

CERVICAL CANCER IN INDIA

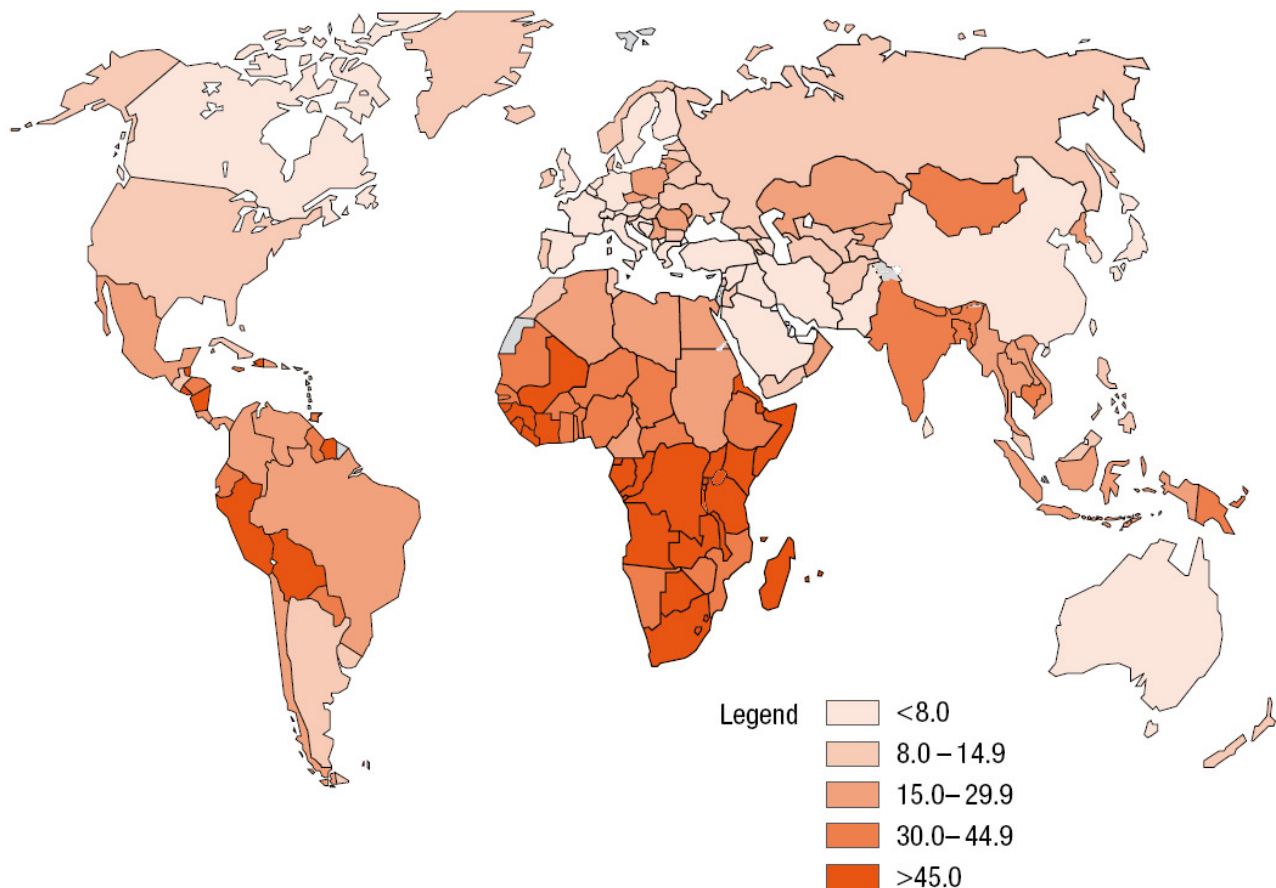
Ambika Satija

South Asia Centre for Chronic Disease

Background

Cervical cancer is one of the most common cancers among women worldwide (WHO, 2009b). Its mortality exemplifies health inequity, as its rates are higher in low & middle income countries (LMICs) (WHO, 2009b), and in low socio-economic groups within countries (Kurkure and Yeole, 2006). Around 80% of global cervical cancer cases are in LMICs (Waggoner, 2003) (figure 1, WHO, 2009a).

Figure 1: Global burden of cervical cancer: Age-standardised incidence rates (per 100,000 women)



Source: World Health Organisation. Comprehensive cervical cancer control: a guide to essential practice. Geneva, WHO, 2006. Available at <http://www.who.int/reproductivehealth/publications/cancers/9241547006/en/index.html>, last accessed November 18, 2009

Much progress has been made in the prevention and control of cervical cancer [Centers for Disease Control and Prevention (b)]. Cancer of the cervix is primarily caused by human papillomavirus (HPV) infection, for which there is a vaccination now available [Centers for Disease Control and Prevention (a); Cancer Research UK (a)]. Additionally, early screening of the disease through cytology has considerably reduced morbidity and mortality from the disease in the developed world (Miller et al, 1990). However, the applicability of these success stories in LMICs is questionable; the vaccine is expensive, and cytology based screening is resource intensive in terms of infrastructure, equipment and manpower. As a result, death and disability from this cancer are high in LMICs, including India (GLOBOCAN 2002 IARC 2009). More research in the LMIC context is needed so that best practices for the prevention and control of cervical cancer in LMICs can be developed and implemented.

This fact sheet will provide a background and basic epidemiology of cervical cancer in India. It will then go on to review current practice in the prevention and management of the cancer, assessing what is most feasible in the LMIC context, providing a summary of what is currently being done in India. It will end with a discussion on gaps and priorities of research.

Cervical Cancer Burden

Global Cervical Cancer Burden

In 2004, cervical cancer was the 5th most common cause of cancer death among women in the world, and had:

- 489,000 new cases
- An age-standardised incidence rate (global) of 16 per 100,000 women in 2002
- 1-year prevalence of 381,033, and 5-year prevalence of 1.41 million in 2002
- 268,000 deaths (3.6% out of 7.4 million cancer deaths)
- 9 age-standardized deaths per 100,000 in 2002
- 3,719,000 DALYs (disability adjusted life-years)

Cervical Cancer Burden in India

In 2004, cervical cancer was the third largest cause of cancer mortality in India, and had:

- An age-standardised incidence rate of 30.7 per 100,000 women in 2002
- 1-year prevalence of 101,583, and 5-year prevalence of 370,243 in 2002
- 72,600 deaths (nearly 10% out of 729,600 cancer deaths)
- 6.5 deaths per 100,000
- 9.5 age-standardized deaths per 100,000
- 987,000 DALYs
- 88 DALYs per 100,000
- 113 age-adjusted DALYs per 100,000

(WHO, 2009b; GLOBOCAN 2002 database, IARC)

What is Cervical Cancer?

Cancer refers to a class of diseases in which a cell or a group of cells divide and replicate uncontrollably, intrude into adjacent cells and tissues (invasion) and ultimately spread to other parts of the body than the location at which they arose (metastasis) (National Cancer Institute 2009).

In cervical cancer, (cancer of the *uterine cervix*), cancer develops in the tissues of the cervix, which is a part of the female reproductive system. The cervix connects the upper body of the uterus to the vagina. The *endocervix* (the upper part which is close to the uterus) is covered by glandular cells, and the *ectocervix* (the lower part which is close to the vagina) is covered by squamous cells. The *transformation zone* refers to the place where these two regions of the cervix meet (American Cancer Society 2009).

There are several types of cervical cancer, classified on the basis of where they develop in the cervix. Cancer that develops in the ectocervix is called *squamous cell carcinoma*, and around 80-90% of cervical cancer cases (more than 90% in India) are of this type [WHO/ICO Information Centre on HPV and Cervical Cancer (a)]. Cancer that develops in the endocervix is called *adenocarcinoma*. In addition, a small percentage of cervical cancer cases are mixed versions of the above two, and are called *adenosquamous carcinomas or mixed carcinomas*. There are also some very rare types of cervical cancer, such as small cell carcinoma, neuroendocrine carcinoma etc. (American Cancer Society). The rest of this factsheet will focus on the first two types, as they constitute the greatest burden, globally as well as in India.

Natural History of Cervical Cancer

Cervical cancer begins with the development of pre-cancerous, benign lesions in the cervicular area. According to WHO classification, the first stage of development is mild dysplasia, which can then progress to becoming moderate dysplasia, severe dysplasia, and then carcinoma in situ (CIS) or invasive cervical cancer. Mild dysplasia usually regresses on its own without treatment, and doesn't progress to moderate or severe dysplasia. A small percentage of women with mild dysplasia, however, will progress to more severe forms, although this can take as long as 10 years. Women with moderate to severe dysplasia are at high risk of developing invasive cancer, although the progression from severe pre-cancerous lesions to cancer may take several years as well (Alliance for Cervical Cancer Prevention, Cancer Research UK).

There are two other systems of classification. According to the Cervical Intraepithelial Neoplasia (CIN) system, mild to moderate dysplasia are classified as CIN1, intermediate dysplasia as CIN2, and severe dysplasia and carcinoma in situ are together classified as CIN3. The Bethesda system simplifies it further, by classifying CIN1 as Low Grade Squamous Intraepithelial Lesion (LSIL), and both CIN2 and CIN3 as High Grade Intraepithelial Lesion (HSIL) (Alliance for Cervical Cancer Prevention, Cancer Research UK).

Once invasive cancer develops, it is further classified into various stages, as per the International Federation of Gynaecology and Obstetrics (FIGO), the details of which have been provided in appendix 1 (Sankaranarayanan and Wesley, 2003).

Although cancer of the cervix can develop in women of all ages, it usually develops in women aged 35-55 years, with the peak age for incidence varying with populations (Zeller et al, 2007); for instance, it was found to be 30-40 years in the UK, and 35-39 years in Sweden (Cancer Research UK). In India, the peak age for cervical cancer incidence is 45-54 years, which is similar to the rest of South Asia [WHO/ICO Information Centre on HPV and Cervical Cancer (a)].

Distribution, prevalence and incidence of Cervical Cancer in India

Prevalence/Incidence of Cervical Cancer

As of 2002, the 1 year prevalence of cervical cancer in India was 101,583, and the 5 year prevalence was 370,243, accounting for approximately 26% of global prevalence, and 83% of total prevalence in South Central Asia* (GLOBACAN 2002 database, IARC). In India, the age-adjusted incidence of cervical cancer (30.7 per 100,000 women, 132,082 incident cases) is the highest relative to that of all other types of cancer, and is higher than the average for the South Central Asia region (GLOBACAN 2002 database, IARC 2009). By 2025, the number of new cervical cancer cases in India is projected to increase to 226,084 [WHO/ICO Information Centre on HPV and Cervical Cancer (a)].

Cervical cancer is the leading cancer among women in terms of incidence rates in 2 out of the 12 Population Based Cancer Registries (PBCRs) in India, and has the second highest incidence rate after breast cancer in the rest of the PBCRs (table 1, National Cancer Registry Programme and World Health Organisation). The age-adjusted incidence is highest in Chennai, a metropolitan city in the south, and lowest in Thiruvananthapuram, the capital of Kerala (National Cancer Registry Programme and World Health Organisation). There is a high incidence belt in the north eastern districts of Tamil Nadu, as well as in two districts in the North-Eastern region of the country (figure 2, National Cancer Registry Programme and World Health Organisation).

Cervical Cancer and Socio-Economic Status (SES)

The prevalence and burden of cervical cancer is much higher among women of low SES, as well as among rural women in India (Vallikad, 2006; Kurkue, and Yeole, 2006). The primary reason given for this is lack of access to screening and health services, and lack of awareness of the risk factors of cervical cancer. HPV infection and precancerous lesions go unnoticed and develop into full blown cancer before women realise they need to go for medical help (Kaku et al, 2008). Moreover, due to difficulties of access and affordability, compliance to, and follow up of, treatment is much worse for women of low SES, leading to further morbidity and mortality from the disease (Laedtke

* South Central Asia, as per GLOBACAN, IARC, includes Afghanistan, Bangladesh, Bhutan, India, Iran, Kazakhstan, Kyrgyzstan, Nepal, Pakistan, Sri Lanka, Tajikistan, Turkmenistan & Uzbekistan.

and Dignan, 1992). Thus the burden of this debilitating disease is highest in the most disadvantaged sections of Indian society.

Table 1: Crude & age-adjusted incidence rates per 100,000 population for cervical cancer in 12 PBCRs in India

PBRC	Crude Incidence Rate	Age-Adjusted Incidence Rate
Bangalore	18.8	21.7
Barshi	42.7	22.4
Bhopal	22.2	24.5
Chennai	24.4	30.6
Delhi	16.3	22.7
Mumbai	14.6	18.0
Ahmedabad	16.2	13.4
Karunagappally	19.2	15.0
Kolkata	17.5	19.9
Nagpur	19.1	23.2
Pune	20.5	22.5
Thiruvananthapuram	13.1	10.9

Source: National Cancer Registry Programme and World Health Organisation, Atlas of Cancer in India

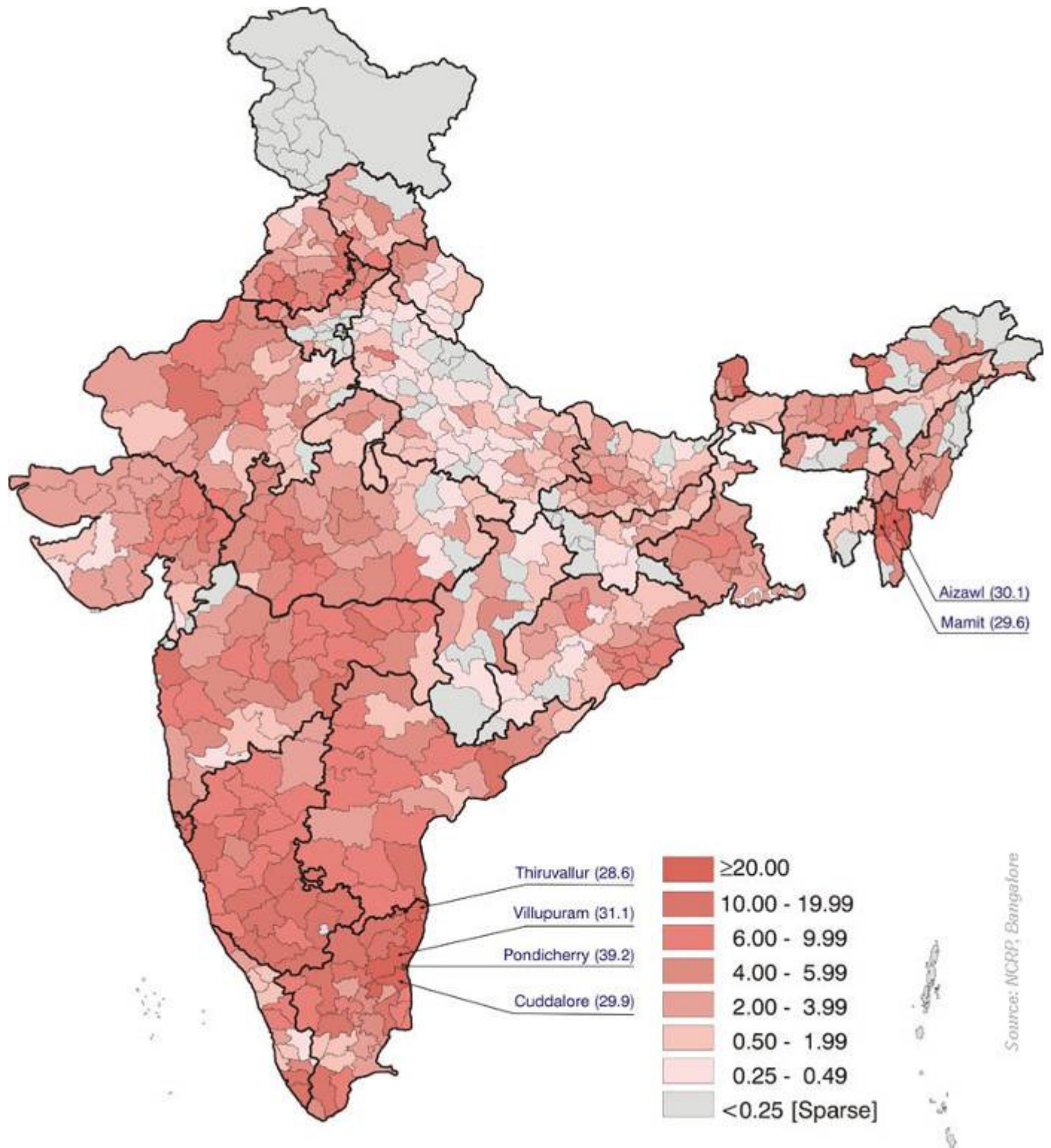
Burden of Cervical Cancer in India

India has a disproportionately high burden of cervical cancer (Shanta et al, 2000). Although its age-standardised death rate of 9.5 deaths per 100,000 population is representative of global rates, it accounts for nearly one-third of global cervical cancer deaths (WHO 2009b, GLOBOCAN 2002, IARC 2009). Figure 3 shows that there is considerable excess mortality from cervical cancer in India relative to the world, and the South Asia region. (National Cancer Registry Programme 2009, WHO 2004)

Cervical cancer is the third largest cause of cancer mortality in India after cancers of the mouth & oropharynx, and oesophagus, accounting for nearly 10% of all cancer related deaths in the country (WHO, 2009b). Among women, it is the leading cause of cancer mortality, accounting for 26% of all cancer deaths (GLOBOCAN 2002, IARC 2009). According to IARC estimates, mortality from cervical cancer is expected to witness a 79% increase from 74,118 deaths in 2002 to 132,745 deaths by 2025 (National Cancer Registry Programme 2009, WHO 2004).

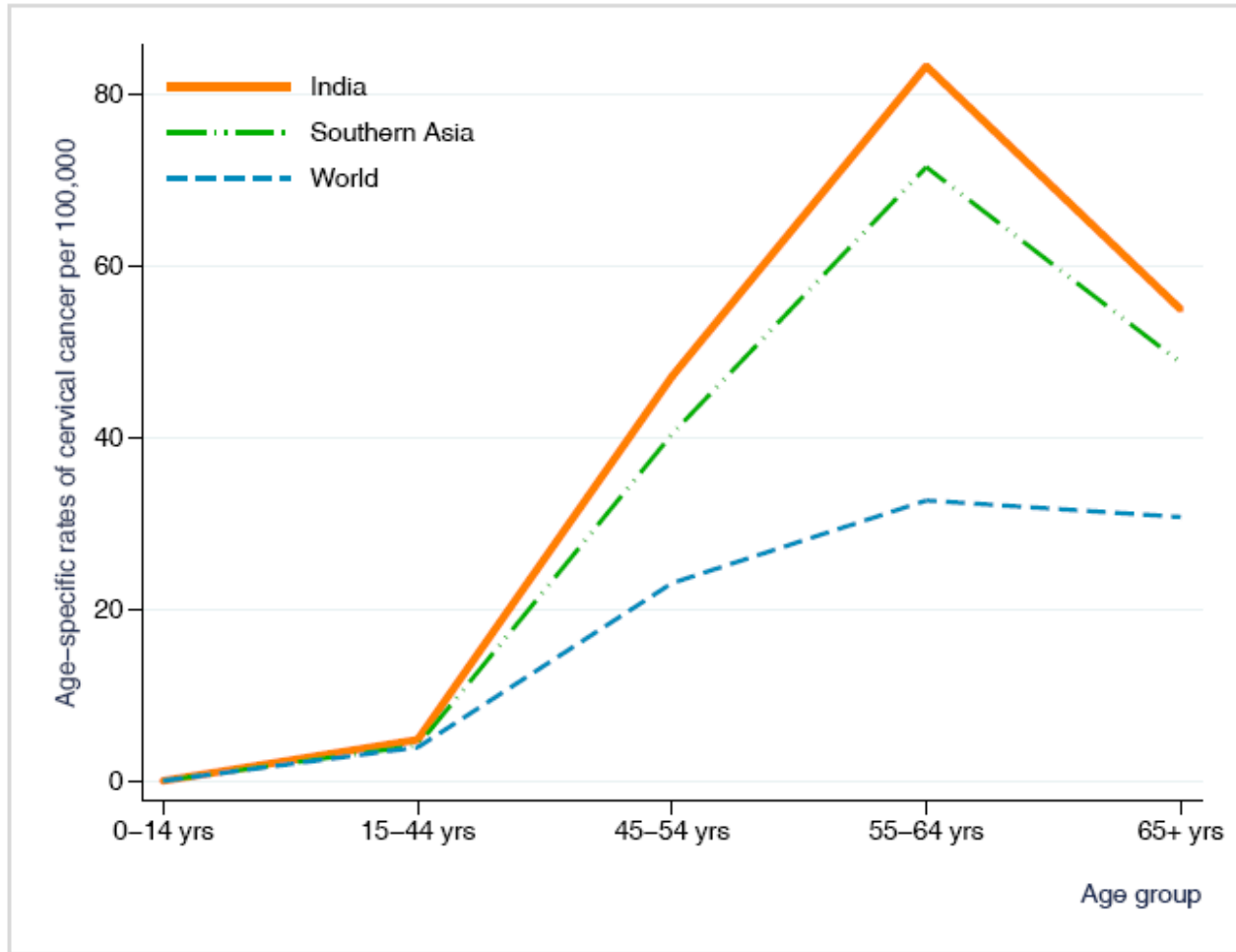
Another measure of disease burden is Disability Adjusted Life Years (DALYs). At a rate of 113 age-adjusted DALYs per 100,000 population, cervical cancer accounts for 26.5% of global cervical cancer DALYs, and 11.6% of total cancer DALYs in India (WHO 2009b).

Figure 2: District wise comparison of age-adjusted incidence of cervical cancer (per 100,000 population)



Source: National Cancer Registry Programme and World Health Organisation, Atlas of Cancer in India,

Figure 3: Age specific mortality from cervical cancer in India, South Asia, and the World



Rates per 100,000 women per year.

Data sources:

IARC, Globocan 2002 | WHO GBD 2004 (for WHO region estimates only)

Source: WHO/ICO Information Centre on Human Papilloma Virus (HPV) and Cervical Cancer (a). Human Papillomavirus and Related Cancers in India. Summary Report 2009. Available at <http://www.who.int/hpvcentre/en/>

Economic Burden of Cervical Cancer

Cervical cancer causes loss of productive life both due to early death as well as prolonged disability (WHO, 2009b). In India, the Years of Life Lost (YLL) due to cervical cancer were 936.3 in 2000, being among the highest in the world, greater than the YLLs caused by any other cancer in India, and constituting almost 4% of total YLLs due to all causes in India (figure 4, Yang et al, 2004). Among women aged 25-64 years, who tend, in India, to be the sole caretakers of the house & family, and in some cases significant contributors to the family income, this mortality burden poses a heavy economic burden on families (Arrossi et al, 2007), as well the country (National Commission on Macroeconomics of Health, 2005). Additionally, the high medical costs that are incurred by families due to cervical cancer (especially since most cases in developing countries are diagnosed at advanced stages when treatment is costly but prognosis poor), further impoverish individuals and communities (Bishop et al, 1996).

Figure 4: Global, regional and India specific YYLs due to cervical cancer in 2000

TABLE III – YEARS OF LIFE LOST (WEIGHTED) FROM CANCER OF THE CERVIX IN WOMEN AGED 25–64, IN 2000¹

Region/country	Number	%	Crude rate (per 1,000)	Age-standardized rate (per 1,000)
SubSaharan Africa	377.8	0.9	3.33	3.95
Zimbabwe	8.5	0.6	4.25	5.75
Latin America/Caribbean	341.0	3.9	2.95	3.21
Peru	16.1	3.6	2.95	3.39
North America	68.1	1.9	0.83	0.80
United States	62.6	1.9	0.85	0.82
Eastern Asia: China	216.3	1.1	0.66	0.74
Eastern Asia: Japan	18.6	1.8	0.53	0.50
Eastern Asia: Other	14.3	1.1	0.73	0.79
South Eastern Asia	294.1	2.5	2.55	2.86
South Central Asia	1,085.5	3.1	3.66	4.10
India	936.3	3.9	4.47	4.91
Middle East/Northern Africa	86.0	1.4	1.22	1.40
Eastern Europe	139.9	2.1	1.65	1.58
Romania	19.2	4.7	3.20	3.16
Southern Europe	32.4	2.3	0.82	0.80
North/Western Europe	66.9	2.4	0.89	0.85
Denmark	1.4	1.9	0.94	0.89
Australia/New Zealand	3.7	1.9	0.61	0.60
Developed countries	329.6	2.1	1.02	0.98
Developing countries	2,379.0	2.0	2.27	2.54
All areas	2,708.6	2.0	1.98	2.10

¹Numbers (thousands) and percent of total, and rates per 1,000 (crude and age-standardized).

Source: Yang et al, 2004

The cost of secondary care of invasive cervical cancer is another source of economic burden. According to the National Commission on Macroeconomics of Health report (2005), the per unit cost of providing secondary care for cervical cancer at the level of district hospitals is 10,016.04 INR, higher than that of all other chronic conditions with the exception of cardiovascular diseases. Due to the high number of cervical cancer cases in the population, it has the highest total cost of secondary care (100,000 INR per 100,000 population) relative to all other cancers. Recognising the high costs incurred in secondary care of cervical cancer, prevention through screening and vaccination may be a more cost-effective option for India.

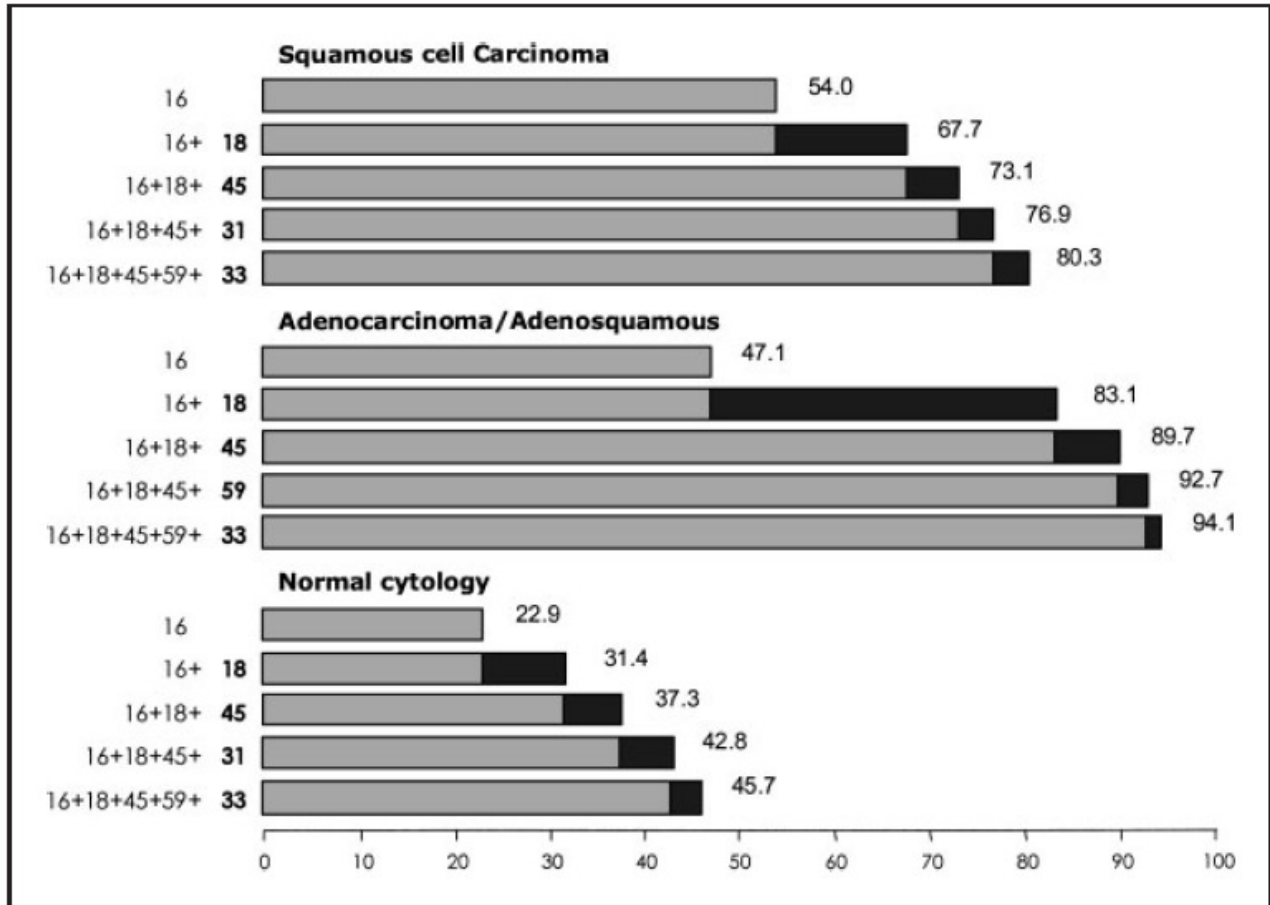
Risk Factors for Cervical Cancer

The main risk factor for the development of cervical cancer is human papilloma virus (HPV) infection, DNA of which has been found in almost all cases of invasive cervical cancer (Bosch and de Sanjosé, 2003). HPV is a sexually transmitted infection, making cervical cancer a chronic disease with an infectious aetiology (Alliance for Cervical Cancer Prevention, Cancer Research UK). At least 50% of sexually active men and women get HPV at some point in their lives [Centers for Disease Control and Prevention (c)]. Most women with HPV infection will not develop cancer, and the infection usually resolves spontaneously; however, around 3-10% of women with HPV develop persistent infections, and are at high risk of developing cervical cancer (Monsonigo et al, 2004).

Although there are several strains of HPV infection, (most of which have been found to increase the risk of developing cervical cancer) two strains: HPV 16 and 18, account for more than 70% of all cervical cancer cases; five other strains: HPV 31, 33, 35, 45, 52 and 58 account for an additional

20% of cases [WHO/ICO Information Centre on Human Papilloma Virus and Cervical Cancer (a); Bosch and de Sanjosé, 2003]. While in squamous cell carcinoma, HPV 16 seems to predominate, HPV 18 seems to play an equally important role in adenocarcinoma (figure 5, Bosch and de Sanjosé, 2003).

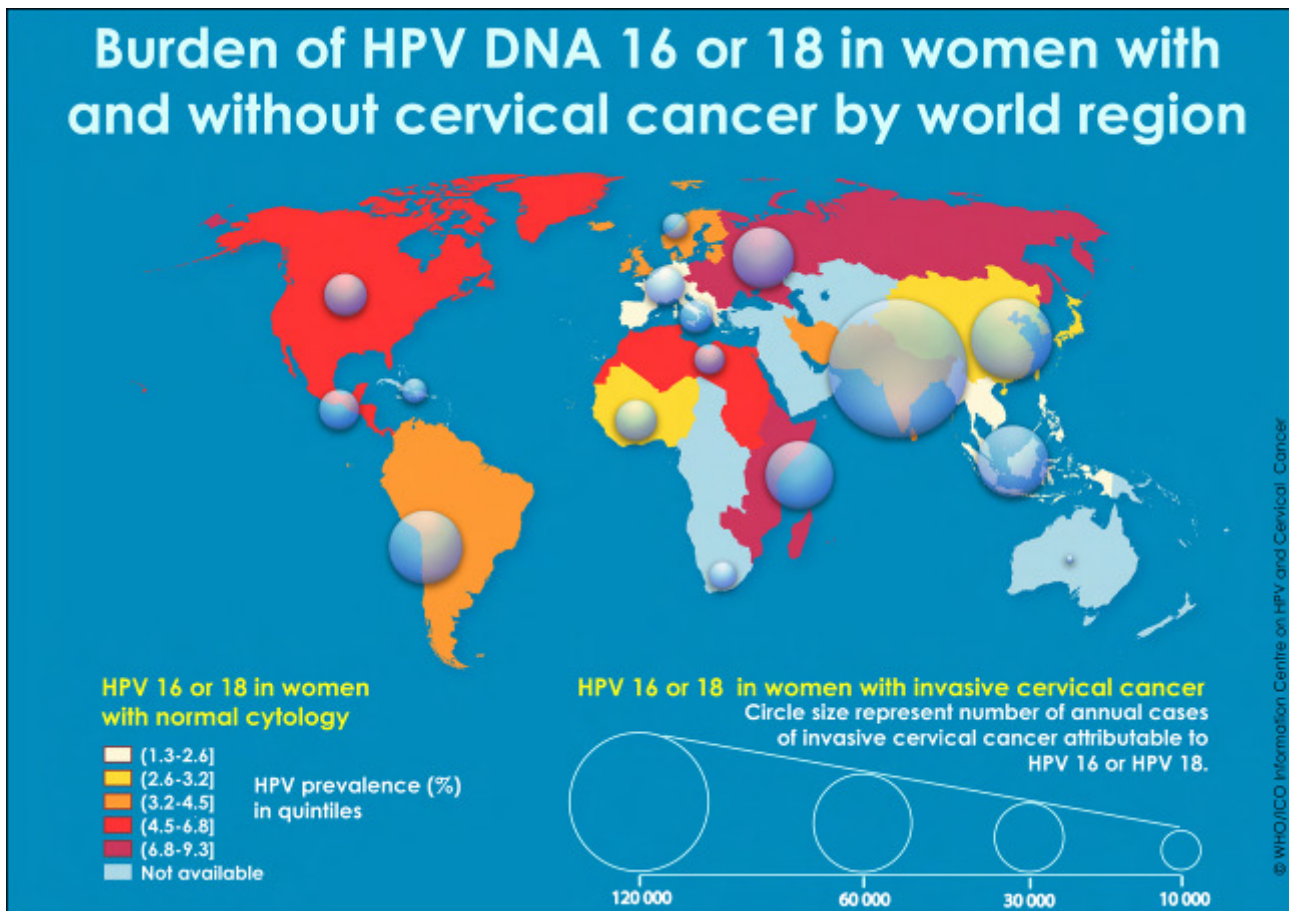
Figure 5: Cumulative prevalence of common HPV types in women with squamous cell carcinoma, adenocarcinoma, and normal cytology



Source: Bosch & Sanjosé (2003), taken from the IARC multicentre control studies

Global prevalence of HPV infection in the general female population is estimated at 11.4% (95% CI 11.3, 11.5) [WHO/ICO Information Centre on Human Papilloma Virus (HPV) and Cervical Cancer (a)]. However, prevalence varies greatly from country to country, ranging from 2% in South Vietnam to 43% in Zimbabwe (Bosch and de Sanjosé, 2003). In India, prevalence of HPV infection is 7.9% (7.5-8.2), lower than the world average [WHO/ICO Information Centre on Human Papilloma Virus and Cervical Cancer (a)]. Despite this, the absolute number of cases of invasive cervical cancer attributable to HPV infection is highest in the South Asia region [figure 6, WHO/ICO Information Centre on Human Papilloma Virus (HPV) and Cervical Cancer (b)].

Figure 6: Burden of HPV DNA 16/18 in women with and without cervical cancer by world region



Source: WHO/ICO Information Centre on Human Papilloma Virus (HPV) and Cervical Cancer (b), http://www.who.int/hpvcentre/statistics/statistics_map_ICO.pdf

The prevalence of HPV DNA is much higher in individuals with invasive cancer than in those with normal cytology (National Cancer Registry Programme 2009, World Health Organisation 2004), and the odds ratios (OR) associated with HPV infection and cervical cancer are among the highest observed in any disease (Bosch and de Sanjosé, 2003). The IARC multicentre case-control study found an OR of 158.2 (95% CI 113.4, 220.6) for squamous cell cervical cancer among cases (with any HPV infection) relative to controls, with the highest OR for HPV 16 infection (434.5 [278.2–678.7]), and the lowest OR for HPV 6 infection (4.3 [0.5–38.4]) (Muñoz et al, 2003).

However, there is considerable regional and between-country variation in this association, with HPV 16/18 prevalence in invasive cervical cancer cases ranging from 65% in South/Central America to 76% in North America (Smith et al, 2007). In India, prevalence of HPV 16/18 in invasive cervical cancer cases is 82.5% (95% CI 9.5, 85.1) (National Cancer Registry Programme and World Health Organisation). A case-control study conducted in Chennai, India, found an almost 500 fold increase in the odds of having cervical carcinoma in cases with any HPV infection relative to controls with no HPV infection (figure 7) (Francheschi et al, 2003).

Figure 7: Odds of having cervical cancer among individuals with HPV infection relative to those without, in Chennai, India

	Cervical carcinoma		Controls		OR (95% CI) ²
	No.	(%)	No.	(%)	
HPV					
Negative	1	(0.5)	133	(72.3)	1 ³
Positive (any type)	190	(99.5)	51	(27.7)	497.9 (67.7–999)
Multiple infection					
No	160	(83.8)	44	(23.9)	1 ³
Yes	30	(15.7)	7	(3.8)	1.2 (0.5–3.0)
HPV type(s)					
HPV 16	115	(60.2)	32	(17.4)	1 ³
HPV 18	28	(14.7)	2	(1.1)	3.9 (0.9–17.4)
HPV 16 and HPV18	5	(2.6)	2	(1.1)	0.7 (0.1–3.8)
HPV 16-associated types ⁴	25	(13.1)	1	(0.5)	7.1 (0.9–54.4)
HPV 18-associated types ⁵	8	(4.2)	4	(2.2)	0.6 (0.2–2.0)
Other types	9	(4.7)	10	(5.4)	0.3 (0.1–0.7)

OR, odds ratio; CI, confidence interval; HPV, human papillomavirus.¹HPV information was not available for 14 cases and 29 controls.
²Estimates from unconditional logistic regression equations including terms for age and area of residence.³Reference category.⁴HPV 31, 33, 35, 52 and 58, in absence of HPV 16 and 18.⁵HPV 39, 45, 59 and 68, in absence of HPV 16 and 18.

Source: Francheschi et al, 2003

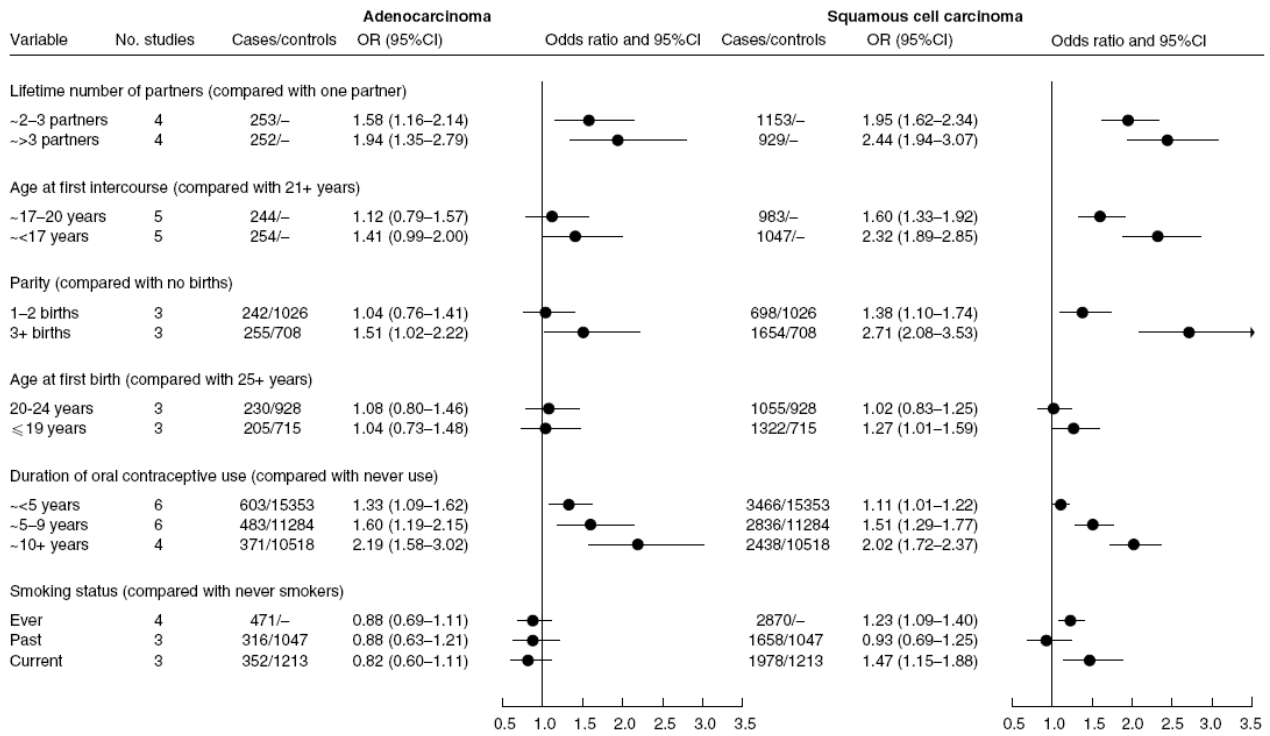
The level of sexual activity of a person will affect the risk of acquiring HPV infection. Early age of first intercourse, multiple sexual partners, unprotected sex and sex with uncircumcised men, have been found to increase the risk of contracting HPV infection (figure 9) (Francheschi et al, 2003; World Health Organisation, 2006; Biswas et al, 1997). For example, having more than 3 sexual partners during a woman's lifetime will increase the risk of cervical cancer by 94% compared to women with one lifetime partner (figure 8). Among men, high lifetime number of sexual partners [multivariate OR for 2-9 partners relative to none 2.11 (1.17-3.78)] and recent number of sexual partners [multivariate OR for 2 partners in 3 months relative to none 2.09 (1.25-3.49)] have been found to increase the risk of contracting HPV infection, while not having had sex in the past 3 months [multivariate OR 0.42 (0.22-0.81)] and circumcision [multivariate OR 0.70 (0.52-0.94)] have been found to have a protective effect (Giuliano et al, 2009).

There are additional factors that increase the risk of developing cervical cancer after contracting HPV infection. These include smoking, oral contraceptive use, high parity, and infection with other sexually transmitted diseases such as HIV, Herpes, Chlamydia, gonorrhoea, and syphilis (de González et al, 2004; Plummer et al, 2003; Moreno et al, 2002; International Collaboration of Epidemiological Studies of Cervical Cancer, 2007; Smith et al, 2003; Muñoz et al, 2002) (figure 9, de González et al, 2004). For example, high parity (3 births or more) increases the risk of cervical cancer by 51% compared to women with no births (figure 8).

Prevention, Management & Treatment of Cervical Cancer

Cervical cancer is preventable and curable if detected at an early stage (WHO, 2006). The 5 year survival rate of cervical cancer when detected at the earliest stage is 92%, and the combined 5 year survival rate for all stages is 71% (American Cancer Society 2009).

Figure 8: Odds ratios for cervical cancer by histology in relation to risk factors



Test for heterogeneity between adeno and squamous cell carcinoma risks for:
 Partners: 2-3 partners $P=0.2$; >3 partners $P=0.2$; age at first intercourse: 17-20 years $P=0.04$; <17 years $P=0.009$
 Parity: 1-2 births $P=0.08$; 3+ births $P=0.006$; age at first birth: 20-24 years $P=0.8$; <20 years $P=0.4$
 Oral contraceptive duration: <5 years $P=0.1$; 5-10 years $P=0.7$; 10+ years $P=0.7$
 Smoking status: Ever $P=0.003$; past $P=0.8$; current $P=0.001$

Source: de González et al, 2004

Prevention

Health Promotion & Education

According to a WHO report on comprehensive cervical cancer control, health education and promotion should be an integral part of any national cervical cancer control programme (WHO, 2006). It should incorporate an awareness component, informing women and/or their families:

- that cervical cancer is preventable,
- about the signs and symptoms of the disease,
- what they should do if signs and symptoms are present,
- that regular screening is essential to detect the cancer early and avoid disability and death from the disease.

It should also include aspects of behaviour modification, informing the population about:

- the sexual and behavioural risk factors of cervical cancer,
- the use of condoms (although condoms do not provide 100% protection from HPV infection, their use should be encouraged, as they have been shown to allow for faster clearance of HPV infection, regression of cervical lesions, and prevention of other sexually transmitted diseases which increase the risk for developing cervical cancer (WHO, 2006).

- avoiding multiple sexual partners,
- delaying first sexual intercourse,
- reducing parity,
- reducing tobacco use.

Lastly, counselling should be incorporated in all cervical cancer prevention programmes (WHO, 2006).

An awareness programme initiated by the National Cancer Registration Programme at Barshi, a rural area in India, showed marked improvement in the stage at diagnosis of cervical cancer from 1988-89 to 1990-92, with a control site (no awareness programme) showing no such improvement. The methodology consisted of educating the general population about the symptoms of the cancer, and encouraging women who had such symptoms to undergo screening (Jayant et al, 2006). Similar findings were reported by a study in a district in Western India (Sankaranarayanan et al, 2001). These studies demonstrate the importance of incorporating health education in a national screening programme.

Vaccination

HPV is largely asymptomatic, making it difficult to recognise and detect among the general population, which will limit any behaviour modification (Singh, 2005). Vaccinations may thus provide a solution for prevention.

Two different vaccines that have been developed to prevent infection from HPV 16 and 18 and one of these offers added protection against HPV 6 and 11 (which cause genital warts). This vaccine called 'Gardasil[®]', manufactured by Merck, has been licensed for use in several countries, including USA (The Future II Study Group, 2007). Both vaccines need to be administered with 3 doses over a 6 month period, can be given to females aged 9-26 years, and are most effective if given before the female's first sexual encounter [Centers for Disease Control and Prevention (d)]. In USA, the vaccine is available to girls aged 11-12 years. [Centers for Disease Control and Prevention (a)]. In the UK, a national HPV vaccination programme has been initiated, offering the vaccine 'Cervarix[®]' to all girls aged 12-13 [Cancer Research UK (a)]. However, regular screening is still recommended following the vaccination, as it doesn't confer protection from other HPV strains [Centers for Disease Control and Prevention (a)]. Although Gardasil has been licensed for use in males (in USA) (MedPage Today, October 16, 2009), it has not been introduced for boys at the population level as yet, as that hasn't been established as a cost-effective strategy (Kim and Goldie, 2009).

In developing countries like India where HPV infection is high [WHO/ICO Information Centre on Human Papilloma Virus and Cervical Cancer (a)], introducing a national HPV vaccination programme may reduce the incidence of cervical cancer. However, the primary obstacle to this is financial, as the vaccines are expensive in relative terms. Public sector spending in health is very low in India (India spent 3.6% of its GDP on health in 2007) (WHO 2009), making it difficult for the government to independently take on the task of introducing the vaccine in the national immunisation programme, without external support. Thus although the vaccine is available for personal use in India, it has not been implemented at the population level (Nagarajan, 2009). However, with an annual per capita income of 38,084 INR (for the year 2008-09) (Rediff News, February 9, 2009), the average Indian cannot afford to pay for the HPV vaccine which costs 12,000

INR at 2009 prices for 3 doses (Hindustan Times, December 23, 2009). It is yet unclear how many women in India have taken this route although one study demonstrated that parents of adolescent girls in Mysore have a positive attitude towards the vaccine (Madhivanan et al, 2009). Nevertheless, the vaccine is still surrounded by controversy in the country. Voices have been raised against the pharmaceutical manufacturers of the vaccine for incorrectly claiming that it ‘prevents cervical cancer’, when actually it just immunises women against certain HPV strains (Hindustan Times, December 23, 2009). It is thus crucial that complete information about the kind of protection the vaccine confers is given to parents and individuals considering it for their daughters or themselves, so they may be able to make informed decisions.

Screening

Since early detection predicts better prognosis, one of the most effective ways of preventing and controlling cervical cancer is regular screening and early diagnosis. Despite the fact that more than 80% of cervical cancer cases are in developing countries, only 5% of women there have ever been screened for cervical abnormalities (WHO 2006).

The most effective method of screening employed in the developed world has been cytology based using Pap smears, which has contributed considerably to reducing incidence of, and mortality from, cervical cancer (Miller et al, 1990). However this method of screening requires excessive resources in terms of laboratories, equipment, trained personnel, and transport of specimens. (Miller et al, 2000). Lack of adequate financial and human resources in developing country settings has prevented the quick uptake of such cytology based screening programmes at the population level.

This has led to a search for alternative screening methods that can be more cost-effective for application in low-resources settings. Visual inspection-based screening tests, such as naked eye visual inspection or ‘downstaging’, visual inspection with 3-5% acetic acid (VIA), VIA with magnification (VIAM), and visual inspection post application of Lugol’s iodine (VILI), are a set of alternative screening mechanisms which have been studied for their effectiveness in LMIC settings, including in India (Sankaranarayanan et al, 2004).

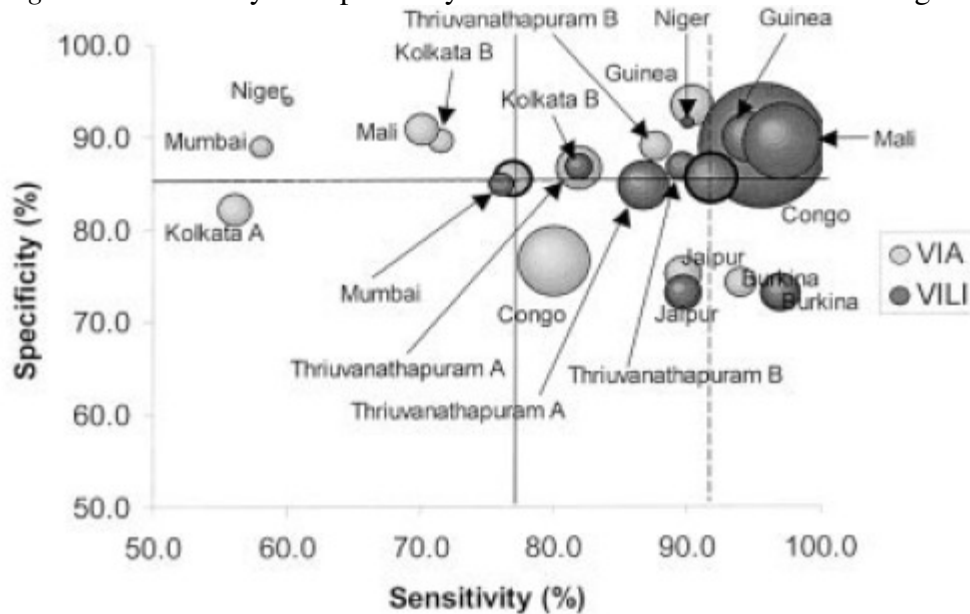
Downstaging has been shown to have inadequate sensitivity and specificity for detecting cervical lesions (figure 9, Sankaranarayanan et al, 2004). VIA, VIAM, and VILI have been assessed in multiple settings for their effectiveness relative to cytology based screening (Sankaranarayanan et al, 2003; Goldie et al, 2005; Jeronimo et al, 2005). Although the sensitivity and specificity of VIA has been found to vary considerably from study to study and country to country (figure 9, Sankaranarayanan et al, 2004), the general finding has been that the sensitivity of VIA tends to be similar to that of cytological screening, but its specificity tends to be lower (Sankaranarayanan et al, 2004). Visual inspection based methods have many advantages: they are less expensive than cytology based screening, easy to administer and train appropriate health care workers, and provide real-time results. For instance, Legood et al (2005) found the costs of screening with VIA, cytology and HPV DNA testing to be 3,917 USD, 6,609 USD and 11,779 USD per 1000 women who were eligible for screening. They may be a viable screening option in low-resource settings such as India (WHO, 2002); however, their long-term effectiveness in reducing cervical cancer incidence and mortality has not yet been established. Preliminary data from an Indian cluster randomised control trial based in Tamil Nadu suggests that screening using the VIA method substantially reduces

incidence of, and mortality from, cervical cancer [incidence hazard ratio of 0.75 (0.55–0.95) and mortality hazard ratio of 0.65 (0.47–0.89)] (Sankaranarayanan et al, 2007).

Another screening method is HPV DNA testing, which although expensive, can be cost-effective in the long run, as it has higher sensitivity than cytological screening, can detect CIN lesions at an earlier stage than cytology, and hence can be implemented with longer intervals between screenings while at the same time reducing cervical cancer incidence, and averting more deaths from the disease (Bulkmans et al, 2007; Ronco and Segnan, 2007). Sankaranarayanan et al (2009) found a single round of HPV testing in a rural setting in India to result in a decrease in incidence of, and death from, advanced cervical cancer.

However, there are socio-cultural barriers to cervical cancer screening in India. Dabash et al (2005) found lack of privacy and confidentiality during screening, cultural norms encouraging modesty among women and insufficient importance given to women’s health issues to be significant barriers to cervical cancer screening. They also found that getting the disease was associated with stigma due to the belief that it is caused by high parity, sexual promiscuity, poor hygiene, and use of contraceptives. A recent pilot project sponsored by the WHO found that educated, working women avoided getting themselves screened for breast and cervical cancer, as they believed that they didn’t need to visit the doctor if they were “healthy” and had no symptoms (The Times of India, 29, June 2009). These socio-cultural barriers can be dealt with through the incorporation of a health education component in a nation-wide screening programme.

Figure 9: Sensitivity and specificity of VIA and VILI in different settings



Source: Sankaranarayanan et al, 2004

Management, treatment and rehabilitation

A screening programme will not be successful if an effective treatment and management programme is not established to run along side it. The management and treatment of cervical cancer

entails accurate diagnosis of pre-cancer or cancer cells followed by appropriate treatment and follow up of the patient, and effective rehabilitation and palliative care for advanced cancer patients (WHO, 2006). The WHO (2006) prepared a set of recommendations for the comprehensive control of cervical cancer, in which evidence based practices in cervical cancer management can be found. (<http://www.who.int/reproductivehealth/publications/cancers/9241547006/en/index.html>).

The Alliance for Cervical Cancer Prevention (ACCP) has been doing considerable research in cervical cancer control in several developing countries including India, on the basis of which they have come up with recommendations for cervical cancer management in low resource settings (Alliance for Cervical Cancer Prevention, 2007). They found either HPV DNA testing or VIA, followed by cryotherapy to treat pre-cancerous lesions during the same visit, to be the most efficient and effective strategy for the secondary prevention of the cancer in LMICs. Cryotherapy has been found by them to be a highly safe procedure with high cure rates. It has also been found to protect HPV positive women from the future development of cervical cancer.

Best Practices for Cervical Cancer Management

India has a set of guidelines for implementing a cervical cancer screening programme (National Cancer Control Programme and WHO-India, 2006, available at <http://www.cytoindia.com/Cytology%20EQA/CCSP%20Guidelines.pdf>). This has been developed through consultations with experts from the Regional Cancer Centres, the Federation of Obstetrics and Gynaecologists of India, the Indian Academy of Cytologists, Indian medical colleges such as AIIMS, the WHO and the International Agency for Research in Cancer (IACR). Realising that cytology based screening, being highly resource intensive, cannot be implemented in resource poor areas of India, these guidelines recommend the use of alternative screening strategies, in particular VIA, at the primary health care (PHC) level, followed immediately by a single visit to the District Hospital (DH) for further management. All women, who on the basis of their VIA results are referred to the DH, should be diagnosed using colposcopy, and on the basis of that, treatment should be offered to the women during the same visit itself, so as to avoid loss to follow up. Confirmation of diagnosis using pap smears and biopsy should be done subsequently (figure 10).

The guidelines have a strong community sensitisation and motivation component, recommending that information, education and communication (IEC) activities be incorporated into the screening programme. In addition the guidelines provide the details of the roles of different healthcare functionaries, training of personnel, preparation and procedures for screening, equipment required at each health care level, protocols for referrals and follow up, and procedures for monitoring and evaluation as well as quality control.

The guidelines recommend that the cervical cancer screening programme be initiated as a series of demonstration projects at districts that have the requisite human and financial resources to screen large numbers of women (figure 11). These should be evaluated, and after making necessary modifications, their scalability to other parts of the country should be looked into.

Regarding the clinical management of cervical cancer, there are no working guidelines in India. It has been found that services for treatment in the public sector are fragmented, and where available, mostly inaccessible to the poor (primarily due to financial reasons) (Basu and Chowdhury, 2009; Dabash et al, 2005). In a study of cervical cancer prevention and treatment services in 3 districts of Uttar Pradesh, Dabash et al (2005) found gaps in the knowledge of most health care providers with respect to the natural history of the cancer, the appropriate treatment of pre-cancerous lesions, as well as current evidence based practices in stage-appropriate management of invasive cervical cancer, particularly at the public, lower-level health facilities. Providers in the military sector, and to a lesser extent those in the private sector, were more knowledgeable of management practices and issues.

There are several international, evidence-based guidelines for cervical cancer control, available at <http://www.library.nhs.uk/Cancer/ViewResource.aspx?resID=155018>. However, all of these have been created by developed countries, and their applicability in India is questionable. Thus context-specific, national guidelines for the prevention and management of cervical cancer need to be developed.

Figure 10: Components of the cervical cancer screening programme at various levels of the health system, National Cancer Control Programme and WHO-India, 2006

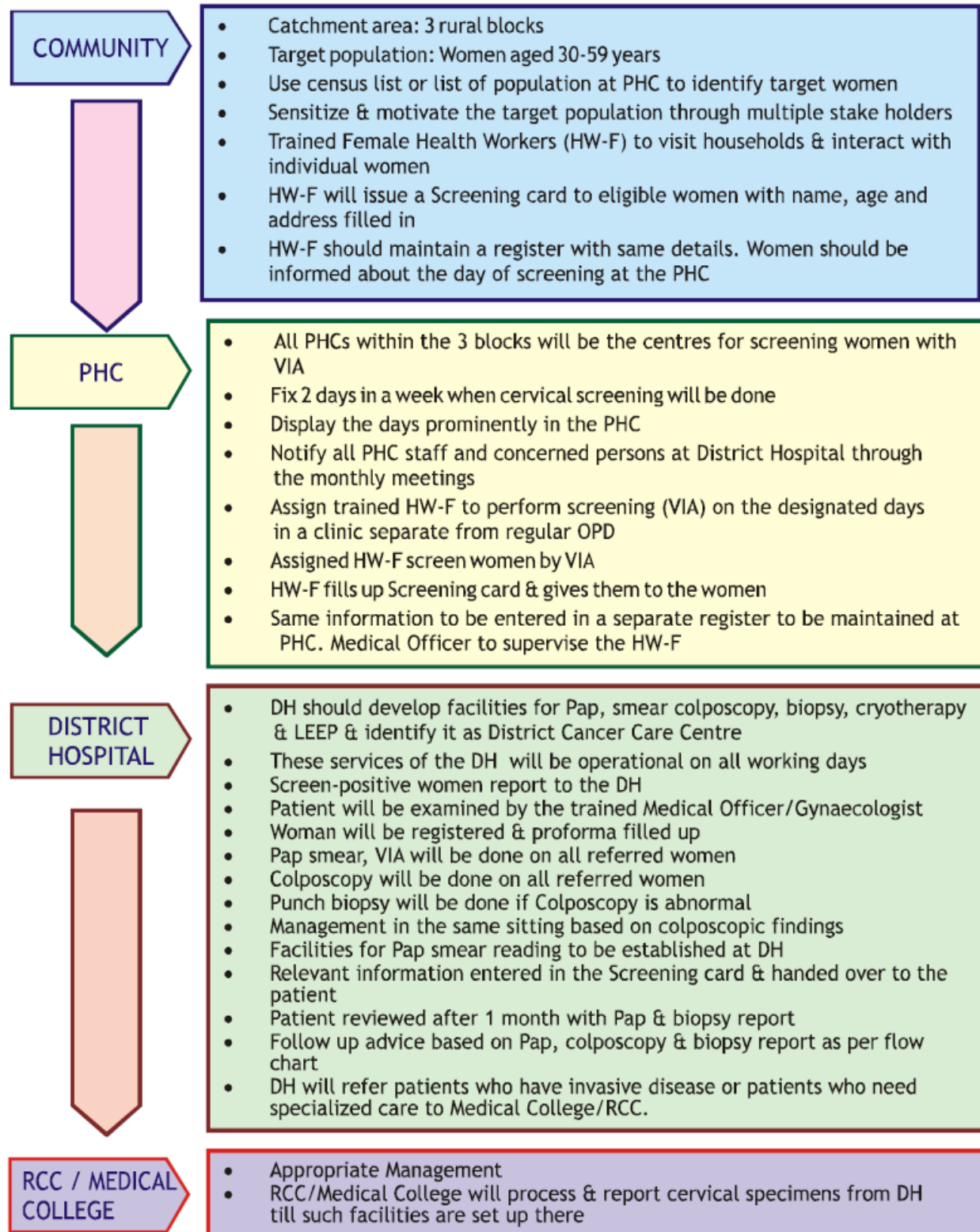
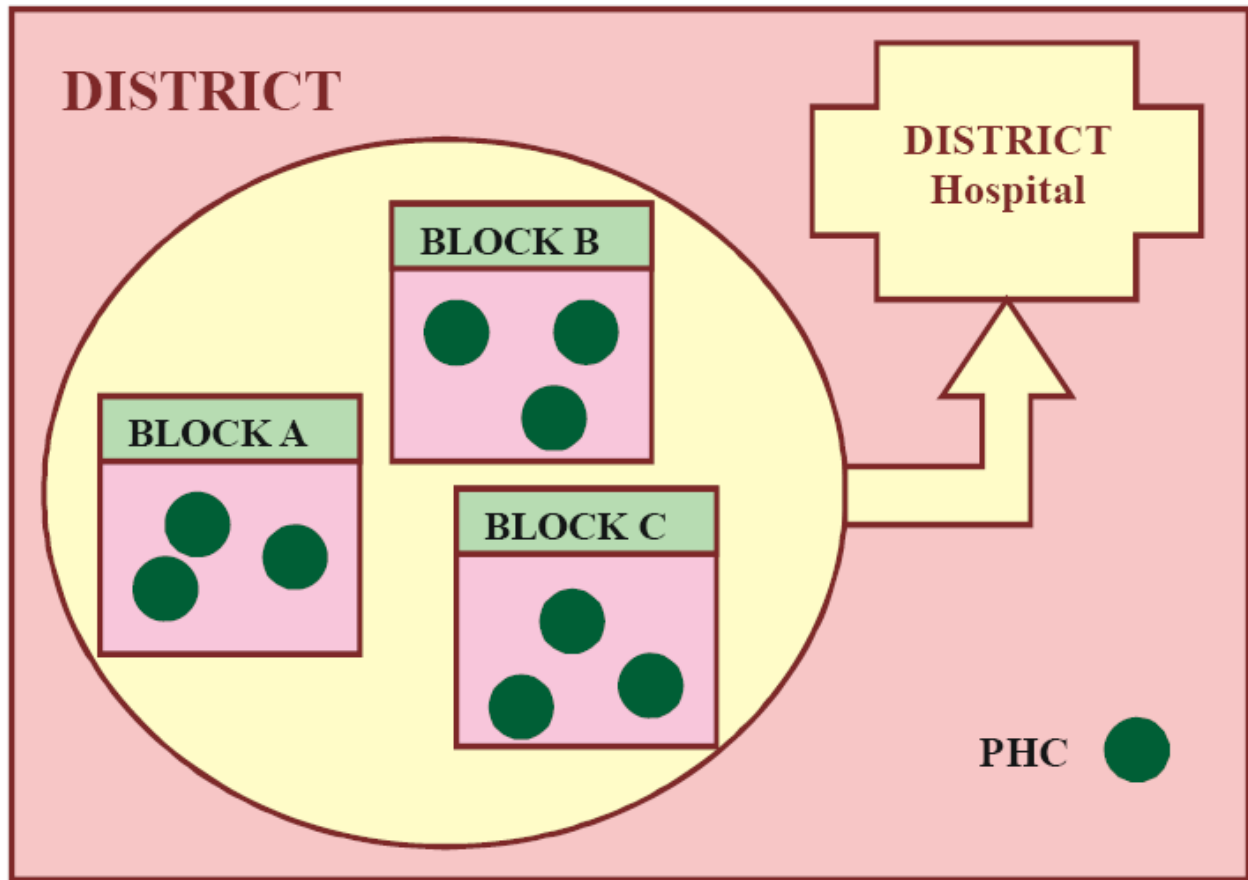


Figure 11: A model demonstration programme for the implementation of the cervical cancer screening guidelines, National Cancer Control Programme and WHO-India, 2006



Ongoing Cervical Cancer Research Programs in India

There are currently several cervical cancer research programmes in India. The National Cancer Registry Programme (NCRP), established by the Indian Council of Medical Research (ICMR) acts as a surveillance system for cancer in India. Under the NCRP, Population Based Cancer Registries (PBCRs) have been established at 19 locations (Mizoram, Sikkim, Imphal, Kamrup, Silchar, Dibrugarh, Bangalore, Chennai, Mumbai, Delhi, Bhopal, Ahmedabad, Nagpur, Kolkata, Aurangabad, Pune, Kollam, Thiruvananthapuram and Barshi) and Hospital Based Cancer Registries (HBCRs) have been initiated at Dibrugarh, Chandigarh, Thiruvananthapuram, Bangalore and Mumbai (ICMR, 2007). The PBCRs collect data on cancer incidence and mortality (ICMR, 2006). The HBCRs collect data on cancer patterns, and also gather information on patient care, treatment options, and assist in patient follow up (ICMR, 2007)

The registries collect data in an ‘active’ manner, visiting government and private sector hospitals, specialised cancer hospitals, and pathology laboratories to get information on the types and

magnitude of cancer cases. Death certificates are verified from the municipal corporation units. Standardised protocols are used for collecting and recording information, and the malignant neoplasms are coded in accordance with the International Classification of Diseases for Oncology (ICD-O). They also have a system of data quality and consistency checks. After analysis, the data is disseminated in the form of periodical reports, which are publicly available (ICMR, 2002).

Another ongoing cervical cancer research study in India is a clinical trial, being funded by the IARC, with the aim of assessing whether a two dose HPV vaccine would confer similar protection against the infection relative to a three dose vaccine (ClinicalTrials.gov). The estimated completion date has been given as May 2014.

In 2009, the Ministry of Health and Family Welfare launched a demonstration project for cervical cancer screening and vaccination in three blocks of the Vadodra district of Gujarat, in association with PATH (Program for Appropriate Technology in Health) and ICMR, one of the aims of which is to assess the feasibility of implementing large scale vaccination programmes in India (Indian Express, 14 August, 2009). As part of this demonstration project, girls aged 10-14 years will be vaccinated with the three dose HPV vaccine, and women 30 years and above will be screened for cervical cancer. It is yet unclear if this programme is going to be evaluated.

Cervical Cancer Policy in India

Policy and Programme for Cancer Control and Prevention

India has a National Cancer Control Programme (NCCP), established in 1975-76, and revised a decade later. There are 5 schemes under this programme, namely, the recognition of new Regional Cancer Centres (RCCs), the improvement of existing RCCs, development of oncology wings in government medical colleges and hospitals, the running of the District Cancer Control Programme, and the establishment of a decentralised NGO scheme under which NGOs are to be provided with grants for conducting IEC activities (National Cancer Control Programme). Despite this however, there is a substantial shortage of cancer treatment facilities in the country, which is further magnified by regional disparities (figure 12, NCCP Task Force Reports for XIth Plan, 2008).

In terms of palliative care, oral morphine has been made available for cancer patients in a number of states through modification rules implemented since 1991. However, even now morphine cannot be prescribed for pain among cancer patients in 21/28 states in India (NCCP Task Force Reports for XIth Plan, 2008).

Figure 12: The distribution of Regional Cancer Centres in India, as on August 31, 2005



Source: NCCP Task Force Reports for XIth Plan, 2008

Cervical cancer policy and programme

India doesn't have a specific national policy on cervical cancer control and prevention, and the NCCP doesn't have a specific cervical cancer component within it. There is no national screening programme in place [although national guidelines have been prepared (National Cancer Control Programme and WHO-India, 2006)]. At present screening for cervical cancer takes place in an opportunistic manner, with cytology based screening facilities being available mainly at the tertiary level, where women are screened only at the most advanced stages of cancer, or if they visit the tertiary hospitals for reproductive tract infections (Dabash et al, 2005). According to the 2003 WHO World Health Survey, only 2.6% of the Indian female population had ever been screened for cervical cancer in the past three years [WHO/ICO Information Centre on Human Papilloma Virus (HPV) and Cervical Cancer (a)]. Additionally, most of the tertiary level facilities do not have the diagnostic and treatment services that can be offered to women post screening, with management essentially consisting of follow up or a hysterectomy (Basu and Chowdhury, 2009).

Nevertheless, some progress has been made in the form of pilot projects of early detection and screening programmes (pap smears) for cervical cancer, set up by the WHO in conjunction with District hospitals, government hospitals and medical colleges in Hyderabad, Mizoram, Meghalaya and Tripura, which are now being integrated into the routine services of these hospitals (WHO, Country Office for India). Unfortunately these are not being evaluated. Early detection projects are also being administered by the Government of India through the family welfare programme, as well as through District Cancer Control Programmes, in 29 districts in the country. In addition, several state governments such as Tamil Nadu and Kerala have attempted to establish state wide screening programmes (NCCP Task Force Reports for XIth Plan, 2008). However most of these have not been

successful, as the primary problem has been an inability of the existing health system to deliver the services envisaged under these programmes, due to:

- 1) Gaps in health system management.
- 2) Shortage of cytologists and pathologists.
- 3) Lack of multi-sectoral integration.
- 4) Use of unsustainable technology.
- 5) Lack of integration with the primary health care system.
- 6) Inadequate and inequitable coverage.
- 7) Lack of a coordinating national strategy (NCCP Task Force Reports for XIth Plan, 2008).

Recently, a National Task Force was constituted for developing a “Strategy for Cancer Control in the 11th five year plan (2007-2011)”, which developed a report in March 2008, summarising the current scenario and developing a comprehensive cancer control strategy for the country (figure 13) (NCCP Task Force Reports for XIth Plan, 2008). The recommendations for cervical cancer are:

- 1) Opportunistic screening using sustainable and financially viable means.
- 2) Capacity building for early detection and diagnosis.
- 3) Development of infrastructure and human resources for appropriate treatment and regular follow up.
- 4) Provision of palliative care for advanced stage cancer across the country.

Regrettably, there are missing components in this strategy. Opportunistic screening has been recommended for India ignoring the fact that the improvements in cervical cancer incidence and mortality in the developed world are based on organised, nation wide screening campaigns. According to ACCP, every woman has the right to get screened for cervical cancer at least once in her life. Following a review of studies conducted in several developing countries including India, ACCP found that the optimal age for screening in low resource settings is between 30-40 years, as that has the greatest public health impact (Alliance for Cervical Cancer Prevention, 2007). The above strategy of screening at the age of 40, thus, is not evidence based, and is not likely to have enough impact at the population level. Additionally, although the strategy talks about following evidence based methods for treatment, national guidelines for the same have not been developed as yet. For both early detection and treatment to happen as envisaged by the above strategy, a scaling up of the current infrastructure and human resources will be necessary, for which political commitment and funding are essential. Lastly, palliative care through the provision of oral morphine might not be fully achievable within the timeframe of this strategy as this is yet to be legalised in more than 20 states of the country.

Figure 13: Summary matrix of the strategy envisaged by the NCCP Task Force for the XIth five year plan

Domain	Cancers	Objectives	Strategy	Agencies
Primary prevention	Tobacco related Cancers	Reduction in incidence of TRC	Tobacco control/cessation	NGOs, Local Govts, Schools etc
Screening	Cervix	Screen eligible women	One smear at the age of 40 yrs	Health services
Early detection	Oral/Breast/ Cervix	75% of cancers in early stages	OSE/BSE/CBE. Visual inspection Diagnostic support	Health services/ NGOs
Treatment	Common cancers	EBM without delay and prompt referrals	Training/ Guidelines/ Infrastructure	RCC Secondary level hosp (Private or public) Med Coll.
Palliative Care	All advanced cancers	Pain and symptom relief	Oral morphine availability Training	PHCs/ NGOs Community

Source: NCCP Task Force Reports for XIth Plan, 2008

The possibility of introducing a national HPV vaccination programme has also not been considered in the strategy, even though GlaxoSmithKline and Merck have both pledged to provide their vaccines to developing countries at lowered prices, and the GAVI has included the HPV vaccine in their Advanced Market Commitment plan (Basu and Chowdhury, 2009). Although in the short term, introducing the HPV vaccine as part of the cancer control programme doesn't seem to be financially feasible, in the long run, a pre-adolescent, 3 dose HPV vaccine programme, when combined with a single-visit screening strategy using VIA may be cost-effective, and may indeed reduce cervical cancer incidence and mortality in India (Basu and Chowdhury, 2009).

Gaps in Cervical Cancer Research Practice in India

- Assessment of HPV burden in men: Although there are some estimates of the burden of HPV infection among women in India, there is insufficient information on the same among men. Identifying the extent of HPV burden among men, as well as high risk groups among them, may prevent further spread of the infection within the population.
- Health systems research: More research is needed in the Indian context, to evaluate interventions for cervical cancer and assess their applicability, success, scalability and sustainability within the constraints of the Indian health care system.
- Longitudinal studies: More evidence is needed for the effectiveness of interventions and their systematic evaluation to assess their impact on reducing incidence of, and mortality from, cervical cancer, both in the short and long-term.

- Economic analysis: Although interventions and preventive strategies are available, their financial viability in a developing country like India is unclear. More studies are required to assess the cost-effectiveness of various interventions, so the most appropriate and feasible intervention strategies are implemented. In particular, research is needed to develop efficient and inexpensive HPV tests, and improved equipment for cryotherapy (Alliance for Cervical Cancer Prevention, 2007)
- Qualitative studies: More qualitative studies are required looking at the psycho-social and cultural barriers faced by women in different parts of the country when it comes to taking steps to avoid getting HPV infection, going for medical check ups, screening and following treatment plans.

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Appendix 1

FIGO staging of cervical carcinomas

Stage I

Stage I is carcinoma strictly confined to the cervix; extension to the uterine corpus should be disregarded. The diagnosis of both Stages IA1 and IA2 should be based on microscopic examination of removed tissue, preferably a cone, which must include the entire lesion.

- **Stage IA:** Invasive cancer identified only microscopically. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm.
 - Stage IA1: Measured invasion of the stroma no greater than 3 mm in depth and no wider than 7 mm diameter.
 - Stage IA2: Measured invasion of stroma greater than 3 mm but no greater than 5 mm in depth and no wider than 7 mm in diameter.
- **Stage IB:** Clinical lesions confined to the cervix or preclinical lesions greater than Stage IA. All gross lesions even with superficial invasion are Stage IB cancers.
 - Stage IB1: Clinical lesions no greater than 4 cm in size.
 - Stage IB2: Clinical lesions greater than 4 cm in size.

Stage II

Stage II is carcinoma that extends beyond the cervix, but does not extend into the pelvic wall. The carcinoma involves the vagina, but not as far as the lower third.

- **Stage IIA:** No obvious parametrial involvement. Involvement of up to the upper two-thirds of the vagina.
- **Stage IIB:** Obvious parametrial involvement, but not into the pelvic sidewall.

Stage III

Stage III is carcinoma that has extended into the pelvic sidewall. On rectal examination, there is no cancer-free space between the tumour and the pelvic sidewall. The tumour involves the lower third of the vagina. All cases with hydronephrosis or a non-functioning kidney are Stage III cancers.

- **Stage IIIA:** No extension into the pelvic sidewall but involvement of the lower third of the vagina.
- **Stage IIIB:** Extension into the pelvic sidewall or hydronephrosis or non-functioning kidney.

Stage IV

Stage IV is carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.

- **Stage IVA:** Spread of the tumour into adjacent pelvic organs.
- **Stage IVB:** Spread to distant organs.

Source: Sankaranarayanan and Ramani S. Wesley 2003; A practical manual on visual screening for cervical neoplasia, International Agency for Research on Cancer Technical Paper No. 41, WHO, IARC Press: Lyon. Original source: TNM Classification of malignant tumours. L. Sobin and Ch Wittekind (eds.), UICC International Union against Cancer, Geneva, Switzerland, pp155-157; 6th ed. 2002.