality control and inefficiency of system for follow ups and treating screen positive women conventional cytological screening programs have been ineffective in reducing disease burden [41-43].

Liquid based cytology: it is the way of preparing cervical sample for examination in the laboratory like pap-smear using spatula which brushes cells from the transformation zone of the cervix then spatula where the cells are lodged is broken off into the glass vial containing preservative fluid or rinsed into the preservative fluid (ethanol for Sure-path and methanol for thin preparation). In the laboratory it is spun and treated to remove obscuring material and representative sample of the remaining cells is taken and a thin layer of cells are deposited onto a slide and is examined by cytologist. The advantages of LBC's are complete transfer of representative cells to the slide and improves readability in microscope and eliminates the errors or problems as poor fixation, air-drying artifacts, uneven thickness of the cellular spread, debris from blood and others inflammatory cells and overlapping of cells and it is also suitable for additional testing procedures as HPV testing. The accuracy of LBC has 61-66% sensitivity and 82-91% specificity [30, 44]. As in some published reviews indicates that LBC improves sample adequacy and is probably more sensitive but less specificity than Pap smear in detecting cervical neoplasia [32, 45, 46]. LBC is not feasible to implement in low-resource setting as it is more expensive and requires additional instrumentation to prepare the smear [46].

Human Papillomavirus testing: it is a test for which samples are collected as a liquid based cytology and sent to the laboratory where it is been examined for the HPV genes. Due to the effect of HPV on DNA it is more likely to develop cervical intraepithelial neoplasia with prolonged infection with high risk types of HPV (16, 18, 31 and 45) [47, 48]. Among which 71% of total world burden can be attributed to infection with HPV 16 and 18 [47].

Hybrid capture is the most tested HPV-DNA detection technique. However polymerase chain reaction and enzyme immunoassay have also been tested [49]. The advantage of HPV-DNA testing is that it has higher sensitivity than conventional cytology for detecting high-graded squamous intra-epithelial lesions. However in younger women the specificity of testing HPV is lower than cytology so it is difficult to adopt this technique as a single screening tool [50]. In a longitudinal evaluation of the test performance, the sensitivity should increase as screening cytology is repeated because an initially false-negative test could be a true positive test in the next screening without resulting in any harm to the women, giving that the precursor lesion take a considerable time to progress [51]. Although the sensitivity is higher than cytology there is no evidence of reducing mortality rate from cancer and should not be used in women under 30 years of age [52, 53] .

According to cross-sectional studies carried out in developing countries the sensitivity of HPV testing for detecting cervical intra-epithelial neoplasia CIN II+ lesion mentioned in table 3 varied from 69-96% and specificity varied from 63%-84%

Author, year of publication	Sensitivity (95% CI)	Specificity (95% CI)
Womack et al 2000 [54]	81% (78-86%)	63% (59-64%)
Wright et al 2000 [36]	84% (71-92%)	83% (80-85%)
Franco et al 2003 [55]	83% (66-100%)	79% (61-96%)
Coste et al 2003 [38]	96% (88-100%)	82% (80-84%)
Mustafa et al 2015 [27]	95% (84-89%)	84% (72-91%)
Suneeta K et at, 2013 [56]	90.4% (84.2 – 97.1%)	85.6% (81.3-91.5%)

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In ACCP (alliance for cervical cancer prevention) cross-sectional studies carried out in India, the sensitivity of HPV testing in detecting CIN 2-3 lesions and invasive cancer varied from 46%-81% and specificity varied from 92%-95% [57]. These data suggest that HPV testing in developing regions could present lower sensitivity than that observed in developed countries. As for the cultural in some population in low-resource setting the vaginal self-sampling HPV test could be an alternative but it has shown lower sensitivity than direct sampling by health practitioners [36, 55].

As in the developed countries HPV-DNA testing has potential to improve health benefits at reasonable cost but for the developing countries where cytology is cheaper HPV-DNA testing could not be feasible as cost-effectiveness [53, 58, 59].

careHPV: it is a powerful, fast and accurate method for the detection of HPV-DNA. It is designed to screen women in setting with limited health care infrastructure, such as area lacking electricity, water or laboratories. This test may be run by a healthcare workers with basic training with no formal laboratories skills are required. Health workers using the care brush in a careHPV collecting medium collect cervical cells. The assay then can run on mains electricity or using battery with an inverter, making it portable and adaptable. The assay can be run in a flexible temperature range from 15-40 degree centigrade. Using an antibody-bound paramagnetic beads technique, the technology can quickly and quantitaticely detect 14 types of high risk HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). It can process 80 specimens in 2.5 hours, thus improving the speed and efficiency of screening as well as allowing the results to be known as the same day, this is a novel, simple, rapid HPV test kit, with cost and time relative to HPV-HC2 equivalent to approximately $1/3^{rd}$ and $1/6^{th}$, respectively [60].

HC2 detection: Second-generation hybrid capture (HC2, QUAGEN) is a commercial reagent used for HPV-DNA detection, which is approved by the U.S. FDA. HC2 can detect 13 types of high risk HPV associated with cervical cancer (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 61) [60].

HPV-PCR detection: the study used PCR fluorescence detection kit for human papillomavirus designed specifically for target sequences of L1 gene of high-risk HPV, which could detect 13 types of HPV-DNA (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) from the cervical exfoliate cells in one PCR procedure and cannot be distinguished each type. This method can detect the types of HPV-DNA and has high sensitivity [60].

In a cross-section study to assess the clinical accuracy of careHPV as a rapid screening test in two hospital of rural china all women were assessed by visual inspection with acetic acid (VIA), Diagene High-Risk HPV HC2 DNA test (HC2), liquid-based cytology, and colposcopy with directed biopsy and endocervical curettage as necessary. The careHPV was done locally y use of self-obtained vaginal and provider-obtained cervical specimens from screening population based set of 2530 women with complete data were screened in which 70 women had CIN2+ of whom 23 had CIN3+. By using of CIN2+ as the reference the sensitivity and specificity of the careHPV test for a cut –off ratio cut-point of 0.5 relative light units were 90% and 84% respectively on cervical specimen and 81.4% and 82.4% respectively on vaginal specimen. Compared with 41.4% and 94.5% for VIA, and 97.1% and 85.6% respectively for HC2 [61]. As from this result careHPV test is promising as a primary screening method for cervical cancer prevention in low resources regions.

China:

China as leading civilization outpacing the rest of the world in the arts and sciences, lies at eastern part of Asia with population of 1367million and women aged 15 and above is more than 556million who are at high risk for developing cervical cancer, and median age of women is 37.7 years, and GDP per capital of china is 12,900$(2014) [62]. In developing country like china, although convinced achievements were acquired in the past few decades, cervical cancer remains as a critical problem threatening women's health with high incidence of 7.5/100,000 and mortality of 3.4/100,000 of cervical cancer and Human Papillomavirus (HPV) infection rate of 16.8% [63, 64].

Epidemiology and etiological studies of HPV and cervical cancer:

Until 1998 the etiology of HPV and cervical cancer remained controversial in china and no population-based cancer-screening program existed then Chinese Academy of Medical Sciences (CICAMS) collaborated with Cleveland Clinic and conducted the Shanxi Province Cervical Cancer Screening Study (SPOCCS) project. For the first time, Chinese researchers identified women with HPV infection who had >250 times higher risk for developing cervical intraepithelial neoplasia Grade II or worse lesions (CIN2+) than those who are HPV negative, with an attributable risk of 98% and 20% of Chinese rural women were infected by HPV [65]. Then a more representative collaborated study among CICAMS, World Health Organization (WHO)/International Agency for Research on Cancer (IARC) and Cleveland Clinic from 2004 to 2007 further identified the predominant types and age distribution of HPV infection among Chinese rural and urban women [64, 66, 67]. In 2007, a nationwide multicenter study was conducted to investigate the HPV prevalence and type distribution in tissue samples from hospital-based patients with invasive cervical cancer (ICC) and CIN2+ in different geographical regions of China. HPV 16, 18, 31, 52 and 58 were identified as predominate HPV types in ICC, among

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which HPV 16 and 18 accounted for 84.5% of the squamous cervical cancer [68].

Cervical cancer screening in china:

In 1999, liquid-based cytology (LBC) and HPV testing were initially introduced in China by CICAMS through a cross-sectional study, which parallely compared the accuracy of six types of cervical cancer screening methods. Based on these two studies collaborated with the Cleveland Clinic, HPV testing in combination with LBC was demonstrated as the most effective strategy for cervical cancer screening, and visual inspection with acetic acid/Lugol's iodine (VIA/VILI) was found to be the surrogate method for primary screening in areas with limited resources [69, 70]. Further- more, with extremely high sensitivity and specificity, HPV testing was considered as a primary screening method for the first time in this study. Thereafter, a variety of studies were conducted to evaluate different screening methods among Chinese women in different geographic areas and races. Specifically, various kinds of LBC methods and HPV-based screening technologies including Hybrid capture 2, Cobas4800, GP5+/6+, SPF10 PCR/DEIA/LiPA25 and real-time polymerase chain reaction (PCR) assay were clinically evaluated in screening trails among Chinese population. In 2010, CICAMS performed pooled analysis for 17 studies which were conducted from 1999 to 2008, and made systematic evaluations for the accuracy of HPV testing, LBC and VIA. The results showed that the sensitivity of detecting CIN3+ for LBC, HPV testing and VIA was 87.9, 97.5 and 54.6%, respectively. The specificity of detecting CIN3+ for LBC, HPV testing and VIA was 94.7, 85.1 and 89.9%, respectively [71]. Consequently, HPV-DNA testing is highly sensitive and moderately specific for CIN3 + with consistent results across study sites and age groups including women <35 years.

Based on the previous experience gained in the past few decades in fighting against cervical cancer from 2003 to 2005, the Chinese Ministry of Health lead Cancer Foundation of China (CFC) and CICAMS developed 'Program of Cancer Prevention and Control in China (2004–2010)', 'Guideline for Cervical Cancer Screening, Early Detection, Diagnosis and Treatment in China' and the Chinese version of 'WHO guideline for Comprehensive Cervical Cancer Control' to help prevent cervical cancer.

In 2005, CFC in Shenzhen and xiangyuan established two national demonstration sites for early detection and treatment of cervical cancer. Both sites established successful models by using VIA as the screening method and played active role in exploring realistic experience for cervical cancer control program in china. Thereafter in 2008, with support from the Public Health Special Subsidy from the Central Government in China, sites for early detection and treatment of cervical cancer have been further expanded to 43 sites in 31 provinces all over the country. From 2009 to 2011, based on the experience gained from the projects and other countries, Chinese government launched nationwide free cervical cancer screening project for 10 million rural women across 221 countries. The big advancement of this project was not only significantly expanding the coverage of screening, but also adding cytology to the previous VIA- based screening method. In the interim, China Worker Union launched cervical and breast cancer-screening program for low-income female city or migrant workers in 2011 with a fund of 40 million Ren MinBi (RMB). From 2012 to 2015, the national screening program for cervical cancer has been expanded to 1140 countries for 30 million rural women [72].

India:

India is the second largest country in Asia and lies in southern Asia with total population of 1,251million among which female of 15 and above is 437million and mean age for the mother to give birth is 19.5 years and literacy among female is 50.8%. India's GDP per capital is 5900$ [73].

Epidemiology and etiological studies of HPV and cervical cancer:

The number of cancer in female in India is 537452 with mortality of 326100 and prevalence of 1125960. Cervical cancer is second most common cancer among female population with incidence of 122,844(22.9%); also second in mortality with 67,477(20.7%) and 5 year prevalence is 308,901 [74]. One in every five women in the world suffering from cervical cancer belongs to India, which has the largest burden of cervical cancer patients in the world. Current data from the National Cancer Registry Program (NCRP) indicates that the most common sites of cancer among women are the breasts and the cervix [75]. The recent NCRP data show that between 2009 and 2011 Aizawl district in the north eastern part of India had the highest levels of cervical cancer at an age-adjusted rate of 24.3, followed by Barshi Expanded at 19.5 and Bangalore at 18.9.[15] In the Bangalore registry, the age-adjusted rate fell from 32.4 in 1982 to 18.7 in 2009, in Barshi from 22.1 in 1988 to 14.1 in 2010, in Chennai from 41 to 16.7 in 2009, and in Thiruvananthapuram from 9.2 in 2005 to 7.7 in 2011. The annual percentage decrease ranged from a minimum of 1.3% in Bhopal to 3.5% in Chennai in the years from 1982 to 2010. All the older PBCRs showed a statistically significant decline in age-adjusted rate from the 25–34 age groups up to 54, although the Barshi registry showed a decline only up to 44 years [76]. The 2010 age-adjusted rate for cervical cancer in the various registries is indicated in Figure 1.

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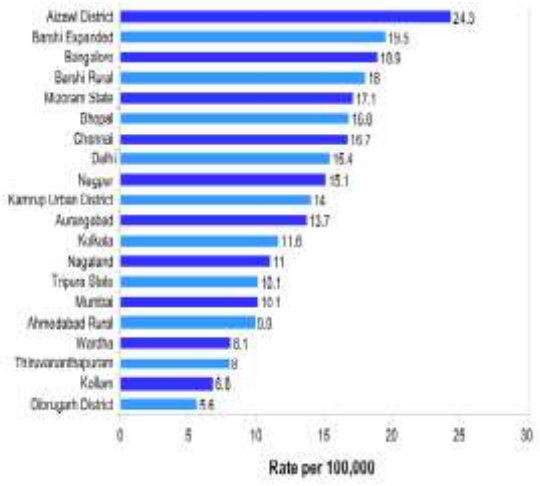

Human papillomavirus is considered as the main sexually transmitted etiological agent for the cause and progression of pre-neoplastic cervical lesions to cervical cancer. The available information on HPV epidemiology is mostly based on research studies addressing cervical screening and HPV infection in selected locations in India. A study on the prevalence of high risk HPV (HR-HPV) infection among apparently healthy populations in various regions of India reported that, the HR-HPV prevalence rates varied between 7–13%, but were mostly above 10%. The most common HPV types reported were HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 and 84.1% of invasive cervical cancer are attributed to HPV's 16 or 18 [77-81].

Screening in India:

India has had a national program of cancer since 1975, when the emphasis was on equipping premier cancer institutions, which by 1984-85 shifted to primary prevention and early detection of cancer cases and, by 1990–1991, to the district cancer control program. As of 2008, creation/recognition of new regional cancer centers, strengthening of existing regional cancer centers, development of oncology wings in medical college hospitals, the district cancer control program, and the decentralized NGO scheme were the priorities of the program [82].

India's national guideline for cervical cancer screening was prepared by expert committee of the ministry that included representatives from the regional cancer centers, federation of obstetrics and gynecologists of India, Indian academy of cytologist, world health organization and international agency for research in cancer, France in the year 2005. Protocol was targeted for the age of 30 to 59 years. Performed by trained health worker female. Firstly in the community where TFW visit households and interact with individual women and inform about the day of screening at PHC where the screening is done with VIA by FHW and supervised by medical officer. If abnormality found then are sent to the district hospital where there the VIA positive women will go through Pap smear, colposcopy, biopsy, cryotherapy and LEEP. After the test is done patient is reviewed in 1 month and if invasive disease diagnosed then sent to RCC/medical College for treatment [83].

The NCRP itself started in 1982 with three Population Based Cancer Registries (PBCRs) and three Hospital Based Cancer Registries (HBCRs). There are 27 PBCRs and 7 HBCRs as of now. In addition, NCRP has started Patterns of Care and Survival Studies (POCSS) in 16 Hospitals for three sites of cancer namely, Cervix, Breast and Head & Neck.

Nepal

Nepal is a landlocked country between china and India in south-Asia and is among the poorest and least developed countries in the world, with one-quarter of its population living below the poverty line. Nepal's gross domestic product (GDP) per capital is only $2400. Nepal has population of 31million and number of female population is 15.9million. Population of women ages 15years and older who are at risk of developing cervical cancer is 11.1millions [84].

Epidemiology and etiological studies of HPV and cervical cancer:

WHO estimates that a crude incidence rate of cervical cancer in Nepal is 24.2 per 100,000 women per year, with 3,504 new cases diagnosed every year and 1872 deaths. Cervical cancer is ranked as the first most common and frequent cancer among women in Nepal between 15 to 44 years of age [85].

Human Papillomavirus (HPV) is considered as the main sexually transmitted etiological agent for the cause and progression of pre-neoplastic cervical lesions to cervical cancer. Nepal has an intermediate burden of HPV infection, lower than many areas in India and china. Approximately 80% of cervical cancer in Nepal is theoretically preventable by HPV 16 and 18 vaccines [86]. Data not available on HPV burden in the general population of Nepal. However in southern Asia the region Nepal belong to, about 7.9% of women in the general population are estimated to arbor cervical HPV infection at a given time and 82.8% of invasive cervical cancer is attributed to HPV's 16 and 18 [85].

Screening in Nepal:

Various screening technique have been introduced for the early detection of cervical cancer in Nepal. For instance papanicolaous smear screening has been reported to be a good method for detecting of early cervical cancer. Although the Pap test has been used as a primary method of screening in Nepal, feasibility of its introduction among the general population is often questioned due to restrictions in the present infrastructure and lack of human and financial resources [87]. More recently, visual inspection after acetic acid application has been found to be a most promising alternative screening test in Nepal, given that it is convenient, affordable and accurate [88-90].

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National guideline for cervical cancer screening and prevention in Nepal was made in 2010 [91]. In context of Nepal the challenge is to start from the grass-root as there is no organized screening program but there has been some efforts made by the tertiary level hospital, INGO's and NGO's, Family Health Division (FHD), department of health services, Ministry of Health and Population (MoHP), federal democratic republic of Nepal has taken initiation to develop national guideline for cervical cancer screening and prevention in the country and coordinated it WHO for support.

Screening method as:

Visual inspection with acetic acid (VIA)

VIA and treatment by cryotherapy as a single visit approach (SVA)

Screening by VIA and immediate treatment of precancerous lesion in one visit referred to as a single visit approach is recommended wherever the resources and trained manpower are available. VIA/SVA will be the final goal in the CCSP aimed to achieving in 5years time from initiation at all level. Collaborators with Bhaktapur cancer hospital, BIR hospital, BPKMCH bharatpur, jipiego, NAHUDA, NESOG, UNFOA, paropkar maternity and women's hospital, tribhuwan university teaching hospital.

The coverage rate for cervical cancer is very low 2.4% in Nepal [85], which may be related to a variety of factors, including socioeconomic and cultural barriers. Studies have documented poverty, lack of information, fear of promiscuity among teenagers, myths and lack of support from the husband's and families as major obstacles to screening [92, 93]. With limited health care resources and competing health care needs, it is very difficult to fund screening programs in low resource settings like Nepal, and this may lead to low and unequal uptake of cervical screening by various subgroup of the population. It has been reported that nearly 50% of Nepalese patients are unable to understand informed consent properly due to illiteracy [94].

Due to limited resources, HPV vaccine is not yet easily available in Nepal, although few small programs offering HPV vaccination are reported to have started by NAHUDA and Nepal fertility care center (NFCC) by an official publication of WHO did not report any introduction of HPV vaccine in Nepal indicating the absence of a formal HPV vaccination program [85].

Factors related with late diagnosis of cervical cancer in Nepal because of 66% were illiterate and 77% were rural inhabitants. High level of illiteracy among women and their problematic health seeking behavior for gynecological symptoms are responsible for late diagnosis of cancer in Nepal [95].

Conclusions

In summary this study indicates/identifies the most affordable and feasible primary screening in the areas where the resources are not adequate to provide high coverage, accuracy and the appropriate management for the test positive women. China, India and Nepal all have the same protocol of primary screening with VIA and then forward with the cytology or cryotherapy for the test positive women. As VIA has low sensitivity then cytology and HPV-DNA testing but has high specificity, CareHPV has higher sensitivity than VIA and cytology and low specificity then VIA, so VIA and CareHPV can be combined and accomplish the high sensitivity and specificity for the detection of pre-cancerous lesions and both the tests can be performed at same time with minimum time requirement and women can get the result in the same day with the further treatment plan. Doing this can cover large number of women in rural area and can be performed in less time with limited resources. Also HPV infections is responsible for more than 80% of cancer in all three country, prophylactic vaccination would decrease the incidence of cervical cancer.

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