Prevalence of Carcinogenic Human Papilloma Virus Infection and Burden of Cervical Cancer Attributable to it in the District of Gampaha, Sri Lanka

Ministry of Health

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Prevalence of Carcinogenic Human Papilloma Virus Infection and Burden of Cervical Cancer Attributable to it in the District of Gamapaha, Sri Lanka

Authors

Dr. Deepa Gamage
Consultant Community Physician, Medical Epidemiologist,
Epidemiology Unit,
Ministry of Health,
Sri Lanka

Prof. Lalini Rajapaksa
Former Head and Professor in the Department of Community Medicine,
Faculty of Medicine,
University of Colombo,
Sri Lanka

Dr. M.R.N.Abeysinghe
Fromer Chief Epiddemiologist, EPI Manager,
Epidemiology Unit,
Ministry of Health,
Sri Lanka

Prof. Amala de Silva
Health Economist,
Professor in the Department of Economics,
University of Colombo,
Sri Lanka

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and
The Epidemiology Unit, Ministry of Health, Sri Lanka

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List of Abbreviations and Acronyms

CI	Confidence Interval
CIN	Carcinoma In Situ
DNA	Deoxyribonucleic Acid
ERBT	External Beam Radiotherapy
FHB	Family Health Bureau
HDR	High Dose Rate Brachytherapy
HPV	Human Papilloma Virus
IARC	International Agency for Research on Cancer
ICR	Intracavitary Brachytherapy
IEC	Information Education and Communication
ISCO	International Standard Classification of Occupation
LRT	Ligation and Resection of Tubes
NCCP	National Cancer Control Programme
OR	Odds Ratio
Pap	Papanicolaou
PAR	Population Attributable Risk
PCR	Polymerase Chain Reaction
RR	Relative Risk
VIA	Visual Impact with Acetic Acid and Naked Eye
VILI	Visual Inspection with Lugol's Iodine

Executive Summary

Globally, cervical cancer is the second commonest cause of cancer deaths in women and in developing countries it is the leading cause of female cancer mortality. In Sri Lanka, it is the second most common cancer among women. Nearly 850 women die each year and approximately 7.74 million women constitute the group at risk.

Research has identified genital infection with Human Papilloma Virus (HPV) as the major aetiological factor for developing cervical cancers in almost all countries (World Health Organization, 2005) and genotype 16 and 18 together accounts for 70% of the attributable risk in the aetiology of cervical cancer (Harper et al., 2004). Sexual behaviour is the main factor associated with high rates of acquisition of HPV infection among sexually active women (Harper et al 2004; Munoz et al., 2003).

Until recently, the mainstay in prevention of cervical cancer has been the early detection of cervical cell abnormalities and the prevention of progression into life threatening malignant stages. The Papanicolaou smear test is the most commonly used screening test although several other low cost methods have been described. A community based cervical cancer screening programme using the Papanicolaou smear test was initiated in Sri Lanka in 1996. However, only about 5% of the target group between 35-60 years has been screened up to 2005. This has led to continuing high hospital admission rates for cervical malignancies in advanced stages. The National Cancer Control Program has identified that three fourth of hospital admissions are advanced invasive types above stage 2 of cervical cancer categorization, where cost of patient management is high.

The availability of a vaccine against HPV provides much promise for primary prevention of cervical cancer in the future. In considering the use of vaccination as a strategy for the prevention of cervical cancer, knowledge on the population prevalence of HPV infection among married women with normal cervical cytology, the most prevalent carcinogenic genotypes and their aetiological contribution to cervical cancer in the Sri Lankan population is essential. Furthermore, the cost of the different options available for prevention and treatment of the different stages of cervical cancer needs to be compared. Thus, the present study was designed with the objective of determining the prevalence of carcinogenic HPV infection and its determinants among ever married women between 20-59 years of age in a district in Sri Lanka. It also aimed to estimate the proportion of cervical cancer attributable to HPV infection, to estimate the unit cost incurred by the government in screening for the precancerous stages of cervical cancer and the unit cost incurred in treatment of the different stages of cervical cancer at the Cancer Institute, Maharagama.

The study consisted of four components; a community based descriptive cross sectional study, a case control study, a clinic based cost estimation study of screening and a hospital based cost estimation of treatment of the different stages of cervical cancer.

Community based descriptive study

The present study was carried was carried out in the Gampaha district, which is one of the three districts constituting the Western Province of Sri Lanka. The district has a heterogeneous mix of ethnic, religious and socio-economic groups. The population of the district is mostly rural (85.4%). There is a negligible (0.04%) proportion classified as estate population who are very similar in characteristics to the rural population and have been considered together in the present study. Ever married women 20-59 years of age, resident within the district continuously for at least three months prior to the date of the survey were considered as the study population.

A total of 2000 study subjects were selected using a multistage stratified cluster sampling technique for the community based descriptive cross sectional study. Hundred clusters comprising 20 subjects each were selected by probability proportionate to size of the population in “Grama Niladhari” divisions. Eligible women were recruited with their consent and in each cluster women were selected to represent the population proportion of married women in each ten year age groups.

Information on socio demographic, socio economic, reproductive health and sexual health related factors relevant to HPV infection was collected using an interviewer administered questionnaire. Cervical swab specimens for HPV DNA detection and Papaniculoau specimens for detection of cervical cytology were collected from all study participants.

HPV DNA detection was carried out by the PCR method using GP5+/GP6+ primer system. Cytological examination was carried out by trained cytoscreeners. The repeatability of all instruments and tests used in the study were examined prior to the study and all field procedures were closely supervised to ensure quality of data collected. Participation rate in the study was high (99.5%).

The study revealed that the overall prevalence of cervico vaginal HPV infection among clinically normal women was 3.3% (95% CI 3.15-3.44). HPV prevalence among women with normal cytology was 3.1% (95% CI,2.96-3.24) and the prevalence of highly carcinogenic genotypes 16 and 18 was 1.20 % (95% CI 1.15-1.25).

The prevalence of HPV was highest in the 20-29 age group. It was seen to decreas with advancing age butwith a second peak among the 50-59 year age group. Lower level of education, being employed, lower income and lower social class were seen to be significantly associated with higher prevalence of HPV infection. High prevalence rates were observed with high parity and also among women who have never been pregnant, but this difference was not statistically significant.

Young age (≤19 years) at first sexual exposure, current or life time multiple sex partners, exposure to forced sex, multiple sex partners of the husband were associated with higher prevalence of HPV and were statistically significant in the univariate analysis.

In the Logistic regression analysis, lower income levels (OR=2.15,CI 1.22-3.76), experience of forced sex (OR=5.61,95% CI 1.91-16.48) and multiple sex partners of the husband (OR1.29, 95%CI 1.16-4.53) were found to have a statistically significant association with HPV infection.

Study showed that promiscuity was low in the community (only 6% reporting multiple sex partners). It was seen that coverage of the cervical cancer screening programme was low (6.7%).

Case control study

This component was planned to quantify the risk association of HPV infection with cervical cancer. A case control study was carried out among 40 newly diagnosed cervical cancer patients living in the Gampaha district and presenting to the Cancer Institute, Maharagama. Four controls per case were randomly selected from the same Grama Niladari area as the case, matched within 10 year age groups. The selected controls were examined to ascertain their cervical cancer status. None of the selected controls had abnormal cervical cytology.

Information on socio demographic, economic, reproductive health and sexual behaviour characteristics which are reported in the literature to be associated with cervical cancer, was collected using an interviewer administered questionnaire. Cervical swab specimens were collected to determine the HPV infection status.

The risk of cervical cancer associated with HPV infection was high (OR=102.67, 95%CI 29.84-302.20) and the risk estimated for vaccine preventable genotypes 16 and 18 was 134.31 (95% CI 35.00-598.31)

Young age (<19 years) at first vaginal sex (OR=3.22, 95% CI 1.49- 6.99), extramarital sexual exposures (OR=8.08 95% CI 2.98-22.22), multiple partners (≥2 partners) (OR=12 95% CI 4.55-34.59) and extramarital sex exposures of the husband (OR=4.35, 95% CI 1.48-12.85) were associated with increased risk of cervical cancer. High parity, lower age at first pregnancy, time since last delivery, were also seen to be significantly associated with cervical cancer in the univariate analysis.

HPV infection (OR 172.31, 95% CI 34.63-857.31), being employed (OR=7.64 95% CI 1.52-38.37), time since last delivery (OR=9.08, 95% CI 1.76-46.67) and extra marital sexual exposures (OR=32.37, 95% CI 4.61-227.00) remained significant in the multivariate analysis. The adjusted odds ratio of cervical cancer associated with HPV infection was 172.31 (95% CI 34.63-857.31) while the adjusted odds ratio for vaccine preventable genotypes 16 and 18 was 190.30 (95% CI 36.54-991.03).

The population attributable risk of cervico-vaginal HPV infection (all types), in the development of cervical cancer was 85% and for genotype 16 and 18 the population attributable risk was 69%.

Cost estimation of cervical cancer screening

Component three of the study estimated the unit cost incurred by the government in the cervical cancer screening programme. This was estimated to be Rs.308.18. The minimum number of women needed to be screened for the detection of one cervical cancer was 1,739, and the estimated cost was Rs. 535,925.02. Prevention of one cervical cancer attributed to HPV type 16 and 18 (through vaccination) requires the vaccination of a minimum of 2,521 women.

Cost of management of cervical cancer

A hospital based study for estimating the unit cost incurred by the government in cervical cancer management was carried out at the Cancer Institute, Maharagama, Sri Lanka

Cervical cancer stages and the treatment protocols as decided by the Consultant Oncologist is given below:

- Stage 1a, 1b, 11a treatment is radical hysterectomy (Werthime's hysterectomy)
- Stage 11b, 111a, 111b IVa, IVb,Chemoradiation Cisplatin 40mg weekly for 5 weeks + EBRT(External Beam Radiotherapy/teletherapy) 25 doses to all patients and optional ICR (brachytherapy)/2 doses or HDR (High Dose Rate Brachytherapy) one dose for selected patients.

According to the Consultant Oncologist, chemotherapy would not be prescribed to some patients, depending on the clinical situation. However, the standard treatment protocol, given above was used for the cost estimation procedure.

Information was collected in consultation with relevant authorities in the hospital, Ministry of Health, Biomedical Engineering Division, Medical Supplies Division, Radiation Protection Authority and relevant equipment companies and suppliers.

The ward cost for a patient day, cost of a radical hysterectomy, cost of 25 doses of chemoradiation and the cost of external beam radiotherapy were calculated.

The total cost of management of a case of cervical cancer stages 1a, 1b, and 11a was estimated to be Rs. 13,668.50. The total cost of treatment of an advanced case of cervical cancer (stages 11b, 111a, 111b, 1Va, 1Vb) was estimated to be Rs. 23,341.76.

Taking into consideration the costs of human suffering as well as cost of treatment, it is imperative that cervical cancer be prevented. The study highlights that at current levels of HPV infection and cost of the vaccine, screening remains the feasible option for prevention of cervical cancer in Sri Lanka. It is important to note that even if a vaccination programme is commenced, screening will have to be continued for the current cohort of women above the age for vaccination. Thus, strengthening of cervical cancer screening programme to increase coverage is of great importance.

1. Introduction

1.1 Global situation

Globally, cervical cancer is the second commonest cause of cancer deaths among women. World Health Organization has documented that in the year 2006, 1.4 million women were suffering from cervical cancer and that around 450,000 new cases are identified around the world annually. Of this, 239,000 women die and, approximately 80% of the deaths are in women from developing countries. Thus, cervical cancer is the leading cause of cancer mortality among women in developing countries (World Health Organization, 2005). Sexually active females above 15 years of age constitute the population at risk of developing cervical cancer. Research in to the aetiology of the condition has identified genital infection with Human Papilloma Virus (HPV) as the major aetiological factor for developing cervical cancers in almost all countries (World Health Organization, 2005).

Sexual behaviour is the main factor associated with high rates of acquisition of HPV infection among sexually active women (Harper et al.,2004; Munoz et al.,2003). Multiple sex partners or having a sex partner with multiple sex exposures are identified as high risk factors. In addition, age is an important determinant of the risk of HPV infection. Infection is more common in sexually active young women of 18-30 years and a reduction in acquisition of infection is observed after 30 years. Life time acquisition rate among sexually active women is observed to be 75 percent with a majority identified in young ages (Adam et al.2000; Molano et al., 2002). A population based follow up study, with mean duration of observation of 17.6 months, reported the rate of acquiring new infection as 2.9% per month in some areas in the United States of America(Giuliano et al., 2002). Another study among sexually active young female university students in New Jersey identified acumulative incidence of 43%at the end of a three year follow up period (Ho et al., 1998).Acquisition of genital HPV infection alone is not an adequate cause for cervical cancer. Many studies have described persistence of infection as a pre-requisite for the development of malignancy (Mandel et al., 2005, Harper et al., 2004).

Worldwide differences are observed in prevalence rates of HPV among women at risk. General population prevalence rates ranging from 6%–46% have been reported from different countries (Harper et al., 2004; Munoz et al., 2003). The International Agency for Research on Cancer reported an overall worldwide prevalence of 10.5% (95% CI 9.9-11) among 15-74 year age group during the period 1993-2003 (Clifford et al.,2005), while a similar study in South America reported a prevalence of 14.3% among women at risk (Clifford et al., 2005). A pooled analysis of recent research carried out by the World Health Organisation, describes a prevalence of 6.6% (CI 6.2-6.9) for the South Asia region (World Health Organization, 2008). The different prevalence rates are described to be closely related to the corresponding risk of cervical cancer relevant to the region.

More than 100 HPV genotypes have been identified and approximately 30 different types are sexually transmitted (Fields et al., 1996). These are broadly divided into carcinogenic and non carcinogenic genotypes, of which 10-15 carcinogenic genotypes are causally associated with cervical cancer (Shiffman et al.,2000). Based on the level of risk associated with developing cervical cancer, carcinogenic genotypes are classified as “high risk” and non-carcinogenic genotypes as “low risk” (Munoz et al., 2003). HPV genotypes 16,18,31,33,35,39,45,51,52,56,58 and 73 are mainly considered as high risk types and HPV genotypes 6,11,42,43,44,54,61,72 and 81 are mainly considered as low risk genotypes. Genital tract infections with low risk types are associated with the development of non-cancerous growths.

In sexually active females, genotype 16 and 18 together accounted for 70% of the attributable risk in the aetiology of cervical cancer (Harper et al., 2004). Ostor(1993), conducted a pooled analysis of studies published from 1950-1993 and identified the progression probabilities of pre malignant stages to invasive cervical cancer. He reported that one percent of CIN 1, 1.5% and 12% from CIN 2 and CIN 3 respectively, will progress into invasive cervical cancer with time.

Measures for early detection and successful interventions of screen detected cervical cell abnormalities ensure prevention of progression into life threatening malignant stages. Papanicolaou smear test remains the ideal screening test applicable to large populations with limited resources and is the most widely used test. Other methods of screening such as VIA (Visual Impact with Acetic acid and naked eye), VILI (Visual Inspection with Lugol'sIodine) and colposcopy are alternative low cost methods introduced in screening programmes in some countries (Sellors and Sankaranarayanan,2003).

The development of a new vaccine against HPV provides much promise for primary prevention of cervical cancer in the future. The HPV vaccine consists of a genetically engineered non-infectious virus like particle with capsid protein, which resembles HPV. Initial consideration is towards development of a prophylactic vaccine (cervical cancer, 2006) recommended for HPV naive young women (World Health Organization, 2005).

Two types of prophylactic HPV vaccines, namely;a quadrivalent vaccine consisting of a mixture of four genotypes of HPV specific virus like particles prepared from L1 protein of HPV genotypes 6,11,16, and 18 and a bivalent vaccine consisting of a mixture of two HPV type specific virus like particles prepared from L1 protein of HPV genotypes 16 and 18 are currently available. The development of these vaccines was based on the most prevalent carcinogenic HPV genotypes identified through research studies in developed and developing countries. Both vaccines protect against HPV genotypes 16 and 18 which are responsible for approximately 70% of cervical cancers globally (World Health Organization,2006;Villa et al.,2005).

1.2 Sri Lankan situation

Cervical cancer is identified as the second most common cancer among women in Sri Lanka and approximately 7.74 million women are included in the risk category. It is reported that nearly 850 die from cervical cancer each year. The absence of a population based cancer registry has resulted in the unavailability of a population based incident rate. Based on admissions to government hospitals in the country, the National Cancer Control Programme (NCCP) reported 544 women diagnosed with cervical cancer in 2005 accounting for 2.6% of the total cancer notifications. This constitutes a hospital based incidence of 16.4 per 100,000 women. This is compatible with the estimated world incidence rate (16/100,000) but is lower than the estimated incidence rate for South Asia (21.5/100,000) (Sankaranarayan et al., 2008).

In accordance with the concept of reproductive health promotion articulated during the International Conference on Population and Development in Cairo, 1994, screening for cervical cancer cytology was included in the Reproductive Health policy of the Ministry of Health and a screening programme using the Papanicolaou smear test was initiated at community level in 1996. The services are provided in each Medical Officer of Health area through Well Women Clinics (Family Health Bureau, 2003). National guidelines that describe the community level cervical cancer screening and follow up procedure are available. However, many gaps and deficiencies have been identified in the implementation of the programme and only about 5% of the target group between 35-60 years has been screened upto 2005. The failure of the programme has been

attributed to a variety of reasons such as inadequate resources, lack of commitment of field staff, insufficient laboratory facilities, and other logistic problems. In addition, inequity in distribution of services in remote areas has also contributed to the low coverage. In an effort to improve the programme a new target of screening 70% of women between 35-40 years by 2010 has been set (Family Health Bureau, 2006).

Limited coverage of cervical cancer screening, cultural barriers for detection such as reluctance of women to seek help for gynaecological morbidities have resulted in continuing high hospital admission rates for cervical malignancies in advanced stages. The NCCP has identified that three fourth of hospital admissions are advanced invasive types above stage 2 of cervical cancer categorization. This has resulted in the Government having to bear the increased cost of managing late stages of cervical cancer in addition to the cost of screening and management of screen detected early stages of cervical cancers.

Given this scenario, vaccination offers a new hope and an option for the control of cervical cancer in the country. In Sri Lanka the vaccination programmes implemented through the primary health care staff have been very successful and community acceptance of vaccination is very high. This is evident by the high coverage for expanded programme on immunization vaccines and the ready acceptance of new vaccines whenever they are introduced in to the programme.

In considering the use of vaccination as a strategy for the prevention of cervical cancer, knowledge on the population prevalence of HPV infection among married women with normal cervical cytology, the most prevalent carcinogenic genotypes and their aetiological contribution to cervical cancer in our population is essential. However, data on HPV prevalence among the Sri Lankan general population is not available. Such data would also serve as a baseline for monitoring the vaccination programme if it is introduced. Furthermore, the cost of the different options available for prevention of cervical cancer needs to be compared. As such, information on the unit cost of detection and management of early stages of cervical cancer is important. The present study was planned to provide some of the information necessary for planning an optimal cervical cancer prevention programme.

1.3 Objectives

The current study was planned with the objective of identifying the community prevalence, the prevalence of the different genotypes, and identifying cervical cancer risk attributable to HPV infection in a defined Sri Lankan population. In addition,studies were planned to estimate the unit cost of a Papanicolaou smear test within the national cervical cancer screening programme carried out through Well Women's Clinics. The unit cost incurred by the government in the management of newly diagnosed cases of cervical cancer at the Cancer Institute, Maharagama, was estimated separately for the different stages of the disease.

The research study comprised of four components;

Component 1	Community based descriptive cross sectional study, to assess the prevalence of HPV among married women 20-59 years of age and to describe some epidemiological features of HPV infection.
Component 2	Hospital based case control study to determine the aetiologic fraction of cervical cancer attributable to HPV infection
Component 3	Clinic based study to estimate the cost incurred by the government in population screening for cervical cancer
Component 4	Hospital based study to estimate the cost incurred by the government in cervical cancer management for the different stages of disease.

2. Community based descriptive study

The community based descriptive cross sectional study to determine the prevalence and selected epidemiological features of cervical HPV infection was carried out among married women in the Gampaha district, which is one of the three districts constituting the Western Province of Sri Lanka.The district has a heterogeneous mix of ethnic, religious and socio-economic groups. The population of the district is mostly rural (85.4%), the urban population being 14.6%. There is a negligible (0.04%) proportion classified as estate population, who live on coconut estates in the area and are very similar in characteristics to the rural population unlike the estate populations in the tea growing areas of the country. In the present study the rural and estate sectors are considered together.

2.1 Methods

The Gampaha district was selected for study taking in to consideration the urban rural population proportions, age structure and sex ratios of this district and heterogeneous mix of ethnic, religious and socio economic conditions of the district. Ever married women 20-59 years of age resident within the district continuously for at least three months prior to the date of the survey, were considered as the study population.

The sample size was calculated according to the standard formula for descriptive, cross sectional studies (Lwanga & Lemeshow, 1991). The expected population proportion of HPV infection was taken as 6.6% (World Health Organization, 2008). A design effect of 2 was considered since cluster sampling was planned. Thus the final sample size was taken as 2000. The 2000 study units needed were identified using a multistage stratified cluster sampling technique. The primary sampling unit was a Grama Niladhari division. A cluster consisted of 20 eligible women. Clusters were allocated to urban and rural areas based on the population proportion and the primary sampling units selected probability proportionate to size of the population. In each cluster women were recruited to represent the population proportion of married women in each ten year age groups.

The sampled women who consented to participate were invited to attend the closest Well Women's clinic. Information on socio demographic, socio economic, reproductive health and sexual health related factors relevant to HPV infection was collected using an interviewer administered questionnaire. Cervical swab specimens for detection of HPV DNA and Papanicolaou smears for cervical cytology were collected.The repeatability of all instruments and tests used in the study were examined prior to the study and all field procedures were closely supervised to ensure the quality of data collected. Participation rate in the study was high (99.5%).

HPV-DNA detection by PCR amplification was the most commonly used method at the time of the present research study and was considered a sensitive method for the detection of cervico-vaginal HPV infections in a research setting (Karlsen et al.,1996). This was also the only method available within Sri Lanka and was carried out only at the Genetech laboratory, Colombo, at the time of the study. GP-PCR primer set for detection of HPV types was considered as the most robust and effective method in screening a healthy general populations.(Karlsen et al., 1996). In the current study PCR using the primer GP5+/GP6+ was used to amplify L1 regions of HPV genome. This method was compared with the more sensitive short PCR fragment primer (SPF) method in a sub sample of 50 specimens. The GP5+/GP6+ primer system was found to be 100%

sensitive and specific. Geno typing (DNA sequencing) was carried out in the Eton Bioscience Laboratory, United States of America. (Eton Bioscience North Carolina Branch, Inc. 104 T.W. Alexander Drive Bldg 7 Research Triangle Park, NC 27709, USA)

Cytological examination of the Papanicolaou smear specimens were carried out at the reference laboratory at the FHB, Ministry of Health, Colombo, Sri Lanka. Ten participants from ten different clusters initially selected for the study declined to participate. Clusters were extended to replace those who refused so that the final sample studied was 2000. The socio-demographic characteristics of this ten were similar to that of the participants.

2.2 Results

The study estimated that the overall prevalence of cervico vaginal HPV infection among clinically normal women* was 3.3% (95% CI 3.2-3.4). Cervico vaginal HPV prevalence among women with normal cytology** was 3.1% (95% CI 2.9-3.2) and the prevalence of highly carcinogenic genotypes 16 and 18 in clinically normal women was 1.2% (95% CI 1.1-1.3). 3Human Papilloma Virus genotypes detected in the study sample are described in table 1.

*without any signs and symptoms of cervical cancer

**without any cytological abnormality detected by Papanicolaou smear examination

Table 1: HPV genotypes detected in the HPV positive specimens

HPV Genotype	Number	Percent %
16	22	38.6
18	2	3.5
31	1	1.8
33	1	1.8
35	2	3.5
42	7	12.2
45	1	1.8
51	1	1.8
56	4	7.0
62	5	8.7
66	4	7.0
73	2	3.5
81	2	3.5
83	1	1.8
87	2	3.5
Total	**57***	**100**

*successful sequencing was carried out in 57 positive specimens

High risk genotypes 16,and 18 were detected in 42% among HPV-DNA positive sequences.

Table 2 describes the prevalence of HPV infections by selected socio-demographic characteristics.

Table 2: Distribution of HPV infection status by basic socio demographic characteristics

Characteristics	HPV status						
	Positive		Negative		Total		Significance OR&(95%CI)
	No.	%	No.	%	No.	%	
Age in years							
20 – 29[a1]	25	3.6	676	96.4	701	100.0	χ^2 =0.08**
30 – 39[a2]	17	3.2	521	96.8	538	100.0	df=1,p=0.77
(r) 40 – 49[b1]	12	2.7	427	97.3	439	100.0	OR=1.08 (0.63–1.85)
50 – 59[b2]	12	3.7	310	96.3	322	100.0	
Sector							
Urban	15	5.0	285	95.0	300	100.0	χ^2 =3.2
(r) Rural	51	3.0	1649	97.0	1700	100.0	df=1, p=0.07,
							OR=1.70 (0.90–3.16)
Ethnicity							
(r) Sinhalese	60	3.1	1851	96.9	1911	100.0	χ^2 =2.4**
Tamil[a1]	5	14.7	29	85.3	34	100.0	df=1
Moor[a2]	1	1.9	51	98.1	52	100.0	p=0.11,
Other[a3]	0	0.0	3	100.0	3	100.0	OR=2.23 (0.76–5.35)
Total	**66**	**3.3**	**1934**	**96.7**	**2000**	**100.0**	

** Yates corrected test and exact confidence limits for 95% were applied,
a1,a2,a3 and b1, b2 were amalgamated separately for chi-square test & odds ratio calculation, (r) = reference

The prevalence of HPV was highest in the 20-29 year age group, decreasing with age and a second peak occurring in the 50-59 year age group. Higher prevalence was seen among the urban population. The increased prevalence among the Tamil population has to be interpreted with caution due to the small numbers. The study identified that only 7% of the women above 35 years included in the sample had ever undergone cervical screening through the national cervical cancer screening programme.

HPV prevalence status by category of cytological abnormality detected by Papanicolaou smear is given in table 3.

Table 3: Distribution of HPV status by current Papanicolaou smear result

Present Papanicolaousmear result	Status of HPV						
	Positive		Negative		Total		Significance OR & (95%CI)
	No.	%	No.	%	No.	%	
Normal	59	3.1	1874	96.9	1933	100.0	
CIN – I[a1]	2	16.7	10	83.3	12	100.0	
CIN – II[a2]	1	50.0	1	50.0	2	100.0	
CIN - III[a3]	0	0.0	0	0.0	0	0.0	χ^2 =8.9
Cervical malig-nancy[a4]	0	0.0	1	100.0	1	100.0	df=1, p=0.002,

Infective/ Inflammatory changes[a5]	3	7.7	36	92.3	39	100.0	*OR=3.71 (1.37–8.59)*
Endometrial cells above 40 years[a6]	1	7.7	12	92.3	13	100.0	
Total	**66**	**3.3**	**1934**	**96.7**	**2000**	**100.0**	

* Yates correction was applied [a1- a6] were amalgamated for chi-square test(r) = reference

Low level of education (<9 grade), low average monthly income (≤Rs. 10,000.00) and low social classes (social classesVa and Vb, according to International Standard Classification of Occupation, ISCO, 88) were seen to be significantly associated with ahigher prevalence of HPV infection. High prevalence rates were observed also among employed women, women with high parity, young age at first pregnancy, and among nulliparous women, but the differences observed were not statistically significant. The highest HPV prevalence (3.4%) was seen among women who had never used a condom during the year preceding the survey.

Young age (≤19 years) at first sexual exposure, current or life time multiple sex partners, exposure to forced sex(rape), multiple sex partners of the husband as reported by the woman, were associated with higher prevalence of HPV and were statistically significant in the univariate analysis.

In the Logistic regression analysis, lower income levels (average monthly income ≤10,000.00) (OR=2.15,CI1.22-3.76), experience of forced sex (rape)(OR=5.61,95% CI 1.91-16.48) and multiple sex partners of the husband as reported by the wife (OR1.29, 95%CI 1.16-4.53) were found to have a statistically significant association with HPV infection. Study also showed that promiscuity was low in the community (only 6% reporting multiple sex partners) but it is highly likely that there is under reporting of this behaviour.

Study showed that promiscuity was low in the community (only 6% reporting multiple sex partners). It was seen that coverage of the cervical cancer screening programme was low (6.7%).

2.3 Estimates of number needed to be screened

The Papanicolaou smear examinations carried out as part of the study detected 1 invasive cervical cancer, 12 cases of CIN 1 and 2 cases of CIN 2 in (table 3).

According to Ostor(1993) 1% of CIN 1, 1.5% and 12% from CIN 2 and CIN 3 respectively will progress into invasive cervical cancer with time. Applying these proportions to the present study, progression of CIN 1and CIN 2 to invasive cervical cancer will be as follows;

- CIN 1 12 x 1/100 = 0.12 invasive cervical cancer/2000 women screened
- CIN 2 2 x 1.5/100 = 0.03 invasive cervical cancer/2000 women screened

Total contribution of precancerous stages to invasive cervical cancer =0.15/2,000 women screened.One invasive cervical cancer case was detected in the study.Total invasive cervical cancer detected at Papanicolaou smear screening is equivalent to 1.15/2,000 women screened. Based on the above it is estimated that the total number of women needed to be screened in order to prevent a single cervical cancer is 1,739.

3. Hospital based case control study

3.1 Methods

A case control study was carried out to assess the risk of cervical cancer that could be attributed to HPV infection. It was decided to use 4 controls per case and the sample size necessary to detect an odds ratio of six when the prevalence of exposure among controls is taken as 6%, was calculated using the standard formula for multiple controls per case (Schlesselman,1982). Based on the sample size calculation it was necessary to recruit 40 cases and 160 controls. Forty consecutive newly diagnosed cases of cervical cancer presenting to the Cancer Institute, Maharagama among women living in the Gampaha district were selected for study. Four controls per case were randomly selected from the same Grama Niladhari area as the participant matched within the 10 year age groups. The selected controls were examined to ascertain their cervical cancer status. None of the selected controls had abnormal cervical cytology.

Basic socio demographic, socio economic reproductive health and sexual behaviour information which are reported in the literature to be associated with cervical cancer was collected using an interviewer administered questionnaire. Cervical swab specimens from all study participants were collected to determine the HPV infection status by HPV-DNA detection.

3.2 Results

Table 4 shows the distribution of HPV infection among cases and controls.

Table 4: Distribution of cases and controls by HPV infection status

Characteristic	Study group				
	Case		Control		Significance OR&(95%CI)
	No.	%	No.	%	
Status of HPV					
Positive	32	80.0	6	3.8	χ^2 =116.6
(E_0) Negative	8	20.0	154	96.2	df=1, p<0.001, OR=102.67 (29.84–302.20)
Total	**40**	**100.0**	**160**	**100.0**	

(E_0) non exposure

Thirty two of the forty cervical cancer patients (80%) and six (3.75%) among the controls were detected to have HPV infection (table 4). The odds of cervical cancer associated with HPV infection was high (OR=102.7, 95% CI 29.8-302.2). The confidence limits are very wide probably because of the small numbers with the exposure in the control group.

HPV positive specimens were sequenced and the genotypes are described in the table 5.

Table 5: Distribution of cases and controls by HPV genotypes

Study group					
HPV genotype	Case		Control		Phylogenetic categorization of the genotype
	No.	%	No.	%	
Type 16	29	90.6	4	66.7	High risk type for cervical cancer
Type 18	2	6.3	0	0.0	High risk type for cervical cancer
Type 31	1	3.1	0	0.0	High risk type for cervical cancer
Type 42	0	0.0	2	33.3	Low risk type for cervical cancer
Total	**32**	**100.0**	**6**	**100.0**	

Of the 40 cervical cancer patients studied, all 32 HPV positives had high risk genotypes. Among the 160 controls only 4 (2.5%) were in the high risk group.

3.3 Other risk factors

Univariate analysis of other risk factors for cervical cancer are presented in tables 6 to 7.

Table 6: Comparison of selected socio economic variables between cases and controls

Study group					
Characteristic	Case		Control		Significance
	No.	%	No.	%	OR&(95%CI)
Level of education					
No schooling[a1]	1	2.5	3	1.9	χ^2 =8.4
Grade 1 – 5[a2]	13	32.5	14	8.7	*df=1, p=0.003*
Grade 6 – 8[a3]	15	37.5	58	36.2	
(E_0) Grade 9 – GCEO/L completed[b1]					
	8	20.0	62	38.8	*OR=2.99 (1.32–6.87)*
GCE A/L completed[b2]	2	5.0	20	12.5	
University or Higher[b3]	1	2.5	3	1.9	
Average monthly income (Rs)					
<5000[a1]	1	2.5	1	0.6	χ^2 =8.8
5001–10,000[a2]	10	25.0	16	10.0	*df=1, p=0.002*
10,001–15,000[a3]	17	42.5	53	33.1	*OR=3.00 (1.35–6.77)*
(E_0) 15,001–20,000[b1]	9	22.5	67	41.9	
20,001–25,000[b2]	3	7.5	10	6.3	
>25,0001[b3]	0	0.0	13	8.1	
Level of social class**					
(E_0) Class – 1[a1]	2	5.0	6	3.8	χ^2 =5.1
Class–II[a2]	2	5.0	9	5.6	*df=1, p=0.02*
Class–III[a3]	5	12.5	52	32.5	*OR=2.48(1.05–6.03)*
Class–IV[b1]	14	35.0	46	28.8	
Class–Va[b2]	13	32.5	21	13.1	
Class–Vb[b3]	4	10.0	26	16.2	
Employment status					
Employed	15	37.5	33	20.6	χ^2 =5.0

(E_0) Not employed	25	62.5	127	79.4	*df=1, p=0.03,*
					OR=2.31 (1.03–5.18)
Total	**40**	**100.0**	**160**	**100.0**	

[a1,a2,a3]and[b1, b2, b3] were amalgamated separately for chi-square test & odds ratio calculation, (E0) non exposure

Social class was categorised based on the husband's employment. Social classes IV, Va and Vare semi-skilled, unskilled and unemployed workers. These were grouped together in calculations. The risk of cervical cancer is seen to be more among the less educated, those of lower social status and among the employed(table 6).

Table 7: Comparison of reproductive health risk factors between cases and controls.

Study group					
Characteristic	Case		Control		Significance
	No.	%	No.	%	OR&(95%CI)
Parity					
(E_0) 1 [a1]	1	2.5	12	7.5	χ^2 =26.4*
2 [a2]	8	20.0	68	42.5	*df=1, p=0.03*
3 [a3]	8	20.0	56	35.0	*OR=10.23(3.53–30.66)*
4 [a4]	9	22.5	16	10.0	
≥5	14	35.0	8	5.0	
Number of vaginal deliveries					
(E_0) ≤2	9	22.5	87	54.4	χ^2 =13.3
3–4 [a1]	18	45.0	65	40.6	*df=1, p<0.001*
≥5 [a2]	13	32.5	8	5.0	*OR=7.11(1.77–9.97)*
Age at 1st pregnancy (in years)					
≤20	22	55.0	41	25.6	χ^2=12.8
(E_0) 21–25 [a1]	16	40.0	47	29.4	*df=1, p<0.001*
>25 [a2]	2	5.0	72	45.0	*OR=3.55(1.63–7.73)*
Gap between marriage and 1st pregnancy in months					
(E_0) ≤12[a1]	1	2.5	2	1.2	χ^2 =0.36
13 – 24 [a2]	27	67.5	102	63.8	*df=1, p=0.55*
>25	12	30.0	56	35.0	*OR=0.80(0.35–1.78)*
Time since last delivery in years					
(E_0) ≤10[a1]	0	0	11	6.9	χ^2=16.8
11 – 20 [a2]	8	20	79	49.3	*df=1, p<0.001*
21 – 30 [b1]	23	57.5	56	35.0	*OR=5.14(2.10–12.98)*
>30 [b2]	9	22.5	14	8.8	
Mean duration	25.4 ± 6.8		20.3 ± 8.3		
Total	**40**	**100.0**	**160**	**100.0**	

* Yates corrected test was applied (E_0) non exposure

a1, a2, a3, a4 and b1, b2 were amalgamated separately for chi-square test & odds ratio calculation,

Table 7 shows that women who have had five or more pregnancies and those who have had more than two vaginal deliveries are at increased risk of cancer of the cervix. The age at first pregnancy being 20 years or less, and a long period after the last pregnancy (>20 years) are also risk factors.

In addition to the above reproductive health factors, the study inquired into a history of abortion, the number of abortions and the type of abortion a woman had experienced. None of these variables were associated with an increased risk of cervical cancer.

Table 8: Comparison of cases and controls by use of selected contraceptives

Study group					
Characteristic	Case		Control		Significance
	No.	%	No.	%	OR&(95%CI)
History of hormonal contraceptive use>6months					
Yes	19	47.5	69	43.1	χ^2 =0.25
(E_0) No	21	52.5	91	56.9	df=1, p=0.62 OR=1.19(0.56–2.53)
LRT done					
Yes	13	32.5	14	8.8	χ^2 =15.4
(E_0) No	27	67.5	146	91.2	df=1, p<0.001 OR=5.02(1.96– 12.92)
Total	**40**	**100.0**	**160**	**100.0**	

(E_0) non exposure

Data in table 8 suggests that an LRT increases the risk of cancer. This relationship may be confounded by age as well as other reproductive risk factors.

Table 9: Comparison of cases and controls by selected aspects of sexual health

Study group					
Characteristic	Case		Control		Significance
	No.	%	No.	%	OR&(95%CI)
Age at first vaginal sex (years)					
≤19	22	55.0	44	27.5	χ^2 =10.9*
(E_0) 20 – 30[a1]	18	45.0	98	61.2	df=1, p<0.001,
31 – 40[a2]	0	0.0	18	11.3	OR=3.22(1.49–6.99)
Extra marital sex exposures					
Yes	14	35.0	10	6.2	χ^2 =22.4
(E_0) No	26	65.0	150	93.8	df=1, p=0.03, OR=8.08(2.98–22.22)
Number of life time sex partners					
(E_0) 1	23	57.5	151	94.4	χ^2 =38.5
2 [a1]	15	37.5	9	5.6	df=1, p=0.03,
3 [a2]	2	5.0	0	0.0	OR=12.40(4.55–34.59)
Total	**40**	**100.0**	**160**	**100.0**	

* Yates corrected test was applied,

a1,a2 were amalgamated for chi-square test & odds ratio calculation,(E_0) non exposure

As documented in other studies early commencement of vaginal sex, extramarital sexual exposures and more than one sexual partner are associated with a statistically significant increased risk of cancer cervix (table 9).

Table 10: Distribution of cases and controls by sexual health aspects of the husband/sex partner

Study group					
Characteristic	Case		Control		Significance OR&(95%CI)
	No.	%	No.	%	
Extra marital sex exposures of the husband					
Yes	9	22.5	10	6.2	*χ^2=8.0**
(E_0) No	31	77.5	150	93.8	*df=1, p=0.004, OR=4.35(1.48–12.85)*
Total	**40**	**100.0**	**160**	**100.0**	
Number of extra marital sex partners of the husband					
(E_0) No partners	31	77.5	150	93.8	*χ^2=8.0**
1 [a1]	5	12.5	7	4.3	*df=1, p=0.004*
2[a2]	1	2.5	1	0.6	*OR=4.35(1.42–12.94)*
≥3[a3]	3	7.5	2	1.3	
Total	**40**	**100.0**	**160**	**100.0**	

*Yates corrected test was applied

a1,a2,a3 were amalgamated for chi-square test& odds ratio calculation, (E_0) non exposure

Information on extra marital sexual exposure of the husband/sex partner was gathered from the women. There was a small proportion (<5%) of women who reported a previous marriages of the husband. These were also included as an extra partner in the analysis (table 10). It is seen that extra marital relationships of the husband as well as increasing number of his partners increases the risk of malignancy for the woman (table 10).

3.4 Multivariate analysis

A logistic regression analysis to see the relative importance of the multiple risk factors associated with development of cervical cancer was performed using a stepwise procedure.

The adjusted odds ratio for HPV infection (Logistic Regression Model) was 172.31 (95% CI 34.63-857.31). Being in employment (OR=7.64, 95% CI 1.52-38.37), length of the last birth interval being 20 years or more (OR=9.08, 95% CI 1.76-46.67) and extra marital sexual exposures in the woman (OR=32.37, 95% CI 4.61-227.00) were identified to be significant in the multivariate analysis.

3.5 Proportion of cervical cancer attributable to HPV infection

Proportion of cases of cervical cancer attributable to the exposure, the population attributable risk percent(PAR%) was calculated using the following formula given by Henneken and Buring(1987).

$$PAR\% = \frac{Pe(RR - 1) \times 100}{Pe(RR - 1) + 1}$$

Pe=estimated prevalence of risk factor in the population of interest (the overall prevalence of HPV, as determined by the community prevalence survey is 3.3%).

RR= estimate of relative risk – the likelihood of developing the condition in the exposed, relative to the unexposed population. (The adjusted odds ratio of HPV infection given by the logistic regression model was used as the estimate of relative risk (RR), 172.31)

The aetiologic fraction attributed to HPV infection in the development of cervical cancer is:

$$PAR\% = \frac{0.033\,(172.31 - 1)}{0.033\,(172.31 - 1) + 1} \times 100 = 84.97\ \%$$

The estimates reveal that 85 % of the cervical cancer cases are attributed to any genotype of HPV infection.

The prevalence of HPV for high risk genotypes 16 and 18, as determined by the community prevalence survey is 1.2% (95% CI 1.15-1.25).

Univariate analysis to identify risk of cervical cancer due to high risk genotypes (type 16 and 18) is 134.33 (95% CI 35.00-598.31). The adjusted odds ratio for genotypes 16 and 18 HPV infection derived from the Logistic Regression Model is 190.30 (95% CI 36.54-991.03).

Applying the above figures the aetiologic fraction attributable to the high risk genotypes 16 and 18 is 69%. This means that if HPV infection due to genotype 16 and 18is completely prevented, 69 out of 100 cervical cancer cases may be prevented.

The prevalence survey showed that 1.15 cervical cancer patients were generated from 2000 married women of 20-59 years. Hundred cases therefore will be generated by 173,913 women ([2000 x100]/1.15) population of 20-59 years. This means that to prevent one case of cervical cancer attributed to genotypes 16 and 18, 2521 women (173,913/69) needs to be vaccinated assuming a 100% protection rate for the vaccine.

4. Cost estimation of cervical cancer screening

A community clinic based study was carried out to estimate the cost incurred by the government in population screening for cervical cancerin the national cervical cancer screening programme. Unit cost of screening was estimated using the scenario building technique.

Basic health structure and function in all community clinics are the same throughout the country. For the cost estimation of the Papanicolaou smear procedure for cervical cancer screening a well-functioning community clinic in Gampaha district was selected and for estimating the cost incurred in reading the Papanicolaou smear, the reference laboratory at the Family Health Bureau, Colombo was utilized.

4.1 Methods

A total of 510 teenagers, who were pregnant at the time of the study and had conceived before A preliminary survey was conducted among 10 randomly selected Well Women's Clinics, from the 35 available in the district at the time of the study. The purpose of the survey was to examine the differences if any between clinics in the area. The preliminary survey found that the distribution and usage of facilities and functions in the majority of clinics were very similar. It was therefore decided to select one clinic randomly for study. Cost estimation was carried out under the guidance of an expert in health economics with extensive experience in cost estimation.

A checklist was developed to record all instruments and consumable items used in the clinic for obtaining a Papanicolaou smear. A record sheet was developed to record the time taken to complete all activities associated with taking a Papanicolaou smear by the different members of the clinic staff. A check list as well as a record sheet appropriate to cost the laboratory procedure of staining and reading a Papanicolaou smear was developed.

4.2 Costing the clinic procedure

The total number screened at each clinic sessions was recorded consecutively for three months. Average number screened for a month was considered for unit cost estimation. Categories of staff involved in the procedure and staff time spent for each procedure was measured and recorded on three clinic days (one clinic per month). Ten procedures were selected randomly each of the three days and an average time per procedure was calculated.

All items which incurred cost to the government were recorded and any donated items used for the procedure were also included as a cost item under the following categories.

1. Fixed capital cost items – land, building, furniture, and equipment (e.g. furniture, equipment, speculae, spot lamps etc.)
2. Variable costs per clients and services
    a. cost of disposable equipment used (e.g.spatulae, gloves, cotton swabs etc.)
    b. cost of services utilized, fraction contributed from the salaries of health workers involved in the procedure
    c. costing for other services (e.g. physical infrastructure, stationary etc.)

4.3 Laboratory procedure

Data collection was done by the principal investigator. Quantities of all consumables and fixed cost items used for the procedure were noted down in the prepared data sheets. Staff categories and staff time involvements were noted. The items were listed down under the following categories.

1. Fixed capital costs – land, building, furniture, and equipment (e.g. microscopes, tables, chairs, cupboards, instruments used for the staining procedure etc.)
2. Variable costs (per slide and unit cost of services)
    a. cost for consumable items
    b. cost of services utilized
    c. other services (e.g. water, electricity etc.)

4.4 Results

Unit cost estimation for Papanicolaou smear screening procedure at the community clinic was done. This consisted of two costing components.

4.4.1 Cost incurred in obtaining Papanicolaou smear at the community clinic

4.4.2 Cost of reading the Papanicolaou smear in the laboratory

4.4.1 Cost incurred in obtating Papanicolaou smear at the community clinic

Unit cost estimation was carried out under the categories elaborated below and is given in table 11.

- Unit cost estimation of fixed capital cost items
- Unit cost estimation of consumables for the Papanicolaou smear procedure at the community clinic
- Unit cost estimation of the services utilized for Papanicolaou smear procedure at the community clinic
- Unit cost estimation of utility and miscellaneous items for Papanicolaou smear procedure at the community clinic

Table 11: Unit cost estimation of Papanicolaou smear screening at community clinic

No.	Description of costing categories	Cost (Rs.)
1	Unit cost estimation of fixed capital cost items	38.61
2	Unit cost estimation for consumable items for the Papanicolaou smear procedure	67.35
3	Unit cost estimation of the services utilized	107.61
4	Unit cost estimation of utility and miscellaneous items required at the community clinic	16.12
Total unit cost estimation for Papanicolaou smear procedure carried out at the community clinic		**229.69**

4.4.2 Cost of reading the Papanicolaou smear in the laboratory

The unit cost estimation of reading a Papanicolaou smear at the reference laboratory at the Family Health Bureau was done.

Table 12: Unit cost estimation of Papanicolaou smear slide reading procedure at the laboratory

No.	Description of costing categories	Cost (Rs.)
1	Unit cost of the staff involvement at the laboratory for slide preparation and reading procedure	53.86
2	Unit cost for the equipment required at the laboratory for a Papanicolaou smear preparation procedure	4.75
3	Unit cost of chemicals required at the laboratory for preparation of a Papanicolaou smear slide	16.07
4	Unit cost of consumables in Papanicolaou smear preparation	0.74
5	Unit cost of utilities and miscellaneous items in Papanicolaou smear preparation	2.36
6	Unit cost estimation of furniture used	0.71
Total estimated unit cost incurred by the government in the laboratory procedure for Papanicolaou smear preparation and reading		**78.49**

Summary	Cost (Rs.)
Cost estimation for the Papanicolaou smear screening at community clinics	229.69
Cost estimation for Papanicolaou smear reading at the laboratory	78.49
Total unit cost per Papanicolaou smear procedure	308.18

In order to prevent one cervical cancer patient, the number of women needed to be screened was estimated as 1,739 (see chapter 2). The minimum cost required to screen 1,739 women for the prevention of one cervical cancer patient based on current cost estimates will be Rs. 535,925.00

Prevention of one cervical cancer attributed to HPV type 16 and 18 (through currently available vaccines) requires the vaccination of a minimum of 2,521 women before they commence sexual activity. The number is likely to increase depending on the efficacy of the vaccine. The study highlights that at current levels of HPV infection and cost of the vaccine, screening still remains the feasible option for prevention of cervical cancer in Sri Lanka. It is important to note that even if a vaccination programme is commenced, screening will have to be continued for the current cohort of women above the age for vaccination. Thus, the strengthening of cervical cancer screening programme to increase coverage is important

5. Cost of Management of Cervical Cancer

A hospital based study for estimating the unit cost incurred by the government in cervical cancer management was carried out at the Cancer Institute, Maharagama, Sri Lanka. A Gynaecologicalsurgical ward in the Cancer Institute, Maharagama, was selected for the study. The scenario building technique was used.

Cervical cancer stages and the treatment protocols as decided by the Consultant Oncologist is given below:

1. Stage 1, 1a, 1b, 11a – treatment is radical hysterectomy (Wertheim's hysterectomy)
2. Stage 11 b, 111 a, 111 b IV a, IV b Chemoradiation, Cisplatin 40mg weekly for 5 weeks + EBRT (External Beam Radiotherapy/teletherapy) 25 doses to all patients and optional ICR (brachytherapy) 2 doses or HDR (High Dose Rate brachytherapy) 1dose for selected patients

According to the Consultant Oncologist, chemotherapy may not be prescribed to some patients, depending on the clinical situation. However, the standard treatment protocol, given above was used for the cost estimation procedure.

5.1 Methods

Information was collected in consultation with relevant authorities in the hospital, Ministry of Health, Biomedical Engineering Division, Medical Supplies Division, Radiation Protection Authority and relevant equipment companies and suppliers.

5.2 Estimation of ward costs per patient day

Ward cost for a patient day was calculated including all costing components. Appropriate cost estimates were considered for all services and equipment required to keep a patient in a ward per day.

Identified cost items and sources were enumerated as follows:

- Land – the current cost of land in Maharagama area was considered
- Building – current construction cost for the ward building was considered
- Furniture – the replacement cost of furniture was considered
- Equipment – the replacement value of available hardware was considered
- Relevant cost details for electricity, water, telephone, food, security services, laundry and cleaning services were obtained from relevant hospital authorities. Possible proportions of these items per case of cervical carcinoma were decided after discussion with the authorities
- Time costs of staff involved in routine service provision such as consultants, medical officers, nursing officers, attendants, labourers and other ward staff required to facilitate patient care

5.3 Cost estimation for management of cervical cancer stages1a, 1b and 11a

The standard management of the early stages of cervical cancer is radical hysterectomy. Cost estimation was done for an uncomplicated standard surgical procedure carried out at the Cancer Institution, Maharagama.

The following items were considered for the cost estimation:

- Cost of the land and buildings including requirements for a surgical theatre
- Equipment cost for operation theatre for a major surgery and for anaesthesia
- Cost of anaesthetic drugs and drugs for premedication and post-operative pain control
- Cost of instruments, consumables and drugs for one case of cervical cancer undergoing surgery
- Health personnel costs for services provided

5.4 Cost estimation for management of cervical cancer stages 11b, 111a, 111b IVa, IVb

The treatment protocol for the late stages of cervical cancer is as follows:

Chemo radiation Cisplatin 40mg weekly for 5 weeks + EBRT [Teletherapy] 25 doses to all patients and optional ICR [Brachytherapy] 2 doses or HDR 1dose for selected patients.

Chemotherapy may not be used in some patients. However, since it is included in the standard treatment protocol, it was included for cost estimation. Brachytherapy (ICR) is not used at the time of the study according to the information received from the radiotherapy staff. Therefore calculations for this component were not carried out.

Information was collected on the following components:

- Cost of chemotherapy
- Cost of External Beam Radiotherapy (EBRT) - Teletherapy

Data necessary for cost estimation of this component was obtained from experts in the field including, Consultant Oncologists, Radio Therapists, consultants and Head of the Radiation Protection Authority, Medical Physicist and consultants in relevant equipment importation and installation companies.

5.5 Results of ward costs

Cost estimation for a patient day was carried out taking in to consideration the items listed in section 5.2.Estimated total cost of a patient day in hospital (hotel costs) was Rs.527.74.

5.6 Cost of radical hysterectomy

For cervical cancer stages1a, 1b, 11a the treatment is radical hysterectomy (Wertheim's hysterectomy). The theatre buildings and equipment are specifically used only for surgeries and per minute cost were considered for these items. Calculations given here are based on an assumption of an average of two and a half hours per surgery. Given that variations may occur, according to consultant and case, actual time used for procedures and costs may be higher than this. The cost per case of cervical cancer for abdominal hysterectomy is given in Table 13.

Table 13: Total cost incurred per case of cervical cancer for total abdominal hysterectomy

No.	Cost item per patient		Cost (Rs.)
1	Cost of the land and building for requirement of theatre practice		50.42
2	Equipment cost for operation theatre for a major surgery and for anaesthesia		1070.54
3	Cost of anaesthetic drugs for premedication		4.98
4	Cost of drugs and equipment for induction, maintenance and recovery of anaesthesia including oxygen, nitrous oxide and halothane		1,326.90
5	Cost of instruments, consumables and drugs for one case of cervical cancer undergoing surgery, instruments for laparotomy for total abdominal hysterectomy		1,005.92
6	Health personnel costs for services provided		
	a. time cost of Consultant Anaesthetic	811.05	
	b. time cost of Consultant VOG per surgery	337.26	
	c. time cost of medical officers [3]	340.30	
	d. time cost of nursing officers[5]	1,226.22	
	e. time cost of labourers [3]	684.78	
	Total health personnel cost for service provider		5,214.56
Total surgical cost per case			**8,673.32**

An additional 15% of the total cost of surgery was added on to compensate for costs incurred for management of facilities, laundry, sterilization, electricity, water and cleaning facilities provided. Separate costing for these components of theatre were difficult to estimate given the lack of disaggregated billing for utilities, differences in utilization patterns per case etc. Estimated cost of surgery per case of radical hysterectomy was Rs.9,974.32.

Total cost estimation for patients undergoing surgery for cervical cancer stages 1a, 1b, and 11a

Ward cost incurred for 7 days stay in hospital (7 days was the average time period patients who underwent radical hysterectomy (Wertheim's hysterectomy) were kept in the ward)	Rs.3,694.18 (Rs.527.74 x 7)
Cost incurred per case cervical cancer for total abdominal hysterectomy	Rs. 9,974.32
Total cost of management of a patient with cervical cancer stages 1a, 1b, or 11a is Sri Lankan	Rs. 13,668.50

5.7 Cost of Chemoradiation

For cervical cancer stages 11 b, 111 a, 111 b IV a, IV bthe treatment method is chemoradiation.

Cost of chemotherapy	
IV Cisplatin 40 mg weekly for 5 weeks (5 doses)	Rs.78.73
Cost of IV Cisplatin 10 mg vial cost per single dose	Rs.314.92
Since Cisplatin is given as an IV infusion, 0.9% Sodium Chloride 500mg	Rs. 27.76
Total cost per one week dose (one week treatment)	Rs.342.68
Cost of total chemotherapy course (5 dosese, 5 weeks)	Rs.1,713.40

Table 14: Cost of Radiotherapy per case (for 25 fractions of teletherapy)

No.	Cost item per patient		Cost (Rs.)
1	Cost for teletherapy machine		9,300.60
2	Cost for the source of teletherapy		3,985.97
3	Cost of the building and facility rooms for teletherapy		4,566.25
4	Cost of the land for buildings of teletherapy		247.18
5	cost of the personnel time for radiotherapy		3,528.36
	a. Cost for consultant	1,391.75	
	b. Cost for radiotherapists	1,355.36	
	c. Cost for minor staff	781.25	
Cost of teletherapy per case			**21,628.36**

Cost of management of cervical cancer patients in advanced stages of disease	
Cost of chemotherapy per patient	Rs. 1,713.40
Cost of radiotherapy per patient	Rs. 21,628.36
Total cost per patient for management of advanced stages with chemoradiation	Rs. 23,341.76

Ward costs are not included in the cost estimates of chemoradiation as the procedures are carried out on an outpatient basis. Current government approved rates and costs were used in the cost estimation exercise. These values may be subjected to variations.

The following components of management of cervical cancer were not included in the costing:

- Management of individual complicated patients with disseminated cancers and management of patients with complications of other diseases
- Long term management with clinic follow up was also not included due to difficulties in obtaining valid estimations

Conclusions

1. The community prevalence of cervico vaginal HPV infection among married women 20-59 years of age in the Gampaha district was 3.3% (95% CI 3.15-3.44).
2. The community prevalence of cervico vaginal HPV infection among this group, due to genotypes 16 and 18 was 1.2% (95% CI 1.15-1.25).
3. Among married women 20-59 years of age without any cervical cell abnormality (healthy), the cervico vaginal HPV infection prevalence was 3.1% (95% CI 2.96-3.24).
4. Risk behaviours favouring cervico vaginal HPV infection was low (6.1%) in this group of women.
5. HPV infection showed a “U” shaped prevalence with age, and social class. High prevalence rates were seen among those who never became pregnant and among those who delayed their first pregnancy. These associations need further study to elucidate underlying behavioural differences that may account for HPV prevalence.
6. Frequency of HPV infection among cervical cancer patients was 80% (32/40). The majority (91%) of infections were caused by genotypes 16, 6.3% by genotype 18 and there was a single case of genotype 31. Genotype 31 is also considered as a high risk genotype for cervical cancer in the phylogenetic classification. A vaccine against genotype 31 is not yet available.
7. The odds ratio for HPV infection in cervical cancer after controlling for other confounders was 172 (95% CI 35-857). The adjusted odds ratio for HPV genotypes 16 and 18 was 190.3 (95% CI 36.54-991.03).
8. The risk of cervical cancer that may be attributed to any HPV infection was 85%, while the population attributable risk percent of cervical cancer for vaccine preventable genotypes (type 16 and 18), was 69%.
9. The study identified that only 7% of the women above 35 years included in the study sample had undergone cervical screening through the national screening programme.
10. The estimated unit cost for cervical cancer screening at a community Well Women’s Clinic was Rs 308.18.
11. The study estimated that a minimum of 1,739 women needs to be screened to detect one cervical cancer patient. Similarly, a minimum of 2,521 women are needed to be protected from infection with HPV genotypes 16 and 18 to prevent one case of cervical cancer caused by these genotypes assuming the efficacy of the vaccine to be 100%.
12. One case of cervical cancer originating from genotypes 16 and 18 can be prevented by vaccinating 2,521 adolescents assuming the current risk behaviour remains unchanged.
13. Estimated unit cost for management of cervical cancer stages1a, 1b, and 11a which is radical hysterectomy [Wertheim’s hysterectomy] was Rs.13,668.50.
14. Estimated unit cost of management of cervical cancer stages 11b, 111a, 111b,IVa, IV b, treated with chemoradiation was Rs.23,341.76.

Recommendations

1. HPV vaccination (against genotypes 18 and 16) is currently available. However, the cost remains high (US$ 120 per single dose at the time of the study). Adequate protection requires three doses of the vaccine. It appears that at current levels of HPV infection and cost of the vaccine, screening still remains the feasible option for prevention of cervical cancer in Sri Lanka. Even if a vaccination programme is introduced, cervical screening will have to be provided to a large cohort of women and the dual costs should be considered in any evaluation prior to the introduction of vaccination.
2. Considering the burden of advanced stages of cervical cancer presenting in hospitals and the low coverage of screening of cervical cancer at community level, it is recommended that a national IEC programme is undertaken to raise community awareness. Prior to the current study, an education programme was conducted in the area through the Public Health Midwife. Women were also provided information at recruitment to the study. The willingness to participate in the study was high (99.5%) indicating that if information was made available women would seek screening
3. Monitoring trends in the prevalence of HPV infections over time to detect any increasing tendencies as a part of the national screening program would be useful if cost effective methods are available
4. Behavioural surveillance to detect changes towards high risk behaviours is recommended

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