Health Technology Assessment of

Strategies for Cervical Cancer Screening in India

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Executive Summary

Cancer of uterine cervix is the second most common cancer among Indian women and also constitutes the largest burden of cervical cancer patients in the world. The establishment of a strong link between high-risk persistent human papillomavirus (HPV) infections and the occurrence of cervical cancer has resulted in the recent development of HPV related control strategies for the prevention of cervical cancer. These include interventions ranging from prophylactic HPV vaccines to various screening approaches such as visual inspection with acetic acid or Lugol's iodine (VIA/VILI), Papanicolaou test (Pap test or Pap smear) and HPV DNA testing. Experience from developed nations shows that screening either with either Pap smear or HPV DNA is effective as well as cost-effective is reducing more than half of the cervical cancer incidence and mortality. But limited availability of infrastructure and trained manpower in developing country like that of India, poses both financial challenge as well as the challenge of health system feasibility in implementing the desired screening strategy. The present study was designed to undertake a comprehensive health technology assessment of the 3 screening strategies of VIA, Pap smear and HPV DNA among the age group of 30-65 years old women at a frequency of every 3 years, 5 years and 10 years in the context of India.

The present study was based on a markov model for estimating the lifetime costs and consequences in a hypothetical cohort of 30 year old women screened with VIA, Pap smear and HPV DNA test at various time intervals, using a societal perspective. A discount rate of 3% was used to discount for future cost and consequences. Following the standard guidelines of an economic evaluation, the effectiveness estimates in terms of sensitivity and specificity of the screening strategies was based on the recently published meta-analysis of Indian studies. Similarly, most of the probabilities of progression and regression for the natural history HPV based cervical cancer model were based on the meta-analysis of international

studies. Further, primary data was undertaken using bottom up micro-costing methods from the Villupuram district of Tamil Nadu and Ropar district of Punjab, for estimating the cost per person screened with either of the screening strategy. Similarly, cost of treatment for cervical cancer and quality of life (QoL) was based on the primary data collected from a large public sector tertiary care hospital in North India. Following the standard bottom up and economic costing methods, data on health system cost of cervical cancer was collected from departments of Obstetrics/Gynecology and Radiation Oncology. In addition, OOP expenditure incurred by the patients (in different stages of cancer) on various therapeutic interventions was elicited by interviewing a sample of 237 patients. Similarly, a total of 223 cervical cancer patients were recruited from the radiotherapy department and were interviewed for assessing the quality of life (QoL) using standard EQ-5D-5L tool.

The main findings of the present study are as follows:

- Introduction of screening led to reduction in occurrence of cervical cancer cases from 19% to 58% along with decrease in cancer deaths from 28% to 70% as compared to no screening in a lifetime cohort of 1 lakh women.
- There was reduction in lifetime risk of cervical cancer among Indian women from 2.18% in the case of no screening to 0.879 - 1.729 % with implementation of various screening strategies.
- This reduction in cancer cases and associated mortality translated into gain of 3141 to 6848 life years and 3630 to 8198 QALYs among various screening strategies implemented in a cohort of 1 lakh women.
- The overall lifetime cost incurred by the cohort of 1 lakh women in the scenario of no screening was INR 194 million (USD 2.93 million) and treatment expenditure (on invasive cancer) constituted 90% of this cost (INR 175 million; USD 2.65 million).

- Similarly, the overall cost incurred upon implementation of various screening strategies ranged from INR 327 (USD 4.94 million) to INR 951 million (USD 14.38 million) and the treatment expenditure constituted 12% (INR 114 million; USD 1.72 million) to 42% (INR 137 million; USD 2.07 million) of the overall cost.
- This proportional decrease in the cost of treatment during the scenario of screening led to savings in terms of lifetime reduction in per women OOP expenditure of INR 636 (USD 9.6) to INR 810 (USD 12.2) among various screening strategies.
- The study concludes that VIA every 5 years is the most cost-effective option with an incremental cost of INR 21,196 (USD 320) per QALY gained in the context of India.
- A minimum 30% of screened positive patients are needed to be treated for VIA every 5 years to remain cost effective. Similarly, lifetime risk of cervical cancer of at least 0.7 is required for VIA 5 yearly to be cost effective.
- In terms of equity considerations and specifically considering the screening strategy of VIA every 5 years, it was seen that there was around 30% more reduction in cervical cancer cases and subsequent mortality in the bottom 1/3rd of the income population group as compared to upper 2/3rd of the income group in India. Similarly, in terms of financial risk protection, bottom 1/3rd of the income group had greater reduction in OOP expenditure (INR 1073 vs INR 770 respectively) and more households averted catastrophic health expenditure (520 vs 245 respectively) as compared to upper 2/3rd in the cohort of 1 lakh women screened with VIA 5 yearly.

Cost Effectiveness of Strategies for Cervical Cancer Screening in India

Introduction

Cancer of the uterine cervix is the second most common cancer among women world-wide. (1) It is also the second most common cancer among Indian women, which constitute the largest burden of cervical cancer patients in the world. (1) One out of every five women in the world suffering from this disease is an Indian. (1, 2) Besides the high incidence of cervical cancer, owing to its late diagnosis and with consequent poor survival, 25% of global mortality due to cervical cancer occurs in India. (1-3)

The establishment of a strong link between high-risk persistent human papillomavirus (HPV) infections and the occurrence of cervical cancer has resulted in the recent development of HPV related control strategies for the prevention of cervical cancer. (4-6) These include interventions ranging from prophylactic HPV vaccines to various screening approaches. The latter include visual inspection with acetic acid or lugol's iodine (VIA/VILI), Papanicolaou test (Pap test or Pap smear) and HPV DNA testing. (6) Several screening based prevention programs have been initiated in developed countries. (7) These countries have institutionalised Pap cytology test or HPV DNA as primary method of screening. (7) In several of these countries, the annual incidence and mortality from cervical cancer has come down by 50-70% since the introduction of regular population based screening**.** (8) Further, evidence suggests that screening is important from macroeconomic point of view as well. Global investment in cervical cancer prevention could save up to an economic value of USD 1 trillion, both due to gain in disease free life years as well as with reduction in treatment expenditure. (9, 10)

While the techniques like HPV DNA and cytology based Pap smear has been reported to show high sensitivity and specificity respectively, these are also costly and resource intensive in the form of requirement of specialist/trained manpower and laboratory set up. (6) On the contrary, techniques like visual inspection with acetic acid or lugol's iodine with moderate sensitivity and specificity are relatively less expensive and low resource requiring. (6)

Studies from India and other developing countries have demonstrated the usefulness of 'visual inspection with acetic acid' or by 'Lugol's Iodine' as affordable and effective methods in screening women. (11, 12) Government of India, under the aegis of National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) has recently introduced a population based screening for diabetes, hypertension and common cancers (including oral, cervix and breast cancer) in 100 districts of the country on a pilot basis. Screening of cervical cancer is being done using VIA for women between age group of 30-65 years for every 5 years. (13)

Given the limited public investment in the health sector and the rising health care expenditure, it is critical for India that resources are allocated efficiently on interventions that are proven to yield best value for money spent. As India is on the path towards universalizing national level screening program, the present study was designed to assess the cost-effectiveness of three screening strategies of VIA, Pap smear and HPV DNA as compared to no screening scenario at the frequency of every 3 years, 5 years and 10 years among women in the age groups 30-65 years in India. In addition, we also evaluated the costs and consequences of a scenario comprising of screening with HPV vaccination as compare to screening alone or do nothing.

Methodology

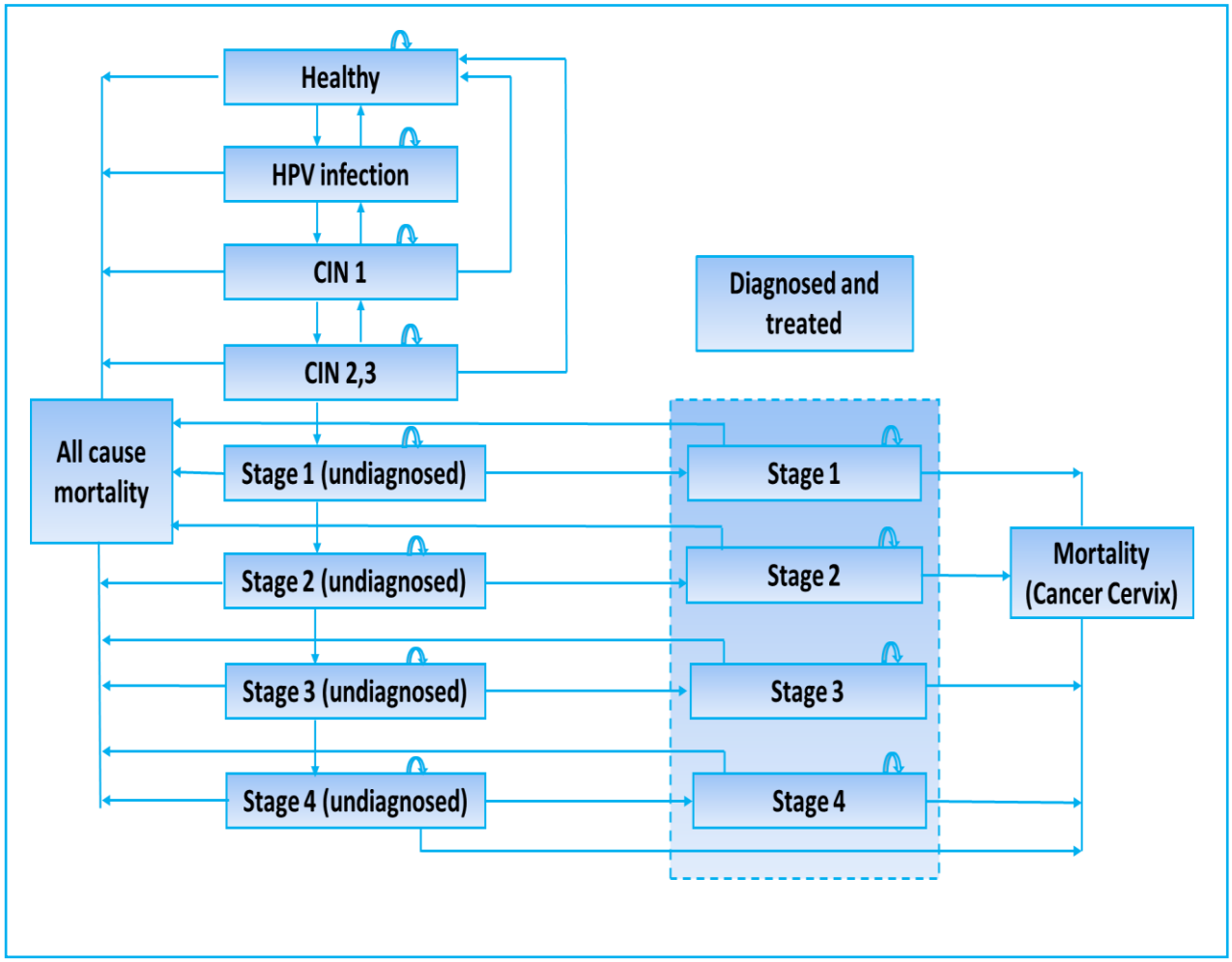
Model overview

The present study was a model-based cost-utility analysis for estimating the lifetime costs and consequences in a hypothetical cohort of 30 year old women screened with VIA, Pap smear and HPV DNA test at various time intervals, using a societal perspective. The outcomes were measured in terms of reduction in cancer incidence/mortality, gain in life-years (LYs)/quality adjusted life years (QALYs) and reduction in out of pocket (OOP) expenditure/catastrophic health expenditure. A discount rate of 3% was used to discount for future cost and consequences. The cycle length of the model was taken as 1 year, i.e., the hypothetical cohort of women was assumed to move in annual cycles through different health states of the model.

Based on the previously published and validated models for cervical cancer, we developed a markov model on MS Excel spread sheet, considering the natural history of HPV infection and cervical cancer (Fig 1). (14-17) The markov health states are denoted in rectangle boxes and the arrows from one box to another indicates the annual probability of transition or movement from one health state to another. The arrow from a rectangle back into itself shows the likelihood of remaining in the same health state. As per the model, women with no infection (healthy state) can get an HPV infection or remain in the same state in the next cycle. Further, women infected with HPV can develop precancerous state i.e., cervical intra-epithelial neoplasia 1 (CIN1; LSIL; low-grade squamous intraepithelial lesion) and CIN2/CIN3 (HSIL; high-grade squamous intraepithelial lesion), who can in turn move back to the previous healthy state or can remain in the same precancerous state during the next cycle. Persistent HPV infection can transform into invasive cancer, from where the patient cannot return to the previous or a healthy state, but can progress to next advanced cancerous

stage in the subsequent cycle of the model. (14, 18-21) Once a women enters the invasive cancer state, she can either get diagnosed/treated for the same or can remain in the undiagnosed state and will continue to progress to the advanced stages. Finally, the patient can die (from each of the health state) from causes other than cervical cancer according to age-specific all-cause mortality rates (22) or due to cervical cancer (in invasive cancer state) as per mortality rates of an untreated cervical cancer and survival rates of the treated cancer cervix. (14, 18) It was assumed that patients with an undiagnosed cervical carcinoma can die due to cancer, only after progressing through all the stages of the cancer (as per natural history of the cervical cancer) and within the first year of moving into the stage 4.

Fig 1: Markov model



The present model did not consider all infections due to various HPV types separately, but the parameters used were specific to all high-risk HPV types (including HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82) thus, accounting for majority of the HPV infections associated with more than 85% of the cervical cancer cases in India. (23, 24) Considering that utility of screening is through the early detection of precancerous lesions or those in those in the early stages of cancer, it was assumed that women in precancerous stage could be detected only through screening (based on the sensitivity of the screening strategy) and those in the invasive cancer stage could be detected both either through the screening or by the onset of symptoms. (12, 25) Invasive cancer was assumed to be treated according to the India's National Cancer Grid Guidelines for the treatment of invasive cervical cancer. (26) Similarly, precancerous lesions were assumed to be treated as per standard guidelines i.e., with cryotherapy, loop electrosurgical excision procedure (LEEP) or surgery depending upon the spread of the lesion (Annexure 4: Table 2). (27) (11, 25) Women treated for precancerous lesions were considered treated for HPV infection and were assumed to return to the healthy state, but were still at risk for future disease based on the age specific incidence of HPV infection.

We compared 3 screening strategies i.e., VIA, Pap smear and HPV DNA test at 3 different screening interval of every 3 years, 5 years and 10 years among women in the age groups 30-65 years, resulting in the assessment of 9 different screening scenarios versus a scenario of no screening. The age group to be screened was as per India's NPCDCs guidelines of women aged 30 years or older till 65 years of age. (13) Following the guidelines of NPCDCS, screening was assumed to be undertaken at the level of sub-centres (first point of contact with the community) by the auxillary nurse midwives (ANM), supported and supervised by the concerned lady health visitor/Staff nurse. (13) It was also assumed (as per guidelines) that

screening would be done on the fixed days preceded by the mobilization and awareness events to ensure high level of participation in the screening. (13) While the results of screening with VIA were immediately available, the results of screening with Pap smear and HPV DNA test were assumed to be available at 2 weeks following screening. Those screened positive with either of the screening strategy are offered colposcopy/biopsy at the level of community health centre (CHC) or district hospital (DH). Finally, for the treatment of the precancerous and cancerous lesions patients were assumed to be referred to the DH and tertiary care hospital respectively. As per care seeking behaviour in the scenario of no screening, it was assumed that women diagnosed of invasive cancer would avail health care treatment from a mix of public and private health care facilities based on utilization pattern (40% and 60% in public and private facilities respectively) reported from National Sample Survey 2104-15. (28) However, in the scenario of organised population based screening, women diagnosed of invasive cancer were systematically referred and treated in a public sector tertiary care hospital.

Model parameters

Using the annual incidence rate of 0.008 for the HPV infection (HPV 16 and 18) among 20-25 year old women immunised with 2 doses of HPV vaccine and vaccine efficacy of 93%, we computed the incidence rate of HPV infection as 0.116 among unvaccinated cohort of the same age group. (29, 30) Further, using the differential of prevalence of HPV infection among other age groups relative to 20-25 year old, we estimated the age specific incidence of HPV infection till 50 years of age (Table 1). Beyond 50 years of age, prevalence of HPV infection gets increased by more than 2 fold. (31) However, since it is a cumulative effect of the incidence in the preceding age groups and in the setting of lack of lack of organised screening program, it was not possible to derive an incidence beyond this age group. We used

incidence rate of 0.005 among those beyond 50 years of age as derived from a mathematical model (18) and calibrated it to Indian specific incidence, based on the percentage difference in the incidence in the preceding age groups as derived in the present model to that of the reported incidence in the mathematical model (Annexure 4; Table 1).

Prevalence of HPV infection, precancerous lesions and invasive cancer among 30 year old women was based on the data from Indian cancer registries and other primary studies. (31, 32) Natural history parameters in the form of annual probabilities of progression or regression in an unscreened population were derived from the literature (Table 1). Specifically, the probability of progression from HPV infection to precancerous states or invasive cancer and regression to previous or normal stage was based on the pooled estimates of 2 meta-analyses conducted globally. (21, 33) The data on probability of progression from an undiagnosed stage of cancer to the next advanced stage was based on a mathematical model on the natural history of HPV infection and cervical cancer. (18) Similarly, proportion of patients showing symptoms in any of the cancer stage was also determined from the same mathematical model. (18) However, the likelihood of showing symptoms in any of the cancer stage was not considered equivalent to diagnosis of the carcinoma because of the possibility of unmet need and wrong diagnosis due to lack of sufficient health care owing to issues of accessibility, availability and affordability. We adjusted the parameter value of those showing symptoms of cancer with the proportion of those with unmet need (3.62%) and those availing cancer treatment from the informal sector (11.64%) based on the data from Indian NSS 2014-15. (28) Stage-specific annual death rates due to cervical cancer was based on the stage specific survival rates following its treatment, as reported from an Indian randomised control trial (RCT) in which patients were followed up to 14 years. (34) Probability of age specific all-cause mortality was obtained from the Census of India Sample Registration System life tables for the female population (Annexure 4; Table 2). (35)

Table 1: Model parameters

Parameters	Categories	Base value	Standard error	Source
Prevalence among 30 year old women in India	HPV infection	0.07	0.00714	(31, 32)
	CIN 1	0.04	0.00408	
	CIN 2,3	0.009	0.00092	
	Invasive cervical cancer	0.0001	0.000010	
Incidence of HPV infection among Indian women (age in years)	30-34 years	0.06	0.00612	(29, 30)
	35-39 years	0.047	0.00480	
	40-44 years	0.047	0.00480	
	44-49 years	0.046	0.00469	
	50 years and above	0.0125	0.00128	
Annual progression probabilities	HPV infection to CIN 1	0.078	0.01592	(21, 33)
	CIN 1 to CIN 2/3	0.071	0.01448	
	CIN 2/3 to invasive cancer stage 1	0.072	0.01469	
	Stage 1 to stage 2	0.438	0.08939	(18)
	Stage 2 to stage 3	0.536	0.10939	
	Stage 3 to stage 4	0.684	0.13959	
Annual regression probabilities	CIN 2/3 to CIN 1	0.055	0.01122	(18, 21, 33)
	CIN 1 to HPV infection	0.082	0.01673	
	CIN 2/3 to normal (without HPV infection)	0.085	0.01735	
	CIN 1 to normal (without HPV infection)	0.142	0.02898	
Proportion showing symptoms	Stage 1	0.127	0.01297	(18)
	Stage 2	0.191	0.01946	
	Stage 3	0.578	0.05901	
	Stage 4	0.867	0.08851	

Annual mortality rates	Stage 1	0.025	0.00255	(34)
	Stage 2	0.078	0.00796	
	Stage 3	0.141	0.01439	
	Stage 4	0.444	0.04531	
Health state utility values	Stage 1	0.698	0.04210	a*
	Stage 2	0.632	0.02257	
	Stage 3	0.637	0.04269	
	Stage 4	0.591	0.09074	

*****HPV: human papillomavirus; CIN: cervical intra-epithelial neoplasia; a: primary data

Sensitivity and specificity of each of the screening strategy reported as per the pooled estimates generated from a meta-analysis of Indian studies was used (Table 2). (36) While the sensitivity of diagnosing stage 1 of the cancer was assumed to be same as that of the precancerous states, the sensitivity was assumed to be 100% for diagnosing women in stage 2 to stage 4. Sensitivity and specificity of colposcopy was derived from a meta-analysis of international studies. (37) Further, it was assumed that the biopsy always resulted in the diagnosis of true health state. Based on the pilot studies undertaken in different states of India on the feasibility of different screening strategies, coverage of screening attendance for each of the screening strategy was assumed as 80%. (11, 12, 25) Further, a loss of 10% each was considered for those screened positive and undergoing colposcopy, and subsequent treatment respectively.

Table 2: Sensitivity and specificity of screening strategies

Parameter		Screening strategies			Colposcopy
		Visual inspection with acetic acid	Pap smear	HPV DNA	
Sensitivity	Pre-cancerous stage	0.676 (0.034)	0.621 (0.0316)	0.778 (0.0396)	0.95 (0.0242)
	Stage 1	0.676 (0.034)	0.621 (0.0316)	0.778 (0.0396)	
	Stage 2,3,4	1	1	1	
Specificity		0.843 (0.0430)	0.935 (0.0238)	0.915 (0.0233)	0.42 (0.0107)

*Figures in parenthesis indicate standard error; Pap test: Papanicolaou test

Cost data

Primary data was collected using bottom up micro-costing methods for estimating the cost per person screened with either of the screening strategy. This cost data was based on a camp based screening program conducted on a pilot basis in the Villupuram district of Tamil Nadu, India. As part of this program, all the eligible women in the age group of 30-65 years were screened for cancer cervix with VIA as well as with HPV DNA test. Samples were also taken for Pap smear for those women who were screened positive with HPV DNA. Screening was organised for 2-3 days at each of the selected village, preceded by 1-2 day awareness activity by the social workers, who also did enumeration of the eligible women in the respective village. Sample collection/visual inspection was done by a trained health worker (equivalent to ANM), under the supervision of medical officer. HPV DNA samples were processed at the district level itself by the trained health workers (equivalent to lab technicians). However, Pap smears were processed at the cytopathology laboratory of a tertiary care hospital located in Chennai. Methodological details of cost data analysis and its results are shown in Annexure 1. Unit cost of each of these 3 screening strategies, considering per patient cost of

sample collection, laboratory processing and support activities (IEC activities, administration, documentation, travel, etc.) is shown in Table 3.

Cost of treatment for cervical cancer was based on the primary data collected from a large public sector tertiary care hospital in North India (Annexure 2). Following the standard bottom up and economic costing methods, health system cost of surgical hysterectomy, radiotherapy (3-dimensional radiotherapy), chemotherapy and brachytherapy for the treatment of cervical cancer was estimated and is shown in table 3. In addition, OOP expenditure incurred by the patients (in different stages of cancer) on various therapeutic interventions was elicited by interviewing a sample of 237 patients. OOP expenditure on account of the treatment before coming to the study hospital was also recorded. Indirect expenditure due to wage loss was not included in our analysis. Reimbursement rates of Central Government Health Insurance scheme (CGHS) were used for assessing the cost of colposcopy, biopsy, cryotherapy, LEEP and palliative care. (38) OOP expenditure incurred on treating a patient of invasive cancer in a private health care facility was taken as INR 78,050 as reported from NSS report 2014-15. All the costs are reported in Indian National Rupees (INR), also converted to USD and pertain to the year 2016-17.

Table 3: Cost parameters

Cost parameter		Base value in INR	Standard error
Cost of screening	Per women screened with Visual inspection with acetic acid	344 (5.2)	88 (1.3)
	Per women screened with Pap smear	652 (9.8)	166 (2.5)
	Per women screened with HPV DNA	980 (14.8)	250 (3.8)
Cost of treatment of precancerous lesions	Per patient cost for colposcopy	1102 (16.6)	281 (4.2)
	Per patient cost for biopsy	2070 (31.2)	528 (8)
	Per patient treated with cryotherapy	4000 (60.4)	1020 (15)
	Per patient treated with loop electrosurgical excision procedure	5980 (90.3)	1526 (23)

Health system cost of treating invasive cancer	Outpatient consultation and diagnostics	8470 (127.8)	2161 (33)
	Surgery	13008 (196)	3318 (50)
	Radiotherapy (3-dimensional radiotherapy)	41388 (625)	10558 (159)
	Brachytherapy	33569 (507)	8564 (129)
OOP expenditure in public hospitals for the treatment of invasive cancer	Outpatient consultation and diagnostics	10859 (164)	814 (12)
	Surgery	16992 (256)	4335 (65)
	Radiotherapy (3-dimensional radiotherapy)	13417 (202)	572 (8.6)
	Brachytherapy	5841 (88)	344 (5.2)
	Chemotherapy	4229 (64)	318 (4.8)
	Before visiting tertiary care facility	16342 (247)	16342 (247)
OOP expenditure in private hospital for treating invasive cancer		78050	78050 (1178)

*OOP: Out of pocket expenditure; values in parenthesis indicated INR converted to USD

Health state utility values

A total of 223 cervical cancer patients were recruited from the radiotherapy department of a tertiary care hospital in north India and were interviewed for assessing the quality of life (QoL) using standard EQ-5D-5L tool (Annexure 3). Patients who had undergone treatment for histologically proven cervical cancer, diagnosed in any of the stage I-IVb (FIGO classification) and between the age of 18-70 years were included for the assessment of QoL. Based on the consultation with the oncologists, it was assumed that health-related QoL tends to get stabilised after 4-5 months following treatment. Thus, those patients who had completed at least 4 months following the treatment for cervical cancer were considered eligible for assessing QoL and were interviewed at the time of their follow-up visit in the outpatient clinic of radiotherapy Department. The stage specific QoL based on EQ-5D-5L is shown in table 1.

Sensitivity Analysis

To test the uncertainty in the parameter values, we undertook multivariate probabilistic sensitivity analysis (PSA) to account for joint parameter uncertainty. (39) Under PSA, each of the parameters was assigned specific distribution based on its nature. Specifically, gamma distribution was assigned to cost parameters and beta distribution was used for QoL estimates and other parameters reported as rates, proportion and probabilities. For parameters based on the pooled results of meta-analysis (such as sensitivity and specificity of screening strategies), normal distribution was used. All the health system cost estimates were varied by half to double of the base value. Standard error for OOP expenditure and QoL was based on the results of the primary data. Epidemiological parameters in the form of prevalence, incidence and mortality were varied by 20% of the reported value. Similarly, annual probabilities of progression and regression were varied by 40% of the base value. Further, sensitivity and specificity values were varied 20% on either side of the base value respectively. Finally, the median value of incremental cost effectiveness ratio (ICER) along with 2.5^{th} and 97.5^{th} percentile was computed using 999 Monte Carlo simulations. To assess the comparative cost effectiveness between the various screening strategies, concept of dominance and extended dominance was used. (40-42) We also undertook specific threshold analysis to assess the minimum coverage of treatment for screen positives, as well as lifetime risk of cervix cancer/incidence of HPV infection necessary to maintain cost-effectiveness of screening.

Ethical approval

Ethical approval was obtained from the Institute Ethics Committee of the Post Graduate Institute of Medical Education and Research, Chandigarh, India with reference number: NK/2490/Ph.D/6374. All the respondents during primary data collection were interviewed after obtaining written informed consent.

Results

Health outcomes

As per model, a total of 2186 cases and 1592 deaths occurred due to cervical cancer in a lifetime cohort of 100,000 women in case of no screening scenario implying a lifetime risk of cervical cancer among Indian women as 2.18 (Table 4). It was seen that among the different screening strategies, percentage decrease in the cancer cases varied from 19% (n=1272) to 58% (n=414) with implementation of Pap smear every 10 years to HPV DNA every 3 years respectively (Table 5). Similarly, percentage decrease in cancer deaths varied from 28% (n=1118) to 70% (n=453) with Pap smear every 10 years to HPV DNA every 3 years respectively. This reduction in cancer cases and associated mortality translated into gain of 3141 to 6848 life years and 3630 to 8198 QALYs among various strategies as shown in table 5.

Table 4: Outcome indicators in a cohort of 1 lakh population among various screening scenarios

Screening strategy		Cancer cases	Deaths	Life years	Quality adjusted life years
No Screening		2,186 (1,213-3,482)	1,592 (875-2,520)	1,848,425 (1,818,915-1,877,384)	1,845,428 (1,815,550-1,874,875)
Visual inspection with acetic acid	**3 Years**	1,027 (549-1,741)	549 (295-949)	1,854,995 (1,826,091-1,884,848)	1,853,179 (1,824,387-1,882,354)
	5 Years	1,371 (737-2,249)	781 (421-1,313)	1,853,430 (1,824,629-1,882,600)	1,851,319 (1,822,389-1,880,632)
	10 Years	1,706 (918-2,755)	1,088 (586-1777)	1,851,761 (1822659-1881062)	1,849,442 (1,819,939-1,878,929)
PAP smear	**3 Years**	1,094 (605-1,930)	589 (329-1,033)	1,854,695 (1,824,028-1,885,091)	1,852,967 (1,821,906-1,883,151)
	5 Years	1,430 (779-2,422)	821 (451-1,409)	1,853,248 (1,822,255-1,883,542)	1,851,173 (1,820,195-1,881,013)
	10 Years	1,725 (937-2,963)	1,113 (607-1,909)	1,851,682 (1,820,766-1,881,659)	1,849,287 (1,817,558-1,879,745)
HPV DNA test	**3 Years**	879 (477-1,518)	456 (253-806)	1,855,737 (1,824,647-1,884,304)	1,854,224 (1,823,584-1,882,803)
	5 Years	1,221 (667-2,086)	682 (380-1,175)	1,854,340 (1,823,710-1,882,972)	1,852,438 (1,821,758-1,881,680)
	10 Years	1,576 (890-2,698)	1,001 (560-1,720)	1,852,454 (1,821,878-1,881,845)	1,850,070 (1,820,033-1,879,623)

*Pap: Papanicolaou test; Values in parenthesis represent 2.5th and 97.5th percentile

Table 5: Gain in health outcomes among various screening strategies in a cohort of 1 lakh population as compared to a scenario of no screening

Screening strategy		Cancer cases averted (%)	Deaths averted (%)	Life years gained	Quality adjusted life years gained
Visual inspection with acetic acid	**3 Years**	1141 (52)	1051 (66)	6439	7663
	5 Years	798 (36)	816 (51)	5104	5951
	10 Years	470 (21.5)	504 (32)	3437	3995
PAP smear	**3 Years**	1030 (47)	973 (61)	6057	7132
	5 Years	706 (32)	745 (47)	4698	5448
	10 Years	414 (19)	453 (28)	3141	3630
HPV DNA test	**3 Years**	1272 (58)	1118 (70)	6848	8198
	5 Years	931 (42.5)	890 (56)	5529	6526
	10 Years	559 (25.5)	572 (36)	3839	4467

*Figure in parenthesis indicates percentage decrease in cancer cases and deaths with various screening strategies as compared to the scenario of no screening; Pap: Papanicolaou test

Cost and cost effectiveness

The overall lifetime cost incurred by the cohort of 1 lakh women in the scenario of no screening was INR 194 million (USD 2.93 million) and treatment expenditure (on invasive cancer) constituted 90% of this cost (INR 175 million; USD 2.65 million) (Table 6). Similarly, among various screening scenarios, the overall cost ranged from INR 327 (USD 4.94 million) to INR 951 million (USD 14.38 million) and the treatment expenditure constituted 12% (INR 114 million; USD 1.72 million) to 42% (INR 137 million; USD 2.07 million) of the overall cost. This proportional decrease in the cost of treatment during the scenario of screening led to savings in terms of lifetime reduction in per women OOP

expenditure of INR 636 (USD 9.6) to INR 810 (USD 12.2) among various screening strategies (Table 7).

The incremental cost per QALY gained with screening varied from of INR 33,354 (USD 504) to INR 92,209 (USD 1394) as compared to no screening as shown in table 8. Similarly, the incremental cost per cervical case prevented and death averted was found to be in the range of INR 598,675 (USD 9050) to INR 284,815 (USD 4306) and INR 682,287 (USD 10,314) to INR 264,715 (USD 4002) respectively with various screening strategies as compared to the scenario of no screening.

Table 6: Total cost incurred with implementation of various screening strategies

Screening strategy		Screening cost in million		Treatment expenditure in million		Total cost in million*	
		INR	USD	INR	USD	INR	USD
No organized Screening		19 (11-32)	0.29 (0.17-0.48)	175 (103-291)	2.65 (1.56-4.40)	194 (114-323)	2.93 (1.72-4.88)
Visual inspection with acetic acid	3 Years	583 (429-757)	8.81 (6.49-11.44)	119 (88-155)	1.80 (1.33-2.34)	702(517-912)	10.61 (7.82-13.79)
	5 Years	315 (236-400)	4.76 (3.57-6.05)	128 (96-164)	1.93 (1.45-2.48)	443(332-564)	6.70 (5.02-8.53)
	10 Years	190 (140-251)	2.87 (2.12-3.79)	137 (102-181)	2.07 (1.54-2.74)	327(242-432)	4.94 (3.66-6.53)
PAP smear	3 Years	633 (449-836)	9.57 (6.79-12.64)	121 (86-159)	1.83 (1.30-2.40)	754(535-995)	11.40 (8.09-15.04)
	5 Years	348 (250-459)	5.26 (3.78-6.94)	136 (97-179)	2.06 (1.47-2.71)	484(347-638)	7.32 (5.25-9.64)
	10 Years	209 (152-278)	3.16 (2.30-4.20)	139 (101-185)	2.10 (1.53-2.80)	348(253-463)	5.26 (3.82-7.00)
HPV DNA test	3 Years	837 (625-1155)	12.65 (9.45-17.46)	114 (85-157)	1.72 (1.28-2.37)	951(710-1312)	14.38 (10.73-19.83)
	5 Years	472 (352-647)	7.14 (5.32-9.78)	125 (93-172)	1.89 (1.41-2.60)	597(445-819)	9.02 (6.73-12.38)
	10 Years	284 (211-386)	4.29 (3.19-5.84)	133 (99-181)	2.01 (1.50-2.74)	417(310-567)	6.30 (4.69-8.57)

***** Total cost in a cohort of 1 lakh population; Pap: Papanicolaou test; Values in parenthesis represent 2.5th and 97.5th percentile

Table 7: Per capita reduction in out of pocket expenditure with implementation of various screening strategies

Screening strategy		Life time per capita reduction in out of pocket expenditure in INR (USD)
Visual inspection with acetic acid	**3 Years**	791 (12.0)
	5 Years	732 (11.1)
	10 Years	680 (10.3)
PAP smear	**3 Years**	742 (11.2)
	5 Years	680 (10.3)
	10 Years	636 (9.6)
HPV DNA test	**3 Years**	810 (12.2)
	5 Years	745 (11.3)
	10 Years	686 (10.4)

Comparative cost effectiveness

Screening with Pap smear at any frequency was dominated as shown in table 9 (Annexure 4, Fig 1). Among the non-dominated strategies, VIA every 5 years came out to be most cost-effective option with an incremental cost of INR 21,196 (USD 320) per QALY gained. Furthermore, when HPV vaccination is introduced along with the VIA 5 yearly, it leads to further reduction in around 90% of the cancer cases and deaths as compared to VIA 5 yearly only, with an incremental cost of INR 20,537 per QALY gained (Table 10). It was seen that as the coverage of the treatment (both for precancerous lesions and invasive cancer) increases, the screening becomes more cost-effective. But, if the treatment coverage goes down below 30%, screening with VIA every 5 years ceases to be cost effective (Fig 2). Similarly, lifetime risk of cervical cancer of at least 0.7 is required for VIA 5 yearly to be cost effective (Fig 3).

Table 8: Incremental cost per unit gain in various health outcomes with various screening strategies as compared to a scenario of no screening

Screening strategy		Incremental cost per LY gained		Incremental cost per QALY gained		Incremental cost per Cancer case averted		Incremental cost per death averted	
		INR	USD	INR	USD	INR	USD	INR	USD
Visual inspection with acetic acid	3 Years	78,622(40,975-151,168)	1189 (619-2285)	66,163(34,654-125,275)	1000 (524-1894)	447,126(228,545-853,091)	6759 (3455-12896)	481,465(248,347-929,901)	7278 (3754-14057)
	5 Years	49,139(20,691-96,068)	743 (313-1452)	41,782(17,669-82,076)	632 (267-1241)	315,095(125,443-639,524)	4763 (1896-9668)	305,810(128,874-611,348)	4623 (1948-9242)
	10 Years	38,693(10,027-80,153)	585 (152-1212)	33,354(8,612-69,015)	504 (130-1043)	284,815(74,798-628,884)	4306 (1131-9507)	264,715(71,680-558,106)	4002 (1084-8437)
PAP smear	3 Years	92,314(45,760-184,607)	1396 (692-2791)	78,075(38,747-155,959)	1180 (586-2358)	537,025(263,709-1,101,290)	8118 (3987-16648)	566,034(283,762-1,151,726)	8557 (4290-17411)
	5 Years	61,199(26,621-129,979)	925 (402-1965)	52,494(22,929-111,886)	794 (347-1691)	400,019(168,305-917,198)	6047 (2544-13865)	383,500(164,742-832,170)	5797 (2490-12580)

	10 Years	50,138(15,869-107,469)	758 (240-1625)	43,320(13,712-91,787)	655 (207-1388)	372,246(117,307-867,038)	5627 (1773-13107)	341,327(108,141-746,793)	5160 (1635-11289)
HPV DNA test	**3 Years**	111,071(56,066-209,097)	1679 (848-3161)	92,209(46,698-176,917)	1394 (706-2674)	598,675(301,003-1,178,150)	9050 (4550-17810)	682,287(342,401-1,355,957)	10314 (5176-20498)
	5 Years	73,213(32,919-144,556)	1107 (498-2185)	61,936(27,301-122,713)	936 (413-1855)	434,467(189,553-929,757)	6568 (2866-14055)	454,794(203,646-923,085)	6875 (3079-13954)
	10 Years	57,617(22,138-115,788)	871 (335-1750)	49,192(19,071-100,552)	744 (288-1520)	392,034(152,663-835,923)	5926 (2308-12637)	384,432(147,576-809,014)	5812 (2231-12230)

***** Pap: Papanicolaou test; LY: Life year; QALY: Quality adjusted life year; Values in parenthesis represent 2.5^{th} and 97.5^{th} percentile

Table 9: Dominance and extended dominance

Strategy	Cost per women in INR (USD)	Effect (QALY per women)	ICER in INR (USD)	Status
VIA: 10 years	3279 (46)	18.4944		ND
HPV DNA: 10 Years	4171 (63)	18.5007	142,087 (2148)	ND
VIA: 5 Years	**4435 (67)**	**18.5132**	**21,196 (320)**	**ND**
HPV DNA: 5 Years	5975 (90)	18.5244	137,586 (2080)	ND
VIA: 3 Years	7018 (106)	18.5318	140,651 (2126)	ND
HPV DNA: 3 Years	9512 (144)	18.5422	238,634 (3607)	ND
Pap smear: 3 years	7547 (114)	18.5297		D
Pap smear: 10 Years	3483 (53)	18.4929		D
Pap smear: 5 years	4841 (73)	18.5117		D

*VIA: Visual inspection with acetic acid; Pap: Papanicolaou test; D: Dominated; ND: Non-Dominated; ICER: incremental cost effectiveness ratio; QALY: Quality adjusted life years

Fig 2: Threshold analysis showing the change in ICER value with treatment coverage rate following screening with visual inspection acetic acid every 5 years

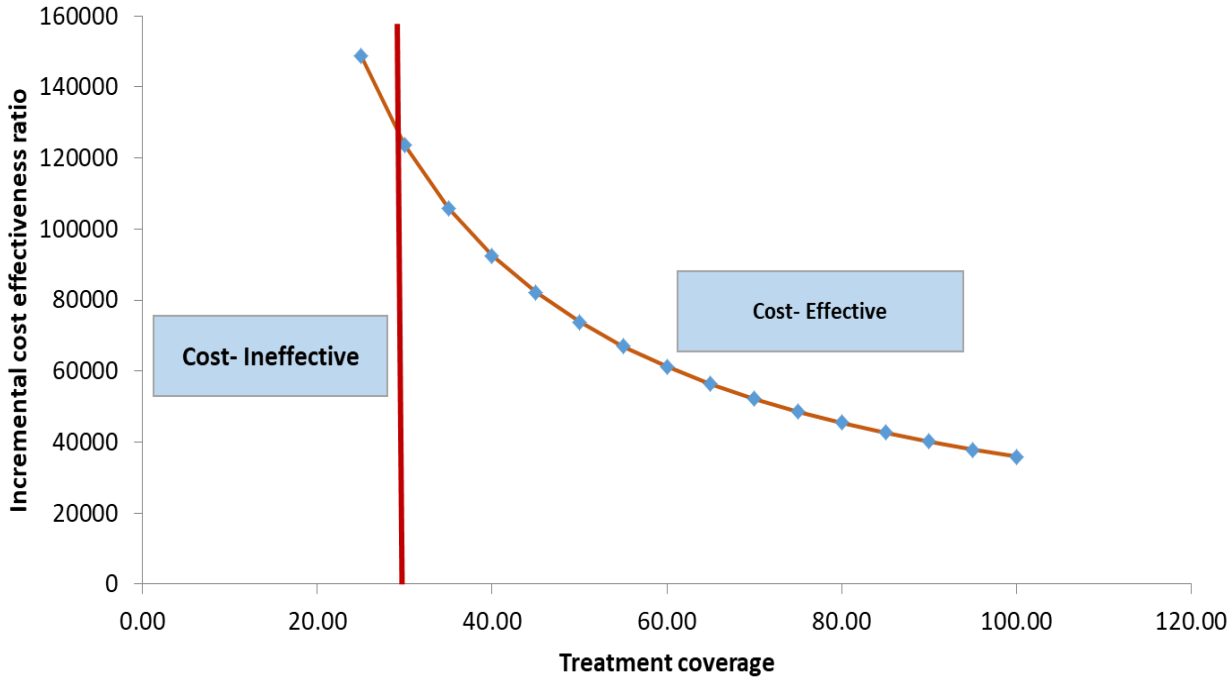


Fig 3: Threshold analysis showing the change in ICER value with lifetime risk of having cervical cancer following screening with visual inspection acetic acid every 5 years

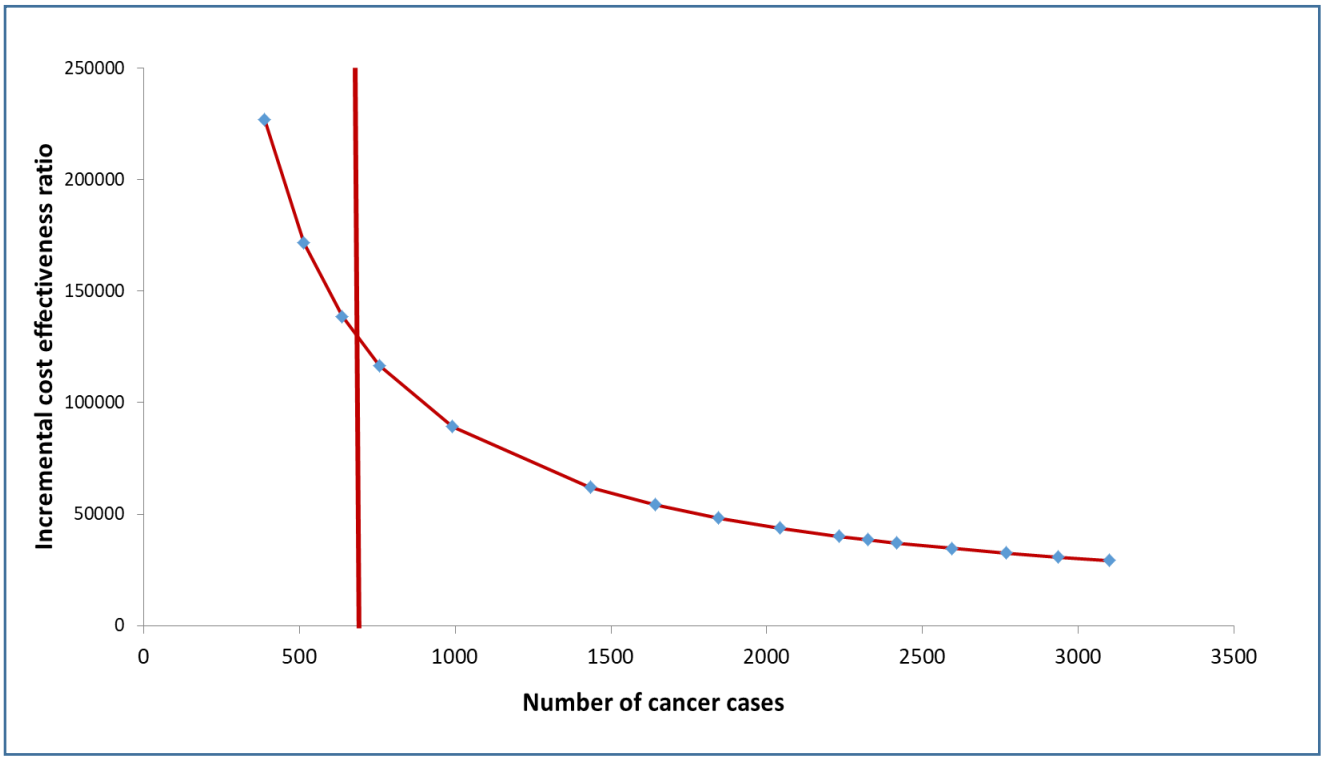


Table 10: Health outcomes and incremental cost effectiveness ratio of introducing HPV vaccination along with VIA every 5 years

Scenarios	Cancer cases	Deaths	Quality adjusted life years (QALY)	Incremental cost per QALY gained in INR (USD)
No screening and no vaccination	2232	1649	12,53,398	__
Screening with VIA 5 yearly	1306	728	12,57.899	53,757 (813)
HPV vaccination and screening with VIA every 5 years	126	65	12,61,848	20,537 (310)

*HPV: Human papillomavirus; VIA: Visual inspection with acetic acid

Equity analysis

Specifically considering the screening strategy of VIA every 5 years, it was seen that there was around 30% more reduction in cervical cancer cases and subsequent mortality in the bottom 1/3rd of the income population group as compared to upper 2/3rd of the income group in India (Annexure 4; Fig: 4). Similarly, in terms of financial risk protection, lower 1/3rd of the income group had greater reduction in OOP expenditure (INR 1073 vs INR 770 respectively) and more households averted catastrophic health expenditure (520 vs 245 respectively) as compared to upper 2/3rd in the cohort of 1 lakh women screened with VIA 5 yearly (Annexure 4; Fig: 2 and 3).

Discussion

Experience from developed nations shows that screening either with Pap smear or HPV DNA is effective as well as cost-effective is reducing more than half of the cervical cancer incidence and mortality. (8) But limited availability of infrastructure and trained manpower in developing country like that of India, poses both financial challenge as well as the challenge of health system feasibility in implementing the desired screening strategy. The present study was designed to undertake a comprehensive health technology assessment of the 3 screening strategies of VIA, Pap smear and HPV DNA among the age group of 30-65 years old women at a frequency of every 3 years, 5 years and 10 years in the context of India. Based on the GDP per capita of USD 1805 (₹ 117,325) during the year 2014-15 of India, the study concludes that VIA at a frequency of every 5 years is the most cost effective strategy for screening women in the age group of 30-65 years in India.

Model Validation

In order to validate the estimates obtained from the model used in the study, we have compared the outcomes of the model with epidemiological data and published literature on

the subject. With the help of bottom- up micro-costing approach, we have calculated the cost per women screened is least with VIA, followed by cytology and HPV DNA test. In 2005, Legood estimated the cost of screening previously unscreened women by VIA, cytology or HPV testing within a large cluster randomised trial involving 131,178 women in rural India, and the findings of the trial had also showed the similar pattern (Table 11). (43-45) Similar trend has also been reported by Diaz et al and Goldie et al. (46, 47) In cytology and HPV DNA testing, we found that largest amount of cost is attributed to laboratory processing, as observed by previous studies.(43, 46, 47) Upon converting the estimates of the respective studies to the Indian currency units and inflating the estimates using cumulative inflation rate for the respective period our cost estimates were found to be higher than what was reported by Diaz et al and Goldie et al. (44, 45) One factor that has led to this increase, is the measurement and inclusion of cost pertaining to information, education and communication (IEC) activities, which has not been measured in these studies. It is worthwhile to mention here that this cost constitutes a large part of total cost attributed to screening, ranging from 70% in case of VIA to 24.6% in case of HPV DNA. As IEC activities play an instrumental role in success of a screening program, especially when the program is thought to be launched for the first time on a countrywide basis, this cost must not be omitted in the calculation of overall cost. Secondly, in contrast with the bottom- up costing used in our study, estimates in these studies were derived from expert consultation (46, 47) which might has led to estimation of lower than actual cost. *(Another explanation may be- Cumulative inflation rate was used to inflate the cost from study year to 2017, which was based on CPI. Ideally, health inflation rate should be used for this, which is higher than the CPI.)*

In 2013, based on the data of cancer registries program of India, International Agency for Research on Cancer has reported cumulative risk (%) of developing cervical cancer in India

as 2.40. (31, 44) Our model predicted this risk as 2.182%. Considering that our model was calibrated to predict risk of cervical cancer as a result of high risk HPV variants, which have been reported to constitute 85% of the total burden, the findings on outcomes of our model for no screening scenario are validated.

Upon screening with VIA, cytology and HPV DNA every 10 years, mean cancer reduction has been estimated by our study as 21.5%, 19% and 25.5%, respectively. Using an individual based stochastic model for population of India, Diaz et al (2008) reported mean cancer reduction as 29%, 21% and 33%, when women are screened thrice per lifetime with VIA, cytology and HPV DNA, respectively.(46) This implies that our estimates are slightly conservative, as we have considered a more realistic 20% loss to follow-up at the stages of colposcopic diagnosis and subsequent treatment seeking. Diaz et al have considered 15% loss to follow up either at the stage of diagnosis and treatment in case of screening with cytology, and 15% loss to follow- up at the stage of treatment with HPV DNA based screening. In case of VIA screening, Diaz et al considered no loss to follow-up assuming that one visit VIA strategy incorporates same-day screening and treatment for women with positive screening results. However, practically in India, since VIA based screening is carried out at sub-centers, test and treat is not a realistic scenario since the screened positive women will have to be referred to higher centers for treatment.

Upon assessing the comparative cost-effectiveness of the three cervical cancer screening strategies, viz., visual inspection, cytology testing and HPV DNA testing at different frequencies, we found that visual inspection performed at the frequency of every five years yields the best value for money, hence most cost-effective. In a computer-based modelling study to assess the cost-effectiveness of screening strategies of VIA, cytology and HPV

DNA, differentiated according to number of clinical visits, frequency of screening, and targeted ages, Goldie et al found that the strategy of one-visit visual inspection is the least costly non-dominated strategy in India. (47) While assessing the dominance of alternative screening strategies, Goldie et al showed that cost per life year saved was least with single visit VIA once per lifetime, followed by VIA twice per lifetime, VIA thrice per lifetime and HPV DNA once per lifetime. Therefore, VIA strategy was shown to be more cost- effective as compared to cytology testing and HPV DNA testing.

Table 11: Cost of cervical cancer screening in India as reported in various studies

Parameter	Present study	Diaz et al (2008), Goldie et al (2005)		Legood et al (2005)	
	INR (2017)	I$ 2005	Converted to INR 2017	US$ 2005	Converted to INR 2017
Cost per woman screened with VIA test	344	1.25	32.21	3.917	396.94
Cost per woman screened with Cytology test	652	3.69	96.11	6.609	773.88
Cost per woman screened with HPV DNA test	980	10.30	265.73	11.779	1404.49

Strengths and limitations

Following the standard guidelines of an economic evaluation, the effectiveness estimates in terms of sensitivity and specificity of the screening strategies was based on the recently published meta-analysis of Indian studies. (36) Similarly, most of the probabilities of progression and regression for the natural history HPV based cancer cervix were based on the meta-analysis of international studies. (21, 33) Further, owing to region specific differences

in the socio-economic factors, health seeking behaviour, utilization and compliance survival rates following treatment of cervical cancer, were obtained specifically from an Indian randomised controlled trail. (34)

Another strength of the study, was use of local data both on the cost of screening as well as treatment of cervical cancer and QoL. Following the guidelines of NPCDCS, the present model had assumed that screening for cervical cancer was being done on a camp or fixed day basis preceded by an awareness activity (by health workers). Based on this assumption, the cost of screening was estimated based on a similar camp based screening approach undertaken on a pilot basis in southern India and specifically assessed unit cost incurred on sample collection, laboratory process and mobilization campaign.

While estimating the cost of cancer treatment, both the health system cost as well as OOP expenditure was estimated following standard bottom-up micro-costing approach and cost of illness methodology respectively. (40, 48, 49) The data on both health system cost as well as OOP expenditure was collected from one of the largest tertiary care public sector hospital located in India, catering to more than 6 Indian states with more than 100 health care personnel involved in cancer care delivery to more than 5000 cancer patients annually. Being a well-equipped tertiary care center, both in terms of infrastructure and human resource and operating at an optimum efficiency, justifies the appropriateness of the cost estimates calculated based on the study hospital. (50)

A limitation of the study was the use of certain parameter values derived from a mathematical model. Due to unavailability of any empirically derived estimates on the natural history of progression in undiagnosed cases of cancer as well as their probability of showing symptoms from India, parameter values derived from a mathematical model developed by Myers et al were used. (18) These estimates have also been used to parameterize models to evaluate

cervical cancer prevention strategies in Thailand, United Kingdom and Germany. (15-17) Moreover, since the natural progression of disease is not expected to vary by region, these estimates were considered appropriate. Similarly, due to lack of Indian specific data on incidence of HPV infection, age specific HPV incidence rates were derived based on data of HPV infection in a vaccinated cohort of adolescent girls. (29) Both these derived estimates could have affected the valuation of health outcomes. However, it was seen that the model predicted life time risk of incurring cervical cancer of 2.2% was almost similar to the lifetime risk reported in Indian cancer registries. (31) Further, these derived estimates were varied in PSA and thus is unlikely to have biased the findings of the study.

Conclusion

Introduction of screening leads to reduction in occurrence of cervical cancer cases from 19% to 58% along with decrease in cancer deaths from 28% to 70% as compared to no screening in a lifetime cohort of 1 lakh women. This further implies reduction in lifetime risk of cervical cancer among Indian women from 2.18 in the case of no screening to 0.879 - 1.729 with implementation of various screening strategies. Furthermore, the decrease in incidence cancer cases with screening led to savings in terms of lifetime reduction in per women OOP expenditure of INR 636 (USD 9.6) to INR 810 (USD 12.2). Finally, the study concludes that among various screening strategies, VIA every 5 year is the most cost effective screening method in the context of India.

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Cervical Cancer Screening in India: Health System Feasibility

Introduction

Cervical cancer represents the fourth most common malignancy affecting women all over the world and is the second most common in developing countries.[1] Evidence from epidemiological and laboratory research has established that a persistent infection with Human Papillomavirus (HPV) causes most cases of cervical cancer, which however can be averted with the help of prevention strategies of vaccination and screening.[2-4] Visual inspection tests, cytology test and HPV DNA are some screening options which can facilitate early diagnosis and prompt treatment of cervical cancer cases.[5] Although the comparative cost- effectiveness of these tests has been assessed in the study to identify the option offering best value for money, this section tries to explore the feasibility of ground implementation of these tests, given the current set of resources health system of India has. Pertinent challenges for successful implementation of each type of test have also been explored in the subsequent discussion.

Among others, the main failure to implement an effective screening programme are related to the complexity of the screening process and the obstacles inherent in the health system. Poverty, limited access of the population to information, lack of knowledge of cervical cancer, the absence of sustained prevention programmes, lack of healthcare infrastructure required and lack of trained practitioners are the main obstacles to implementation of cervical cancer screening programmes, apart from socio- religious and cultural barriers. Lastly,

limited government resources may be allocated to competing public health programmes with higher visibility and international attention than cervical cancer screening.

A good screening programme shall ensure wide coverage of the target population; it must guarantee screening, management and adequate follow-up of patients; it shall be provided on-site and be low-cost, with minimum infrastructure requirement that can lead to immediate treatment if abnormal. Cervical cancer screening should be planned in line with other national programmes for Non- Communicable Disease screening/ control. Moreover, in order to implement cervical cancer screening policies, a sustained funding mechanism from the government is indispensable.

Challenges specific to the type of screening test

For developing countries like India, it is critical that they achieve relatively high screening coverage rates as well as ensure that screen-positive women receive appropriate diagnostic and treatment services. Sustained funding and quality assurance at every step should also be taken care of. Establishing a quality assured screening program, with national coverage can prove to be very challenging looking at the capacity and resources available for India.[6]

1. **VIA:**
    i. VIA-based screening was recommended as it is a low-cost point-of care diagnostic test. However, even a VIA based program needs training of healthcare provider / ANMs, continuous monitoring of quality and reliable quality assurance control, all of which require adequate resources in terms of manpower training. As a consequence and to maintain high quality, implementation of VIA screening at primary healthcare facilities would require close supervision, which is challenging to attain at a national level. It

would also require basic infrastructure such as an examination table, lighting, Cusco's speculum, gloves, swabs and acetic acid.

ii. VIA test also needs to be repeated every 3 years.

iii. Test sensitivity is on par or better than cytology but specificity is lesser than cytology.

2. **Cytology:**

i. A cytology-based screening programme takes around two weeks to make the result of screening test available, hence loss of follow up can be high.[7, 8] This is relevant because recalling patients for additional testing or treatment can be a critical component to a programme's success.

ii. Training needs to be imparted to ANMs (Auxiliary Nurse and Midwives) and LHVs (Lady Health Visitors) for sample collection.

iii. Along with other laboratory instruments/ consumables which are usually available in the hospital supplies, specific instruments (e.g., CERVEX brush) for sample collection will be required. Similarly, specific reagents will be required for microscopic examination of the samples.

iv. Cytopathology labs in Indian public health sector are mostly located at tertiary care centres and in urban areas in the private sector. Diversification of district hospital laboratories will be required in order to implement cytology based screening program at the district hospital.

v. Training of pathologists in pap smear reporting is essential to get sufficient sensitivity / specificity.

vi. Liquid based cytology (LBC) may be considered to increase accuracy and reduce unsatisfactory smears; cost per test is very high.

3. **HPV DNA:**

   i. Specific consumables will be required for sample collection (e.g., Digene Cervical Sampler), which is costly. Specimen Transport Medium (STM) to transport the collected sample to laboratory is also expensive. Sample needs to be carried in ice- box and stored at the temperature of -20 degree Celsius.

   ii. Specific equipment is required for examination of sample (e.g., Hybrid Capture- II assay), which is expensive.

   iii. It takes around two weeks to make the result of screening test available, hence loss of follow up can be high.

   Follow-up of screen positive women

   For any kind of screening test, the screen positive women must undergo colposcopy which is to be performed by a colposcopy specialist (usually a gynaecologist) This also involves training and continuing education.

Human Resource and Infrastructural Requirements for Implementation of Organized Screening Program at National Level:

1. **VIA:**

   VIA based screening program is least resource intensive in terms of both infrastructure and human resource. VIA test can be done by an ANM or LHV with a simple background training.[6] It can be done at the level of Sub- Centres or Primary Health Centres, which are often first line of contact between community and health sector. There is no need of sophisticated instruments or laboratory reagents in order to

perform the screening test. However, close supervision is essential to maintain the quality of the screening as the result of test is dependent upon the visual perception of healthcare provider executing the test. In order to ensure the quality, a cadre of quality- managers will be required to supervise the screening process if a visual inspection based nationwide screening program is opted for implementation. These quality managers may be stationed at district/ divisional level and would supervise screening activities in their area on rotational basis.

2. **Cytology:**

Resource requirements to roll- out cytology based screening programs will be higher as compared to visual based screening. Although samples for cytology based screening can be collected at the level of Sub- Centres or Primary Health Centres, however, the collected samples are required to be sent to cytopathology laboratories for further processing and examination. Specific instrument (e.g., CERVEX brush) is required for sample collection for cytology based screening. Moreover, ANMs and LHVs will require training for sample collection. Such single day training sessions may be held at district level and one healthcare provider needs to be trained only once. Cytopathology laboratories, where the samples are processed and examined, are currently located at the tertiary level health centres and teaching hospitals. These laboratories should be established at District Hospital level for an efficiently functioning cytology based screening program. However, in the initial phase of operationalization, laboratories situated at tertiary level health centres may work as sample processing centres as well as capacity building hubs. Once enough human resource is trained to work at district level and screening program attains pace, new laboratories may be established at District Hospitals.

Once the sample reaches the laboratory, it needs to be processed /stained. There are two ways with which the sample can be stained, manual or machine based. Manual staining is done by cyto-technician and experts suggest that one cyto-technician working according to its full efficiency can stain not more than 200 slides per day.[9] Therefore, for a population based organised screening program, a cadre of cyto-technicians needs to be established. The Indian Academy of Cytologists conducts regular courses and examination for Cytotechnicians and cytotechnologists and about 10 centers in the country are equipped to provide such training.[10] However, as there is no specific cadre / job, even the current cytotechnicians are not effectively being used in screening. Unsatisfactory Staining Rate in manual staining ranges from 5% to 20%.[9] This rate is less than 5% in case of Liquid based Cytology or machine based staining, however, establishing such machines at every District Hospital will also be a resource intensive exercise. A qualified cytotechnologist can be trained to operate these machines; however cost per test is high although larger volumes can offset this to some extent.

As cytology based cervical cancer screening program is not operational in India currently, there is lack of personnel who are exclusively involved in examination of stained samples. In some hospital-based cervical cancer screening programs, this work is being carried out by trainees/ residents working in the respective laboratories. However, once cytology based screening program is started at population level, stained samples need to be examined by qualified cyto-screeners, who are equivalent to senior lab- technicians and exclusively trained for the task. At present, this manpower is not available in the country. Possibility of effective utilization of medical college pathology departments and inclusion of private sector to form PPP

(public-private partnerships) can address the issue of manpower to some extent. A cadre of cyto-screeners needs to be established if cytology based screening program is opted for implementation at national level. Furthermore, continuous monitoring and proficiency testing of cyto- screeners will be required for quality assurance. Experts suggest that such proficiency testing should be done at least twice per cyto- screener per year. Apart from this, external quality assurance needs to be ensured with the help of Quality Managers.

3. HPV DNA:

HPV DNA based cervical cancer screening is most resource intensive among the three alternatives being considered in the analysis. Owing to expensive instruments and consumables required for the test, it is currently being done at selected tertiary care centres in the country only. Sample collection for HPV DNA testing may be done at the level of Sub Centres and Primary Health Centres by trained ANMs and LHVs. However, specific consumables will be required for sample collection (e.g., Digene Cervical Sampler), which is costly. Specimen Transport Medium (STM) to transport the collected sample to laboratory is also expensive. Sample needs to be carried in ice- box and stored at the temperature of -20 degree Celsius. Once the sample reaches the laboratory, specific equipment is required for examination of sample (e.g., Hybrid Capture- II assay), which is expensive. If HPV DNA based screening program is opted for implementation, laboratories for sample processing and analysis can be established at the level of medical colleges.

Indian experience of implementing cervical cancer screening- An appraisal of the journey so far:

Ministry of Health and Family Welfare, Government of India has recently launched the Operational Framework for the Management of Common Cancers which includes the use of VIA in primary care settings across India.[11] Guidelines for population based screening programmes for cervical cancer in India have been established for more than 10 years and are based on visual inspection tests.[12] However, despite the introduction of these national guidelines, screening coverage is still very low.[13] Population based cervical cancer screening program has yet to put in place. Community based cervical cancer screening program has been implemented on pilot basis in various parts of the country. This section tries to appraise these programs in order to identify factors working as facilitators and barriers in the implementation, so that future implementation of cervical cancer screening program at national level can be facilitated. These factors can be categorised as follows:

1. Factors related to screening test
2. Factors related to logistics and infrastructure
3. Factors related to target population
4. Factors related to human resource (quantity and quality)
5. Factors related to program design.

1. **Factors related to screening test:** A good test should be reliable and have good test characteristics (sensitivity and specificity) in addition of being convenient, safe and acceptable by target community members. Between November 2009 and July 2012, 7603 ever married women of age 30-59 years surveyed in a pocket of Dadri Tehsil, Uttar Pradesh, and were targeted for screening by Pap and VIA.[14] The study reported

a 50% sensitivity and 96.7% specificity for VIA in a realistic rural community setting. VIA screening was demonstrated as a feasible primary screening test for detecting high grade CIN and as to perform better when the Pap test is not feasible. In the published literature on cervical cancer screening implementation in India, for test accuracy at CIN Grade 2+, the VIA sensitivity ranged from 16.6% to 82.6%, and specificity 82.1% to 96.8%.[7, 15-20] At CIN Grade 3+, the sensitivity ranged from 7.7% to 67.9%, and specificity from 87.4% to 96.7%.[7, 14, 17, 21, 22]

Following factors have been reported in literature as possible causes of determining sensitivity and specificity for VIA conducted in community-based settings[23]:

i. Variation in test providers training.
ii. Light source when conducting the VIA test in the field settings.
iii. Preparation and storage of diluted acetic acid.

As compared to cytology based screening test, VIA is less resource intensive and easier to perform. Several studies in India have demonstrated that VIA and VILI have comparable sensitivity and specificity to cytology while offering the advantages of being simple to perform and cost-effective for large scale implementation.[24] Visual inspection method using acetic acid (VIA) has shown to be well accepted by women in India and the incidence of discomfort and pain during VIA is less than that reported for when Pap smears are conducted.[25, 26]

2. **Factors related to logistics and infrastructure:** Following logistical issues have been found in the reported attempts of implementation of cervical cancer screening program in India[27, 28]:

i. Ensuring uninterrupted cryo gas supply in the field clinics for treatment.
ii. Road connectivity.

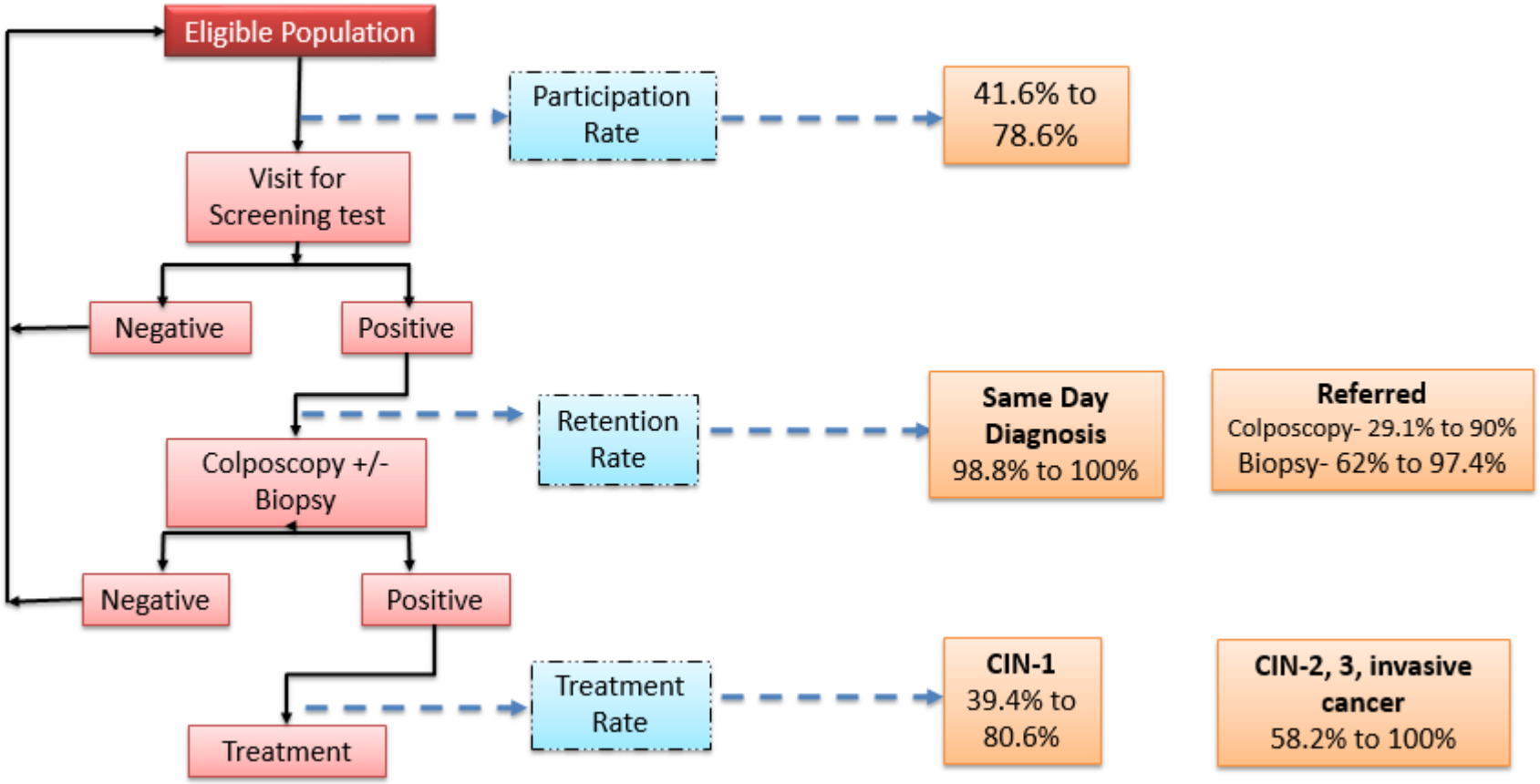
iii. Availability of health centres.

3. **Factors related to target population:** It includes factors pertaining to participation of eligible women in the screening program and their subsequent follow- up rates at different stages of diagnosis and treatment. Figure-1 depicts various process indicators pertaining to target population.

   In the community based cervical cancer screening studies conducted in India, participation rate ranges from 41.6% to 78.6%.[6, 14, 16, 17, 24, 28-30] In a study in rural Andhra Pradesh reported that 58% of the eligible women refused to participate in the study.[17] Reluctance to participate was reported as being related to perception that there was no need to go to the clinic when they have no symptoms.[17]

   Among those who have participated in the screening, retention for the subsequent steps (diagnosis and treatment) is also critical for the success of the screening program. Diagnostic follow-up of screened positive females is usually done using colposcopy and guided biopsies when necessary. This diagnostic follow up can either be done at the same day of screening, or screened positives can be referred to a higher centre for the same. Indian experience on implementation of cervical screening shows that loss to follow up is much higher if same day colposcopy or biopsy is not done. Studies show that loss to follow up is in the range of 0% to 1.2% if same day diagnosis is done.[6, 15, 16, 18-21, 25, 27, 30-33] However, when diagnostic colposcopy is not done in the same visit, loss to follow-up for diagnosis ranged from 10% to 70.9%.[6, 7, 15, 16, 18-21, 25, 27, 30-33] In case of diagnostic biopsies, it has been seen that there is 2.6% to 38% loss to follow up. The most common reason cited for this loss is participant's refusal to undergo biopsy.[15-17,25,28,31]

Figure 1: Process indicators related to target population in cervical cancer screening



Once confirmatory diagnosis of cervical cancer is done, women diagnosed as positives are referred to higher centres for treatment and management. Indian evidence shows that in case of women diagnosed with CIN Grade 1/pre-invasive cancer, treatment compliance rates ranges from 39.4% to 80.6%.[6, 15, 21, 27, 30, 34] Compliance to treatment ranged from 58.2% to 100% for women diagnosed with CIN Grade 2, 3, or invasive cancer.[6, 15-17, 21, 30, 34, 35]

4. **Factors related to human resource:** The need of qualified human resource specific to the type of screening test has been highlighted in the previous section. Apart from the quantity required for implementation of a national level screening program, quality of human resource is also a critical factor. In case of VIA, a subjective test, the staff needs to develop some degree of experience prior to getting comfortable in delivering accurate test results. VIA positivity rates are reported to be higher in the earlier stages compared to the later stages when conducting studies over a period of few years.[7] Therefore, when a national level cervical cancer screening program is planned, it would be highly important to provide adequate training to the test providers. In studies reporting providing training to the screeners in India, the IARC manual was consistently used. However, not all studies provided refresher trainings or evaluated their training.[7] Based on their experience in conducting screening programs, the Alliance for Cervical Cancer Prevention (ACCP) recommended providing screener training using a competency-based curriculum, combining both didactic and hands-on approaches, and conducting the trainings in a clinical setting similar to the service delivery conditions of the program site.[36]

5. **Factors related to program design:** As evidence in the Tamil Nadu Cervical Cancer Screening Pilot Project shows, efforts to mobilize women for participation were restricted due to a lack of health education.[37] In Mumbai also, it has been seen that high levels of participation, diagnosis and treatment compliance is because of effective health education programs.[34] Moreover, women participating in the screening program expects treatment for other health problems they were experiencing and seen to be disappointed to note that the program only provided cervical cancer screening.[25] Thus, it is advisable that cervical cancer screening should not run as a stand-alone program, and needed to be integrated with existing primary health services.

Hence, in order to facilitate the implementation of population based cervical cancer screening program, three major strategies are proposed:

1. There should be standardized training that maintains competency of test providers.
2. There should be collaborations with community-based organizations that encourage health education for population.
3. There should be minimal delay between screening, diagnosis and treatment. Screen-and-treat method may be applied reduce loss to follow-up, however, it may lead to overtreatment in some cases.

Guidelines for population based screening programmes for cervical cancer in India have been established for more than 10 years and are based on visual inspection tests.[12] However, despite the introduction of these national guidelines, screening coverage is still very low.[13]

Experience from the developed countries shows that they have mostly resorted to cytology based cervical cancer screening strategies as resource constraint is not a problem. France and Italy are having HPV DNA based screening program. Among the Asian countries, China has an organized VIA/VILI based screening program. Bangladesh had also started visual inspection based screening program in 2004.[38] Screening program of Sri Lanka is based upon both VIA and cytology.[39]

There are examples where countries aspired to implement organized cervical cancer screening programs but struggled with poor screening and diagnostic test sensitivity, difficulties maintaining quality control and adequate population coverage. Lessons should be learned from these countries and adequate quality control should be put in place in order to assure sustainable cervical cancer screening program in India.

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Annexure-1: Cost of Camp-Based Screening for Cervical, Breast and Oral cancer

Annexure 1 presents the results of the study undertaken to assess the cost of implementing camp based screening for cervix, breast and oral cancer in the Villupuram district of Tamil Nadu. Costs were assessed following the economic costing approach and bottom-up methodology. All costs pertained to the financial year 2016-2017. Data on annual consumption of both capital and recurrent resources, spent on the provisioning of camp based screening during the reference year of 2016-17 were collected and analysed. The total annual cost of this screening activity along with its distribution in terms of inputs and type of services has been computed. In addition, unit costs of specific services have also been estimated.

A total of 10,578 women underwent camp based screening, of which 9,173 women were screened for cervical cancer with VIA/VILI as well as HPV DNA test, as shown in table 1. Of the total women screened for cervical cancer, 5,260 women were also screened with Pap test. A total annual of INR 17,372,512 (INR 17.3 million of 1.73 crores) was spent in organising the screening, including the cost on laboratory processing for HPV DNA and Pap test. Input wise distribution of this annual cost has been shown in table 2 and figure 1. It was seen that of the overall cost, around 43% (INR 7,530,941) was spent on the salaries of the human resource, followed by spending on the purchase of consumables (41%; INR 7,091,592) and equipment (7%; INR 1,201,388).

In terms of distribution of total cost in terms of specific services, more than half (55%) of the overall cost was spent on sample collection (9.6%, INR 1,675,903) and laboratory processing of

the HPV DNA (37%; INR 6,397,502) and Pap test (8.9%; INR 1,541,301) (Table 3 and figure 2). This was followed by expenses for carrying out the household survey (15%; INR 2,624,619) and screening for breast cancer (9.8%; INR 1,702,191). Further, a total of INR 856,496 (5%) and INR 585,449 (3.4%) were spent on transport and administrative activities respectively.

With respect to cost per patient screened, INR 161 and INR 22 was spent for screening a women for breast and oral cancer (table 3). Specifically, unit cost (per patient cost) of screening a women with either of the 3 screening strategies for cervical cancer has been shown in table 4. Unit cost of screening a patient with VIA/VILI was INR 344 of which INR 103 was spent on the visual inspection and rest (INR 241) on the support activities. Further, unit cost of INR 980 was spent on screening a women with HPV DNA, of which INR 162 and INR 578 was spent on sample collection and laboratory processing. Similarly, INR 652 was consumed per women screened with Pap test, of which INR 118, INR 293 and INR 241 was spent on sample collection, lab processing and support activities respectively. Support activities include organising camp, administration, registration, transport, supervision and miscellaneous activities.

Input wise distribution of the total cost spent on the laboratory processing of the HPV DNA and Pap test has been shown in table 5 and 6 respectively. In case of HPV DNA, major spending of 93% (INR 5,975,476) was on the purchase of consumables. While in the case of lab processing for Pap test, major portion of 72% (INR 1,110,941) was spent on the salaries of the pathologist and lab technicians.

Table 1: Number of patients screened during the reference period from April 2016 to March 2017

Variable	N
Number of patients screened	10,578
Patients screened with VIA/VILI as well as HPV DNA	9,173
Patient screened with PAP test	5,260
VIA/VILI positive patients	3,890
HPV DNA positive patients	544
Pap positive patients	159

Table 2: Input wise distribution of total annual cost of camp based screening for cervix, breast and oral cancer during the financial year of 2016-17

Inputs	Annual cost (INR)
Human resource	7,530,941
Space/Building	538,775
Furniture	45,345
Equipment	1,201,388
Consumables	7,091,592
IEC Material	68,619
Stationary	86,056
Overheads	809,796
Total cost	**17,372,512**

Figure 1: Input wise distribution of total annual cost of camp based screening for cervix, breast and oral cancer

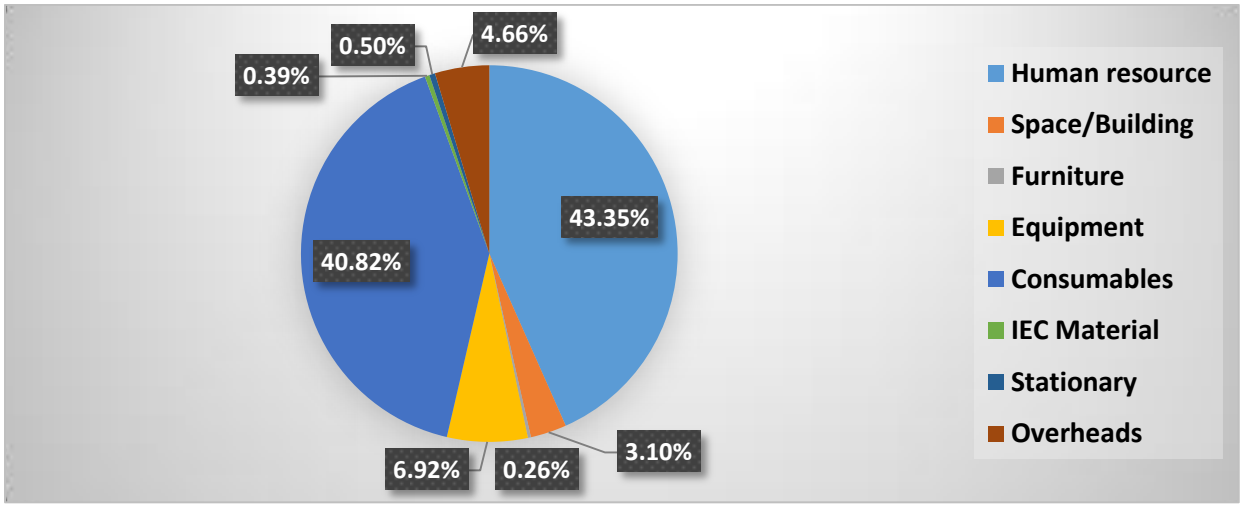


Table 3: Total annual and unit cost of specific services of camp based screening for cervix, breast and oral cancer

Specific activities	Annual cost (INR)	Unit cost (cost per patient) in INR
HPV DNA laboratory processing	6,397,502	578
Survey/IEC	2,624,619	248
Screening of Breast Cancer	1,702,191	161
Screening of Cervical Cancer (sample collection)	1,675,903	183
Pap smear (laboratory processing)	1,541,301	293
Transport	856,496	81
Administration	585,449	55
Research/Report writing	452,045	43

Organising for the camp	348,000	33
Registration of patients	345,322	33
Supervision	301,364	28
Screening of Oral Cancer	231,834	22
Meetings	201,777	19
Miscellaneous	108,708	10
Total	**17,372,512**	**1642**

Figure 2: Services wise distribution of total annual cost of camp based screening for cervix, breast and oral cancer

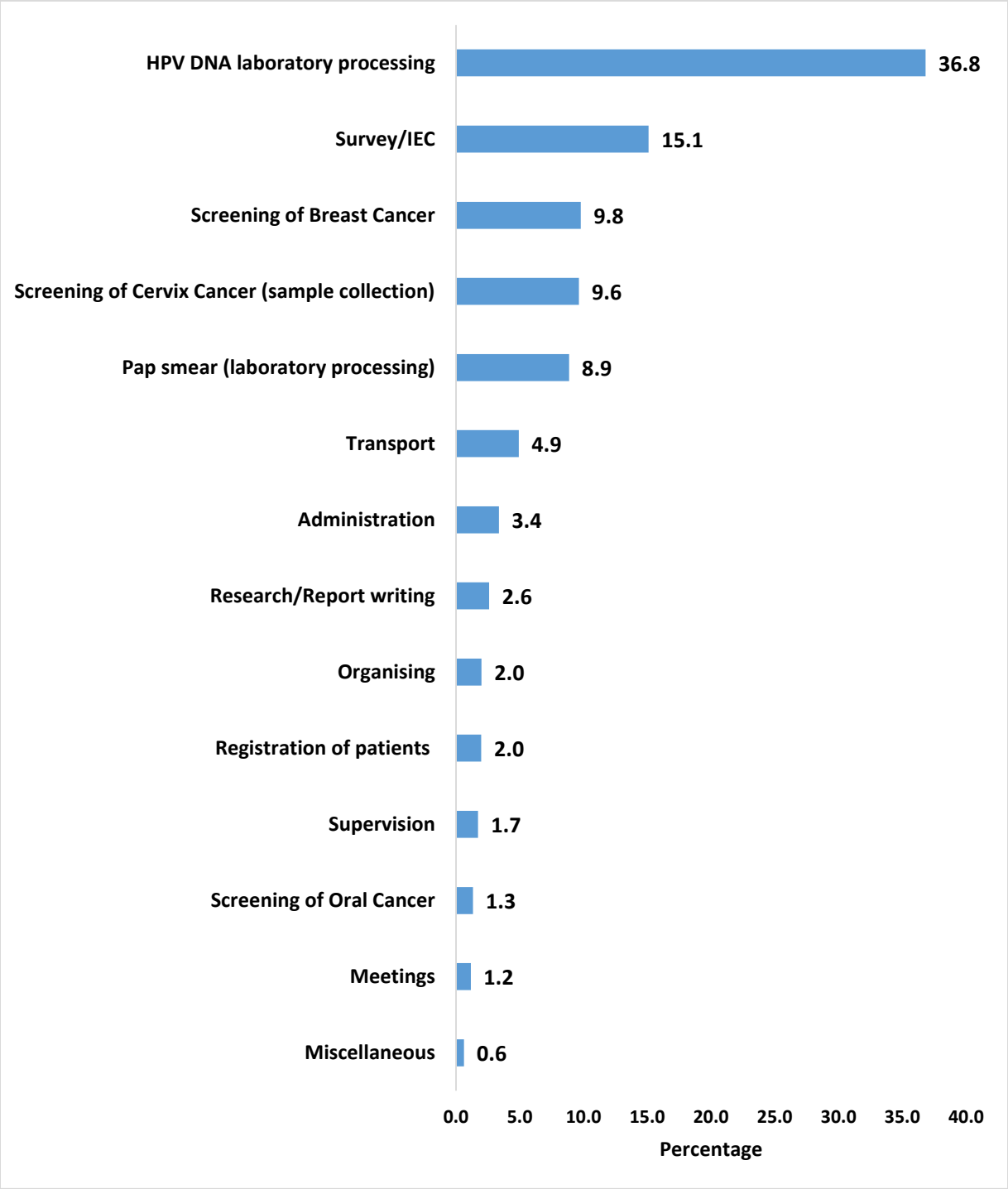


Table 4: Unit costs of various screening strategies for cervical cancer for camp based screening

Screening strategy	Per patient cost			
	Sample collection/visual inspection	Laboratory processing	Support activities*	Total
VIA/VILI	103		241	344
Pap test	118	293	241	652
HPV DNA	162	**578**	241	980

*Support activities include organising for the camp, administration, registration, transport, supervision and miscellaneous activities.

Table 5: Input wise distribution of total annual cost incurred on laboratory processing of HPV DNA test for cervical cancer screening

Inputs	Annual cost in INR
Human resource	132,000 (2)
Capital	15,654 (0.2)
Furniture	12,372 (0.2)
Equipment	177,409 (2.8)
Consumables	5,975,476 (93.4)
Overheads	84,592 (1.3)
Total cost	**6,397,502**

Table 6: Input wise distribution of total annual cost incurred on laboratory processing of Pap smear for cervical cancer screening

Inputs	Annual cost in INR
Human resource	1,110,941 (72)
Capital	315,509 (20.5)
Furniture	8,141 (0.5)
Equipment	15,489 (1)
Consumables	91,221 (5.9)
Total cost	**1,541,301**

Annexure-2: Cost of Treatment for Cervical Cancer in India

Introduction

Cancer is one of the leading causes of adult deaths globally. Globally, about 14 million new cancer cases are detected and 8 million people die of cancer every year. (1) Being the second most prevalent cancer among women, cervical cancer has become a major public health problem worldwide. (2) In low and middle-income countries (LMICs) like India, cancer cervix accounts for one quarter of global cervical cancer burden and 70% of the burden in South East Asia Region (SEAR). (2) It is estimated that approximately every 1 in 53 Indian women have cervical cancer as compared to 1 in 100 women in developed countries. (3) Further, cervical cancer accounts for 17% of all cancer deaths among women of ages 30-69 years in India. (2, 4)

The increase in demand along with the rise in the cost of cancer treatment has imposed a significant financial burden on the health systems. Introduction of high-end diagnostic techniques coupled with the intensive form of therapeutic interventions has led to an increase in the cost of cancer treatment. Since the last 3 decades, Government's budget allocation towards cancer care has increased by more than 500 times i.e., from INR 115 million (1980-85) to INR 60,000 million (2012-17) in India. (5, 6) Also, with the introduction of various publicly sponsored health insurance schemes across Indian states (Maharashtra, Tamil Nadu, Himachal Pradesh, Karnataka, Andhra Pradesh, etc.) since 2007, a large amount of funding has been pooled in towards cancer treatment. (7-9) Further, with initiatives like 'Mukh *Mantri Punjab*

Cancer Raahat Kosh' scheme in states like that of Punjab, free of cost and cashless treatment is provided to cancer patients. (10) Despite such significant spending on cancer care, there is a very limited availability of empirically derived published data on the cost of cancer treatment from India.

Only a single study could be searched from the Indian literature estimating the total cost of head and neck cancer treatment from a societal perspective. (11) Although, there are few other costing studies on cancer care, most of these are specifically focussed on OOP expenditure only. (12-15) Further, the package rates being used in most of the health insurance schemes are based on expert opinion, rather than on scientifically derived methodology. Moreover, as India is on the path of launching the world's largest government-funded healthcare insurance programme – Ayushman Bharat-National Health Protection Mission (AB-NHPM), there is an urgent need of generating estimates on empirically derived provider payment rates. (16) Considering this background, the present study was designed from a societal perspective for estimating both the health system cost and OOP expenditure incurred on the cancer cervix treatment in India. This would finally lead to the development of package rates for various treatment options available for treating cervical cancer.

Material & Methods

Study setting

The present study was conducted in the Departments of Obstetrics/Gynaecology and Radiation Oncology of a tertiary care public sector institute located in North India. With respect to the treatment of cervical cancer, there is availability of surgical care, radiotherapy, brachytherapy and chemotherapy. The Department of Obstetrics/Gynaecology has a total of 16 gynaecologists

and 70 resident doctors involved in providing specialised health care including the treatment for cervical cancer. Further, the radiotherapy department has 10 oncologists, 23 resident doctors, 6 medical physicists and 27 technical staff members involved in the planning/delivery of radiotherapy and brachytherapy. Specifically, the Gynaecology unit of radiotherapy department has a dedicated staff of 1 oncologist and 5 resident doctors for providing treatment to gynaecological cancers. There was an availability of 8 radiotherapy machines i.e., 2 using Cobalt-60, 4 using linear accelerators and 2 brachytherapy machines involved in providing cancer treatment at the time of data collection.

Flow of treatment process

Patients suspected of cervical cancer first reports to the outpatient clinic (OPD) of the Department of Obstetrics & Gynaecology. After clinical investigations (like biopsy, blood tests, etc.) at this level, the decision on the modality of treatment to be given to the patient is decided. Surgical treatment is offered in the Department of Obstetrics & Gynaecology. For further management i.e. radiotherapy, brachytherapy and chemotherapy patients are referred to the Department of Radiation Oncology of the institute.

Data collection

Health system cost

Health system cost was assessed following the concept of economic costing and bottom-up approach. (17, 18) Under this approach, the first step involved identification and classification of cost centres in terms of those directly involved in cancer treatment (Out-patient clinic, operation theatre, in-patient ward and radiotherapy units) and those acting as supportive or indirect cost centres (Laboratory, radio-diagnosis units, pharmacy, dietetics, laundry, etc.). (17) After

identification of respective cost centres, data on the quantity of various inputs i.e., both capital and recurrent resources spent on the delivery of service output was collected for the reference year of 2016-17.

Facility maps obtained from the engineering department of the institute were reviewed for assessing the dimensions of the space and building (in square feet). Further, the non-consumable stock register was reviewed for assessing the quantity of various medical/non-medical equipment and furniture items available in the department. Similarly, recurrent resources in the form of drugs and consumables, surgical supplies and other sanitary/stationary items were estimated by reviewing the consumable stock registers, indents/vouchers and pharmacy records. Data on the salaries (inclusive of all the annual incentives) received by each of the staff members, both partly or completely involved in the cancer treatment, was assessed from the payslips available from the accounts department of the institute. Patient files were assessed for details on the number of various diagnostic tests prescribed to the patient of cervix cancer. Following identification of inputs, data on the service output produced by each of the cost centres (in the form of the number of out-patient consultations, in-patient admissions, surgeries, radiotherapy sessions, etc.) was assessed from the routine medical records of the respective department.

The next step involved assigning a monetary value to each of the inputs. For estimating space costs, the current market rental price of a similar space was used, based on the interview with the key informants. The actual procurement prices as obtained from the procurement department and central store of the study hospital was used for pricing medical equipment, drugs and consumables (surgical, stationary and sanitary). Specifically, the price of the radiotherapy machines included the actual procurement price inclusive of annual maintenance cost and comprehensive maintenance cost paid to the supplier at the time of purchase. In case of non-

availability of procurement price data on any of the above-mentioned items and particularly for furniture items, market prices were used. The expenses incurred on overheads like water, maintenance, laundry and dietetics was obtained from the respective departments of the institute. In addition, the annual expenditure incurred on electricity was based on an actual measurement of the total electricity load in kilowatt-hour (in each of the specific rooms of the department) by the electrical engineers. For estimating the cost of various diagnostic tests, estimates from a previous study conducted in the same hospital were used. (19)

Time allocation interviews were conducted with both the medical and the technical staff for assessing their time spent on the different activities related to cervical cancer treatment. Specifically, medical staff members were asked for their time spent on activities done on regular basis (outpatient consultation, inpatient care, operation theatre, radiotherapy treatment, etc.) and fixed interval (meetings, teaching/training, etc.) i.e., weekly, monthly, annually, etc. Similarly, technical staff (specifically related to radiotherapy treatment) was interviewed for their time spent on planning activities (like CT simulation, contouring, dosimetry, etc.), quality assurance and radiotherapy delivery. Alongside these interviews, observation-based data was also collected for per patient time spent on CT simulation, contouring/dosimetry, and radiotherapy delivery. A total 3 faculty members, 4 senior and 4 junior residents, a medical physicist and 3 technical staff members were interviewed. The average life of the equipment was determined based on the interview with the staff members involved in using these equipment.

Out of Pocket expenditure

"Cost of Illness" approach classifying OOP expenditure into direct (including both direct health care and direct non-health care expenditure) and indirect health-care expenditure was followed. (20) As the main aim of the study was to estimate the cost of cancer treatment, only the direct health care expenditure incurred by the households were estimated. Direct health expenditure included expenses incurred on user fee/procedure fee, diagnosis, drugs and consumables and hospitalization. Further, the expenditure on transportation, boarding/lodging and food, were considered under direct non-health expenditure.

Data on OOP expenditure was elicited from 2 groups of patients. The first group comprised of patients who were recruited at the time of registration in the Department of Radiation Oncology and were prospectively followed up till the entire duration of their treatment. The second group consisted of those patients who had completed their treatment (within the last 6 months) and were retrospectively interviewed at the time of their follow-up visit. Patients from both the groups were first of all contacted in the outpatient clinic (OPD) of the Radiotherapy Department. For the first set of patients, all new registrations of HNC, during the period of data collection, were approached on a continuous daily basis for recruitment in the present study. For the second set, all those post-operative cancer cases, visiting the OPD clinic for their follow up visits, were asked for participation. Thus, consecutive sampling was followed till the number of patients to be included in the study was recruited.

The recruited patients were interviewed based on a pre-tested semi-structured interview scheduled, adapted from previews studies done in the similar settings. (11, 21, 22) It included information on socio-demographic characteristics, duration of treatment, consumption

expenditure, insurance status, OOP expenditure incurred on diagnosis/treatment and coping mechanisms for dealing with the same. Payment receipts and bills were checked where available from the participants to validate the reported expenditure. Expenditure incurred on pre-radiotherapy treatment (in the gynaecology department) and specifically on surgery (if any), was elicited retrospectively from both the groups. If the patient had taken any treatment before coming to the study hospital, OOP expenditure on account of the same was also recorded.

Data analysis

Health system cost

Capital expenditure was annualized to arrive at the equivalent annual cost taking into consideration the discount rate (time preference for money and inflation) and the lifespan of the capital equipment. (23) A discount rate of 3% was used based on the recommended guidelines. (17, 23) Space cost was calculated by multiplying the estimates of floor size of the facility with the local commercial rental price of the similar space. The total cost of the recurrent resources (drugs and consumables) was estimated by multiplying the unit price with the quantity of respective resource consumed. The resources (both capital or recurrent) which were shared in nature and were used in multiple activities, were apportioned towards each of the respective activity using appropriate apportioning statistics. For example, the staff members (consultants, junior/senior residents) which were jointly involved in a number of activities (outpatient consultation, inpatient care, operation theatres, planning and administration of radiotherapy, etc.), proportional time spent in each of these activities by the staff member was used as an apportioning statistic for allocating their salaries towards these particular activities. Finally, the health system incurred per patient on specific treatment modalities (surgery, radiotherapy and

brachytherapy) was estimated. Further, health system cost on an outpatient visit both in the Obstetrics/gynaecology and radiotherapy department was estimated along with the per bed day cost incurred on a patient in the inpatient ward.

Out of pocket expenditure

OOP data was analysed using SPSS version 23 (SPSS Inc., Chicago, IL, USA). (24) Mean OOP expenditure incurred on specific therapeutic modality i.e., surgery, radiotherapy, brachytherapy and chemotherapy was estimated, along with its distribution into direct and non-direct health care expenditure. OOP expenditure on treatment modality accounts for total expenditure incurred on OPD visits, IPD (if any), diagnostics, user fee, procedure fee, etc. for getting the treatment. Whereas cost of procedure includes the expenditure on specific therapeutic procedures like radiotherapy, brachytherapy, surgery etc. Financial risk was assessed in terms of catastrophic health expenditure and distress financing. Expenditure on cancer treatment which exceeded the threshold of 40% of non-food household consumption expenditure was considered as catastrophic health care expenditure. (25, 26) Those households undertaking borrowing (with or without interest) or selling of assets (cattle, land, jewellery, etc.) as coping mechanisms to deal with the OOP expenditure were categorised as suffering from distress financing. (27) ((28, 29) All the cost and expenditure estimates in the present study were calculated in Indian National Rupees (INR) and pertain to the year 2016-17.

Ethical consideration

Ethical approval was obtained from the Institute Ethics Committee of the Post Graduate Institute of Medical Education and Research, Chandigarh, India (Reference number: IEC-12/2017-786). Written informed consent was obtained to interview the patients as well as staff members.

Results

Health system cost

Unit cost

The unit cost per outpatient consultation was INR 324 and INR 547 in the Department of Obstetrics/Gynaecology and Radiotherapy respectively. Further, per bed day cost of INR 2742 was incurred in the inpatient ward of the Obstetrics/Gynaecology department. Specifically, unit health system cost incurred on various treatment options varied from INR 33,569 to INR 41,388 for a patient treated on brachytherapy and 3-dimensional radiotherapy respectively (Table 1).

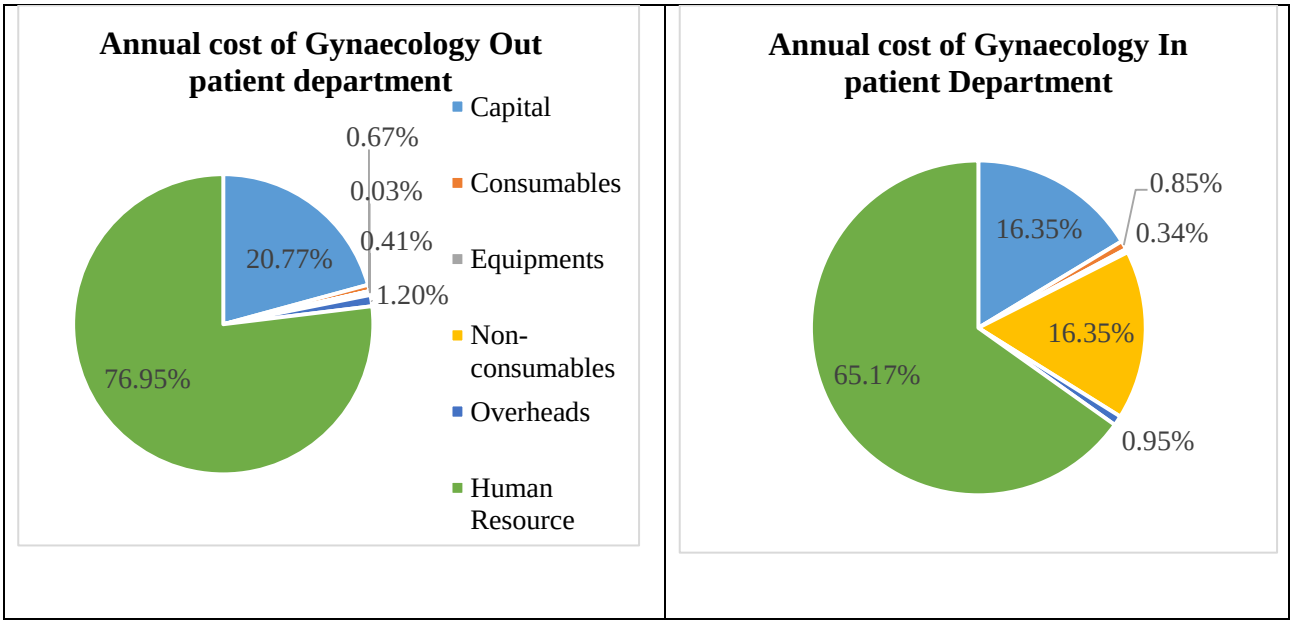
Table 1: Unit health system cost on health services for cervix cancer treatment at a tertiary level public sector hospital

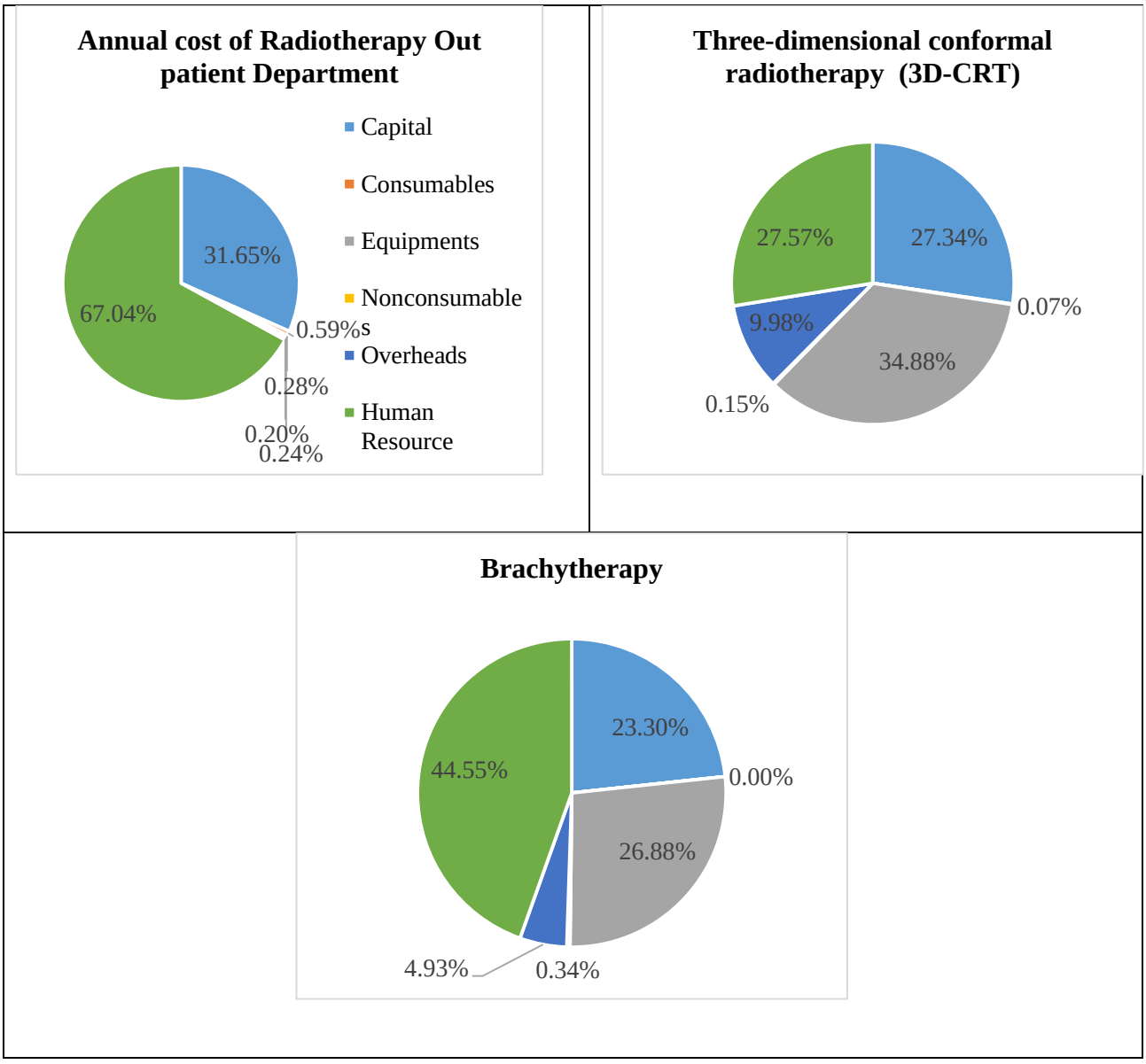
Department	Service	Unit	Unit Cost (INR)
Obstetrics & Gynaecology	Outpatient consultation	per patient visit	324
	Inpatient care	per bed day	2742
Radiation Oncology	Outpatient consultation	per patient visit	547
	3-dimensional conformal radiotherapy (3D-CRT)	per patient	41,388
	Brachytherapy	per patient	33,569
	Diagnostics	per patient	3052

Input wise distribution of cost

To deliver out-patient department (OPD) services in gynaecology and radiotherapy departments, more than 90% of the cost is contributed by human resource and capital cost. Further more than half of the total cost (65%) is contributed by the salaries of the staff followed by both capital (16%) and non-consumables (16%). For delivery of radiotherapy and brachytherapy, 35% and 27% of the cost is attributed to equipment as the sophisticated and expensive machines are used for service delivery. The detailed input wise break up for different services delivered by the health system for cervical cancer care is given in figure 1.

Fig 1: Input-wise distribution of annual health system cost of various services delivered for cervical cancer care





Out of Pocket expenditure

Sample characteristics

A total of 237 patients were recruited, of which 64 were prospectively interviewed and 173 were covered retrospectively. Among these recruited patients, 60% (118/237) were aged 46-60 years, 47% (112/237) were illiterate, 72% (177/237) belonged to Hindu religion, 63% (149/237) resides

in rural areas and 70.5% (167/237) reported not having any type of health insurance (Table 2). Around 65% and 26% of the patients were in stage I/II and stage III/IV respectively at the time of diagnosis of cancer respectively and for 9.7% cancer patients' stage of cervical cancer was unknown. In terms of treatment undertaken, 13% had undergone radiotherapy alone, 25% undertook radiotherapy combined either with brachytherapy or chemotherapy, 60% were treated with radiotherapy along with brachytherapy and chemotherapy and remaining 2% were operated surgically followed by other therapeutic interventions.

Table 2: Socio-demographic Characteristics

Variable	Category	N (%)
Age	Less than 30 years	3 (1.2)
	30-45 years	49 (21)
	45-60 years	139 (59)
	60 years and above	46 (19)
Marital Status	Married	236 (99.6)
Education	Illiterate	112 (47)
	Primary	46 (19)
	Secondary	49 (21)
	Senior Secondary & above	30 (13)
Occupation	Regular salaried/Wage employee	14 (6)
	Rentier/Pensioner/Other remittances	19 (8)
	Too old to work	11 (5)
	Housewife	188 (79)
	Others	5 (2)

Religion	Hindu	171 (72.2)
	Sikh	55 (23.2)
	Others	11 (4.6)
Locality	Urban	88 (37)
	Rural	149 (63)
Insurance	Yes	70 (30)
	No	167 (70)
Income Quintiles	Poorest	47 (19.8)
	Poor	48 (20.3)
	Middle	47 (19.8)
	Rich	48 (20.3)
	Richest	47 (19.8)
Stage of cervical cancer	Stage 1	30 (12.7)
	Stage 2	121 (51.1)
	Stage 3	60 (25.3)
	Stage 4	3 (1.3)
	Unknown stage	23 (9.7)
Treatment modality	Radiotherapy alone	30 (13)
	Radiotherapy along with Brachytherapy	33 (14)
	Radiotherapy along with Chemotherapy	26 (11)
	Radiotherapy along with brachytherapy and chemotherapy	142 (60)
	Surgery followed by other treatment modalities	6 (2)

Out of pocket expenditure

Stage-specific mean OOP expenditure incurred by a cervical cancer patient varied INR 27,886 (95% CI: 24782-30,990) for a patient in stage III to INR 48,477 (95% CI: 38,395-58,558) for a patient treated in stage 1 as shown in table 3. The mean OOP expenditure is high in younger patients ranging from INR 54,156 (SE 13,188) in patients below 30 years to INR 31,322 (SE 1298) in age above 60 years. With rise in education status, OOP expenditure increases from INR 28,326 (SE 1249) in illiterate to INR 47,853 (SE 5147) in senior secondary and above. In terms of household income quintiles, OOP expenditure increases from poorest to richest quintile i.e. from INR 24,995 (SE 1315) to INR 44,668 (SE 3731) respectively. Treatment modality specific OOP expenditure varies from INR 95,724 (SE 17096) for surgery along with other modalities to INR 25,217 (SE 2074) for radiotherapy along with chemotherapy. In terms of specific treatment procedure, maximum OOP expenditure of (INR 95,754; 95% CI: 19426-54441) was incurred on surgery alone, followed by that on radiotherapy alone (INR 36,934; 95% CI:12,295-14,539), brachytherapy (INR 5841; 95% CI: 5166-6518) and chemotherapy (INR 4229; 95% CI: 3606-4853) as shown in table 4. About 95% of the cervix cancer patients incurred a mean expenditure of INR 16, 343 (11,543- 21,142) before coming to study hospital.

Table 3: Out of pocket expenditure incurred during treatment of cervical cancer

Variable	Category	Mean OOP (SE)	p-value
Age	Less than 30 years	54,156 (13188)	0.228
	30-45 years	35,997 (3169)	
	45-60 years	34,340 (1634)	
	60 years and above	31,322 (1298)	

Education	Illiterate	28,326 (1249)	<0.001
	Primary	38,983 (3774)	
	Secondary	35,490 (2228)	
	Senior Secondary & above	47,853 (5147)	
Locality	Urban	36,240 (2476)	0.263
	Rural	33,230 (1456)	
Insurance	Yes	30,185 (2639)	0.038
	No	36,092 (1457)	
Income Quintiles	Poorest	24,395 (1315)	<0.001
	Poor	29,943 (1640)	
	Middle	35,785 (3316)	
	Rich	37,004 (2942)	
	Richest	44,648 (3731)	
Stage of cervical cancer	Stage 1	48,477 (4929)	<0.001
	Stage 2	33,273 (1581)	
	Stage 3	27,886 (1551)	
	Stage 4	32,739 (9087)	
	Unknown stage	38,634 (6078)	
Treatment modality	Radiotherapy alone	26,818 (2578)	<0.001
	Radiotherapy along with Brachytherapy	32,813 (3570)	
	Radiotherapy along with Chemotherapy	25,217 (2074)	
	Radiotherapy along with brachytherapy and chemotherapy	35,477 (1352)	
	Surgery followed by other treatment modalities	95,754 (17096)	
	Total OOP expenditure	34,348 (1298)	

Table 4: Treatment specific direct & non-direct medical out of pocket expenditure

Treatment procedure	Direct Medical Expenditure in INR (95% CI)	Non-direct Medical Expenditure in INR (95% CI)	Total Expenditure in INR (95% CI)
Before coming to study hospital	11,181 (6715-15647)	1828 (934-2722)	16343 (11543-21142)
Pre-radiotherapy*	8143 (7215-9071)	4740 (3878-5601)	10,090 (8922-11259)
Radiotherapy	3724 (3424-4023)	9706 (8673-10739)	13,417 (12295-14539)
Brachytherapy	4049 (3684-4414)	1921 (1433-2408)	5841 (5166-6518)
Chemotherapy	3416 (2906-3926)	871 (684-1059)	4229 (3606-4853)
Surgery	30,166 (17360-42971)	6669 (625-12912)	36,934 (19426-54441)

*Pre-radiotherapy expenditure includes expenditure incurred during the preliminary investigations in the outpatient clinic on the Obstetrics and Gynaecology department.

Financial Risk Protection

Among the recruited patients, 64% (n = 151) suffered from catastrophic health expenditure at the 40% threshold. On changing the threshold to 20%, 30% and 50%, the prevalence of catastrophic expenditure changed to 86%, 77% and 52% respectively. Logistic regression at 40% threshold showed that the odds of catastrophic expenditure were significantly higher in lowest income quintile patients (OR: 32.73, p-value:<0.001), as compared to the highest income quintile (Table 5). Thirty per cent of the patients (n=71) reported having faced distress financing mechanisms during the treatment of cervical cancer in the study hospital. Logistic regression showed that the odds of having distress financing is highest in the age group of 30-45 years (OR: 7.41, p-value:<0.001) (Table 6).

Table 5: Prevalence of catastrophic health expenditure during cervical cancer treatment and its risk factors

Variable	Category	Number with catastrophic expenditure (%)	Odds ratio (95% CI)	p value
Age	Less than 30 years	1 (33)	1.02 (0.040-25.89)	0.993
	30-45 years	30 (61)	1.20 (0.41-3.50)	0.736
	45-60 years	95 (68)	1.94 (0.78-4.83)	0.153
	60 years and above	25 (54)	1	
Education	Illiterate	80 (71)	1.13 (0.37-3.43)	0.828
	Primary	32 (70)	1.73 (0.43-5.35)	0.370
	Secondary	29 (59)	1.76 (0.58-5.34)	0.315
	Senior Secondary & above	10 (33)	1	
Locality	Urban	44 (50)	1	
	Rural	107 (72)	1.52 (0.78-2.98)	0.222
Insurance	Yes	42 (60)	0.85 (0.42-1.72)	0.658
	No	109 (65)	1	

Income Quintiles	Poorest	43 (92)	32.73 (8.31-129.01)	<0.001
	Poor	37 (77)	8.40 (2.92-24.18)	<0.001
	Middle	34 (72)	7.11 (2.55-19.79)	<0.001
	Rich	25 (52)	3.08 (1.20-7.96)	0.020
	Richest	12 (26)	1	
Treatment modality	Radiotherapy alone	21 (70)	0.47 (0.05-4.90)	0.530
	Radiotherapy along with Brachytherapy	20 (61)	0.49 (0.05-5.21)	0.552
	Radiotherapy along with Chemotherapy	19 (73)	0.36 (0.03-3.73)	0.390
	Radiotherapy along with brachytherapy and chemotherapy	87 (61)	0.37 (0.04-3.21)	0.368
	Surgery followed by other treatment modalities	4 (67)	1	

Table 6: Prevalence of distress financing during cervical cancer treatment and its risk factors

Variable	Category	Number with distress financing (%)	Odds ratio (95% CI)	p value
Age	Less than 30 years	0	0	
	30-45 years	24 (49)	7.41 (2.36-23.21)	<0.001
	45-60 years	40 (29)	2.77 (1.01-7.61)	0.047
	60 years and above	7 (15)	1	
Education	Illiterate	45 (40)	2.58 (0.71-9.31)	0.149
	Primary	13 (28)	1.81 (0.47-9.31)	0.389
	Secondary	8 (16)	0.89 (0.23-3.49)	0.871
	Senior Secondary & above	5 (17)	1	
Locality	Urban	18 (21)	1	0.12
	Rural	53 (36)	1.41 (0.69-2.88)	0.342
Insurance	Yes	17 (24)	0.55 (0.26-1.15)	0.113
	No	54 (32)	1	
Income Quintiles	Poorest	22 (47)	1.99 (0.62-6.38)	0.246

	Poor	20 (42)	1.61 (0.53-4.89)	0.402
	Middle	12 (26)	0.92 (0.29-2.95)	0.924
	Rich	9 (19)	0.68 (0.21-2.25)	0.680
	Richest	8 (17)	1	
Treatment modality	Radiotherapy alone	16 (53)	2.02 (0.24-16.74)	0.516
	Radiotherapy along with Brachytherapy	6 (18)	0.60 (0.07-5.40)	0.650
	Radiotherapy along with Chemotherapy	10 (39)	0.84 (0.10-6.85)	0.872
	Radiotherapy along with brachytherapy and chemotherapy	37 (26)	0.68 (0.21-2.25)	0.697
	Surgery followed by other treatment modalities	2 (33)	1	

Discussion

Besides the high disease burden, rising cost of cancer treatment has imposed a huge financial burden both on the health systems as well as on the households. With only 12% of the urban and 13% of the rural population under any kind of health insurance coverage and around 3/4th of the health care expenditure being borne by the families, diagnosis of cancer becomes a devastating news for the household because of the constant financial and psychological hardships caused by its costly treatment. (30, 31) Further, despite the introduction of several publicly financed health

insurance schemes across states in India to reduce the reliance on OOP expenditure, evidence shows that there has been no decline in the OOP payments. (32) Moreover, as India is on the pathway of launching the world's largest health insurance scheme, the need of cost data for various treatment regimens available for cancer treatment gains considerable importance in designing appropriate package rates that could adequately provide financial risk protection to the insured households. (16)

The present study was designed to estimate the health system cost as well as OOP expenditure incurred on various therapeutic procedures available for the treatment of cervical cancer. As most of the cancer treatment is available at the tertiary care level in India, the present study was undertaken in a large public sector tertiary care hospital located in North India. We found that in addition to health system cost of INR 41,388 patient had to spend an additional amount of INR 23,507 (combination of pre-radiotherapy and radiotherapy expenditure) for getting radiotherapy treatment. Similarly, an additional amount of INR 15,931 was borne by the households for getting brachytherapy treatment along with the health system cost of INR 33,569. The study also reports that around 64% and 30% of the households suffered from catastrophic health expenditure and distress financing respectively due to OOP expenditure incurred on the cancer treatment.

The present study is one of its kind in comprehensively estimating the total cost of cancer treatment considering both the health system cost and OOP expenditure. In the context of India, the whole treatment expenditure is paid by the patients (in the absence of any health insurance) for getting health care from private facilities, While, treatment in public health facilities is subsidized by the government, patients still have to bear some proportion of total cost in the form of spending on the drugs, consumables and diagnostics purchased from the market. Thus, it

becomes necessary to estimate both the health system cost and OOP expenditure while estimating the total cost of treatment in public sector hospitals, as estimating only either of these may not reflect the true of cost of the treatment. The literature shows that there is only a single study which has comprehensively assessed the cost of treating head and neck cancer from a societal perspective. (11) Other studies were specifically either focussed either on health system cost or on OOP expenditure. (13-15, 33)

Comparison of OOP expenditure and financial risk protection

A systematic review focusing on low and middle-income countries (LMICs) reported that non-communicable diseases (NCDs) affected households spend a mean OOP expenditure ranging between 5% and 59% of either the household income or consumption expenditure or non-food consumption expenditure. (34) Another review from the same region reported catastrophic expenditure due to NCDs to be in the range of 0-34% of the study population. (35) Further, a study specifically focusing on cancer and conducted across 8 countries of the south-east region (SEAR) stated the prevalence of catastrophic expenditure of 48% as compared to 64% in the present study. (36) This finding of these studies is difficult to be compared with the present study due to variation (included in the review) in the methodology used for measuring catastrophic spending. Firstly, some of the studies included in the above-mentioned review had taken the threshold for catastrophic expenditure as relative to total household expenditure; while others had measured catastrophic expenditure relative to household 'non-food expenditure'. Secondly, the level of the threshold used was varied from 10% to 40%. The high level of catastrophic health expenditure in the present study as the study hospital is a tertiary level public hospital which is a referral site for about 6 states and patients approaches with advance stages of cervical

cancer. Further, lack of screening, late detection, inadequate referral mechanism, treatment modality used affects the catastrophic health expenditure by the patient.

The SEAR study also reported that those in lower income quartiles and without health insurance have significantly higher odds of incurring catastrophic expenditure. (36) The present study was on similar lines with relation to lower income groups, but showed an opposite trend for the latter two findings, as the presence of any insurance/subsidy entitlement did not have any effect on financial catastrophe. A previous review of health insurance schemes in India supports the findings of the present study on the lack of protective effect of insurance on catastrophic spending. This could be due to the design features of the scheme and purchasing mechanisms under current publicly financed insurance schemes.

In a study on head and neck cancer in north India, OOP expenditure on radiotherapy by 3D-CRT is INR 40,377, which is INR 26,818 in the present study for cervical cancer. (11) This variation may be due to difference in number of radiation cycles for various types of cancers. On comparison of package rates under various publicly financed health insurance schemes, the package rates for 3-dimensional conformal radiotherapy (3D-CRT) varies from INR 50,000-75,000 whereas in the present study health system cost is INR 41,388. Similarly, for interstitial brachytherapy package rates varies from 15,000-30,000 and in present study the health system cost comes out INR 33,569 (Table 7). Thus, there is need for further research to develop package rates of publicly health insurance schemes based on scientific methodology and health system costing.

Table 7: Package rated for different treatment modalities for cervical cancer across various publicly financed health insurance schemes

Treatment Modality	Package rates under various Insurance schemes in INR					
	RSBY *	AB-NHPM[$]	CMCHIS[#]	MJPJAY[@]	Aarogyasri[+]	Present study
3-Dimensional conformal radiotherapy	75,000	50,000	75,000	75,000	75,000	64,895
Brachytherapy (Interstitial)	15,000	30,000	15,000	15,000	15,000	49,500

[*]Rashtriya Swasthiya Bima Yojana [$]Ayushman Bharat-National Health Protection Mission; [#]Chief Minister Comprehensive Health Insurance Scheme, Tamil Nadu; [@]Mahatma Jyotiba Phule Jan Arogya Yojana, Maharashtra; [+]Aarogyasri Health Care Trust, Telangana

Like the catastrophic health expenditure, the prevalence of distress financing was also higher among the poorest and decreased in rich households. This finding can be corroborated to the results of the recent NSS round (Jan-Jun 2014), which also showed that those in the upper-income groups show less dependency on borrowing or selling of assets as compared to low-income ones. (30) The issue of distress of distress financing raises another aspect of inequity in availing healthcare services as households undertaking relatively risky coping strategies of borrowings or selling of assets have to not only mobilize additional sums of money for the present treatment but also have to bore the brunt in the future while arranging for basic commodities of food and shelter, finally leaving them vulnerable to impoverishment.

Patients visiting the study hospital were from 6 different north Indian states of India. Further, about 60% of recruited patients were from rural areas, who have to incur additional expenses in form of travelling, boarding and lodging. This is also reflected through the high proportion of non-direct OOP expenditure ranging from 33% to 72% while getting treatment with radiotherapy to brachytherapy respectively. Thus, there is a need for developing an adequate network of radiotherapy facilities so that patients do not have to travel far from home for getting cancer treatment.

Methodological issues

Standard bottom up and economic costing methods were followed for estimating the health system cost and resource data was taken for 1 complete year for excluding seasonal variation in service utilization. Precisely for overhead, data on the quantity of resources were available in aggregated form. For assessing the overheads cost towards cervical cancer treatment, standard apportioning statistics were used. However, in most of the costing studies from India, the contribution of the overhead cost to the total cost is reported to be > 5%. Thus, it is unlikely to bias the overall findings.

Standard Cost of Illness approach was used for estimating the OOP expenditure. Further, among the total recruited patients interviewed for OOP expenditure, around $1/4^{th}$ of them were interviewed from the start of treatment till its end on a daily basis to minimize the recall bias. Whereas, the remaining $3/4^{th}$ were interviewed following up to 6 months of the treatment. The national sample survey of India, recommends a reference period of the last 365 days or 1 year for assessing the expenditure incurred in rare events like that of hospitalization. Cancer treatment in the form of surgery or radiotherapy/brachytherapy given either alone or in combination is an

intense form of treatment, spanning over the duration of 3-4 weeks. Hence, a recall period of up to 6 months was considered appropriate. Moreover, there was no significant difference in the average OOP expenditure among those recruited prospectively and those interviewed retrospectively, suggesting the absence of any systematic recall bias.

Conclusion

High OOP expenditure incurred on cancer treatment results in a lack of adequate financial risk protection. This calls for strengthening the capacity of existing public health sector in terms of its infrastructure and supplies such that patients are not forced to spend out-of-pocket. Further, as India moves on towards Universal Health Coverage (UHC), high rates of catastrophic health expenditure on account of cancer treatment implies that there is a need to enhance coverage of risk pooling mechanisms for reducing reliance on OOP payments. Although various publicly sponsored health insurance schemes provide for cancer treatment, there is a need to adequately revise the height of benefit packages (the level of financial protection as a percentage of total health care costs) of these schemes based on empirically derived cost estimates. Lastly, there is a need to focus on prevention interventions like that of screening and vaccination leading to the reduction both in the incidence of cancer and the treatment expenditure.

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Annexure-3: Health Related Quality of Life in Patients of Cervical Cancer in India

Introduction:

In diseases like cancer, both the disease and the treatment have negative impact on the quality of life of cancer patient. Therefore, patients of such diseases not only focus on how long they live, but also on the quality of life for the duration for which they would be living. Health related quality of life has been described as an individual's perception of their position in life, and in the context of culture and value systems in which they live, and also in relation to their goals, expectations, standards, and concerns.[1] It encompasses the physical, psychological, and social domains of health, seen as distinct areas that are influenced by a person's experiences, beliefs, expectations, and perceptions.[2] Evaluation of health related quality of life in cervical cancer patient is important to monitor and evaluate the effectiveness of treatment and intervention as well as for undertaking health technology assessment (HTA) studies and for designing the intervention for improving patients' outcome. Moreover, measurement of quality of life becomes important to capture the broadened definition of health which goes beyond accounting for just the traditional measures of mortality and morbidity.

Measurement of quality of life of cervical cancer patients aspires to capture comprehensive aspect of how the disease and treatment impacts in terms of symptoms, therapeutic effects, side effects, patient functional status, and financial impact. Some functional disorders occur following therapies such as surgery and radiotherapy, which adversely impact the health related quality of life. It involves surgical alteration of female genital anatomy affecting directly their perception of

body image and sexual functions; radiotherapy which could damage the vaginal mucosa and epithelium; and chemotherapy which could induce various adverse effects like nausea, vomiting, diarrhoea, constipation, mucositis, weight changes and hormonal changes.[3, 4] In addition to it, various psychological factors including low self-esteem, changes in self-image, beliefs about the origin of cancer, marital tensions, fears and worries can substantially affect the quality of life of cervical cancer patients.[3, 4]

Two types of instrument could be used to measure health related quality of life in cancer patients, namely generic instrument and specific instrument.[5] The generic instruments are used to collect information on healthy as well as ill patients at the population level or in clinical practice, and allow for the comparison of HRQOL across different conditions and settings and between healthy and ill patients.[6, 7] Disease-specific instruments, on the other hand, aim to collect information on symptoms or disease-specific health problems from more specific populations with a given disease or symptom.[6, 7] The examples of specific instrument that can be used for measuring health related quality of life in cervical cancer patients are European Organization for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30)[8], Quality-of-Life questionnaire cervical cancer module (QLQ-CX24)[9], Functional Assessment of Cancer Therapy-General (FACT-G)[10], and Functional Living Index-Cancer (FLIC)[11]. The examples of generic instrument for measuring health related quality of life are the EuroQOL 5-Dimension questionnaire (EQ-5D)[12], Short Form-6 Dimension (SF-6D)[13], and Health Utilities Index Mark 2 and Mark 3 (HUI2/3)[14]. The generic preference-based measures of health related quality of life are commonly used in the HTAs, as they provide a multidimensional description of health that is combined with survival to generate quality-adjusted life-years (QALYs)[15], which is an outcome in the cost utility analysis method of economic evaluation.[16]

Barring a few examples from Thailand and Indonesia, not many studies have been done on QoL of cancer cervix survivors in the developing world including India, and hence there is less literature on this subject.[17-19] Studies done in India to assess the quality of life of cervical cancer patients have used disease specific instruments[3, 19], however, the EuroQol five-dimensional questionnaire (EQ-5D) is a preferred instrument for assessing quality of life in HTAs in many countries.[20, 21] Therefore, there is a lack of India specific study which gives information about generic preference based quality of life status of cervical cancer patients, which can be used in estimation of QALYs and HTA studies in India. This study aims to measure health related quality of life of cervical cancer patients using EQ-5D-5L, which has not been performed in India so far.

Methodology:

Study settings

A cross sectional study was carried out to recruit study participants from department of radiotherapy of a tertiary care hospital in North India. Participants comprised of those cervical cancer patients whose radiotherapy treatment had completed at least 4 months ago and were now visiting the department for follow- up. A gap of 4 months after the completion of treatment was considered so that immediate deterioration in health related quality of life of patients because of treatment related side effects of radiotherapy wanes off and patient achieves a stable quality of life.

Data collection

A total of 223 patients of cervical cancer treated in radiotherapy ward were recruited during the period between January 2017 and March 2018. All the patients, whose radiotherapy treatment had completed between four months and two years prior to the date of recruitment in the study, were considered eligible to participate. Patient recruitment was done using consecutive sampling by appropriately qualified and trained research assistants. Eligible participants were identified by trained research staff and OPD registers were reviewed daily. All baseline interviews were administered face-to-face at the hospital by trained staff.

Quality of life tools

To measure health related quality of life, EuroQOL five dimensions questionnaire with five levels (EQ-5D-5L) and EuroQOL Visual Analogue Scale (VAS) were selected for interviewing the patients with cervical cancer. VAS is a direct tool most widely used to measure the preferences of individuals for health outcomes directly.

EQ-5D-5L

EQ-5D is a generic questionnaire intending to cover the crucial aspects of health significant to patients consisting of five attributes: mobility, self-care, usual activity, pain/discomfort and anxiety/depression.[22, 23] Each attribute of EQ-5D-5L has five levels: (1) no problems, (2) slight problems, (3) moderate problems, (4) severe problems and (5) extreme problem. The EQ-5D health state is converted into a utility score using a country-specific scoring algorithm, namely, value set. EQ-5D was used to produce a single utility score between <0 and 1 based on individuals' responses to questions regarding the impact of cervical cancer on their lives, thus defining 3125 (5^5) possible health states, along with 'unconscious' and 'dead' state making a

total of 3127 in all.[22] Utility score of '1' means perfect health and '0' implies death with a range of 1 to -0.549.[24] It is an indirect method as utility scores are calculated on the basis of a reference population. We used the reference population value set of Thailand, a neighbouring country of India, as quality of life (QOL) tariff values for EQ5D5L or EQ5D3L health states for Indian population are not available.[25-28] Moreover, the draft Indian reference case for undertaking economic evaluation for undertaking HTA in India, which is being developed by Health Technology Assessment in India (HTAIn), Ministry of Health and Family Welfare, Government of India recommends the generation of Indian value sets as a long term strategy. However, in the interim period, it recommends using the Thailand value-set to calculate quality of life index scores.[29]

In the current study, 223 patients of cervical cancer who received treatment in department of radiotherapy of a tertiary care institute in the north India were administered this tool. The patients were asked to rate the five attributes of health individually. For example, if a patient attributed score 3 in mobility domain, 2 in self-care, 2 in usual activity, 3 in pain/discomfort and 4 in anxiety/ depression, a single heath state was computed for this patient as 32234. Further, a single utility score using reference population for Thailand (with a range of 1 to -0.412) was computed for cumulative single health states of 223 patients. Afterwards, mean stage specific utility scores for patients falling into FIGO classification Stage I, II, III and IV[30] were calculated.

EQ-VAS

EQ-VAS is another generic yet direct tool used to measure the preferences of individuals for health outcomes. In the current study a total of 223 patients were asked to rate their present health state between 0-100 through EuroQOL Visual Analogue Scale (VAS).[12] It is one of the

direct and simplest techniques based on the approach of ranking health as per the respondent's perspective. It is often referred as the thermometer with a rating scale of 0-100. It consists of a line, often 10 cm in length, with clearly defined endpoints. The scores represent the ordinal rankings of the health outcomes, where '0' denotes the worst health state and '100' denotes the best health state from the patients' perspective.

Ethical considerations

A written informed consent was obtained from the study participants. In case of inability of the patient to give informed consent, the same was sought from the immediate attendant/caregiver accompanying the patient. Ethical approval to undertake the study was obtained from Institute Ethics Committee of the tertiary care hospital in which the study was conducted. Administrative approval to collect data was also obtained from concerned authorities of the respective department of the institute.

Results

Sample characteristics

A total of 223 patients of cervical cancer who received treatment in department of radiotherapy of the tertiary care institute were recruited for estimation of quality of life measures. Over one-third of patients (36.3%) were 41- 50 years old and 44.8% of the patients were illiterate. Majority (61.1%) of the recruited patients were having Stage-II cervical cancer. Majority of the patients were inhabitants of rural area (65.47%) and married (76.7%). Annual household income of 54.26% of the study participants was between Rs. fifty thousand and two lac. Detailed sample characteristics are presented in Table-1.

Table 1: Sample characteristics

Characteristics	Percentage of patients
Age in years	
<=40	12.1
41-50	36.3
51-60	30.9
61-70	17
>70	3.6
FIGO Staging	
Stage- I	11.1
Stage- II	61.1
Stage- III	26.8
Stage- IV	1.0
Religion	
Hindu	71.3
Muslim	2.2
Sikh	26.0
Christian	0.4
Other	0.0
Residential Status	
Urban	34.53
Rural	65.47

Educational status	
Illiterate	44.84
Primary	20.63
Middle	11.21
Matric	9.87
Senior Secondary	7.17
Graduate and above	6.28
Marital status	
Unmarried	0.00
Married	76.68
Widow/ Separated/ Divorced	23.32
Annual household income	
Less than 50,000	8.07
50,000-2 lac	54.26
2 lac- 5 lac	29.60
>5 lac	8.07

Quality of life estimation

The mean EQ-5D utility score among 223 patients of cervical cancer was 0.64 [95% Confidence Interval (CI) = 0.61-0.67]. The mean EQ-VAS score among 223 patients was estimated as 67.6 (95%CI= 65.17-70.03). Stage specific mean EQ-5D and EQ-VAS scores along with confidence intervals has been presented in Table-2.

Table 2: EQ-5D and EQ-VAS score classified by cancer stages

Sr No	FIGO Staging	Mean EQ5D Score (95% CI)	Mean EQ-VAS Score (95% CI)
1	Stage-I	0.6984 (0.6158- 0.7809)	69.74 (64.1- 75.37)
2	Stage-II	0.6323 (0.5881- 0.6766)	69.01 (65.46- 72.56)
3	Stage-III	0.6371 (0.5535- 0.7208)	67.57 (60.77- 74.37)
4	Stage-IV	0.591 (0.4127- 0.7684)	60.00 (40.4- 79.6)
5	All stages	0.6437 (0.6135- 0.6738)	67.6 (65.17- 70.03)

Discussion

The present study is the first attempt in India to measure health related quality of life of cervical cancer patients in the country. Mean EQ-5D and EQ-VAS utility scores for cervical cancer patients were estimated as 0.6437 and 67.6, respectively. We also found a declining gradient in EQ-5D and EQ-VAS utility scores of cervical cancer patients from Stage-I to Stage-IV. (Figure-1 and Figure- 2) These findings are in line with those of other studies[31], as well as biological understanding of the disease that health related quality of life of the patient declines as the disease progresses.[32]

Figure 2: Stage specific EQ-5D utility scores as observed in the study

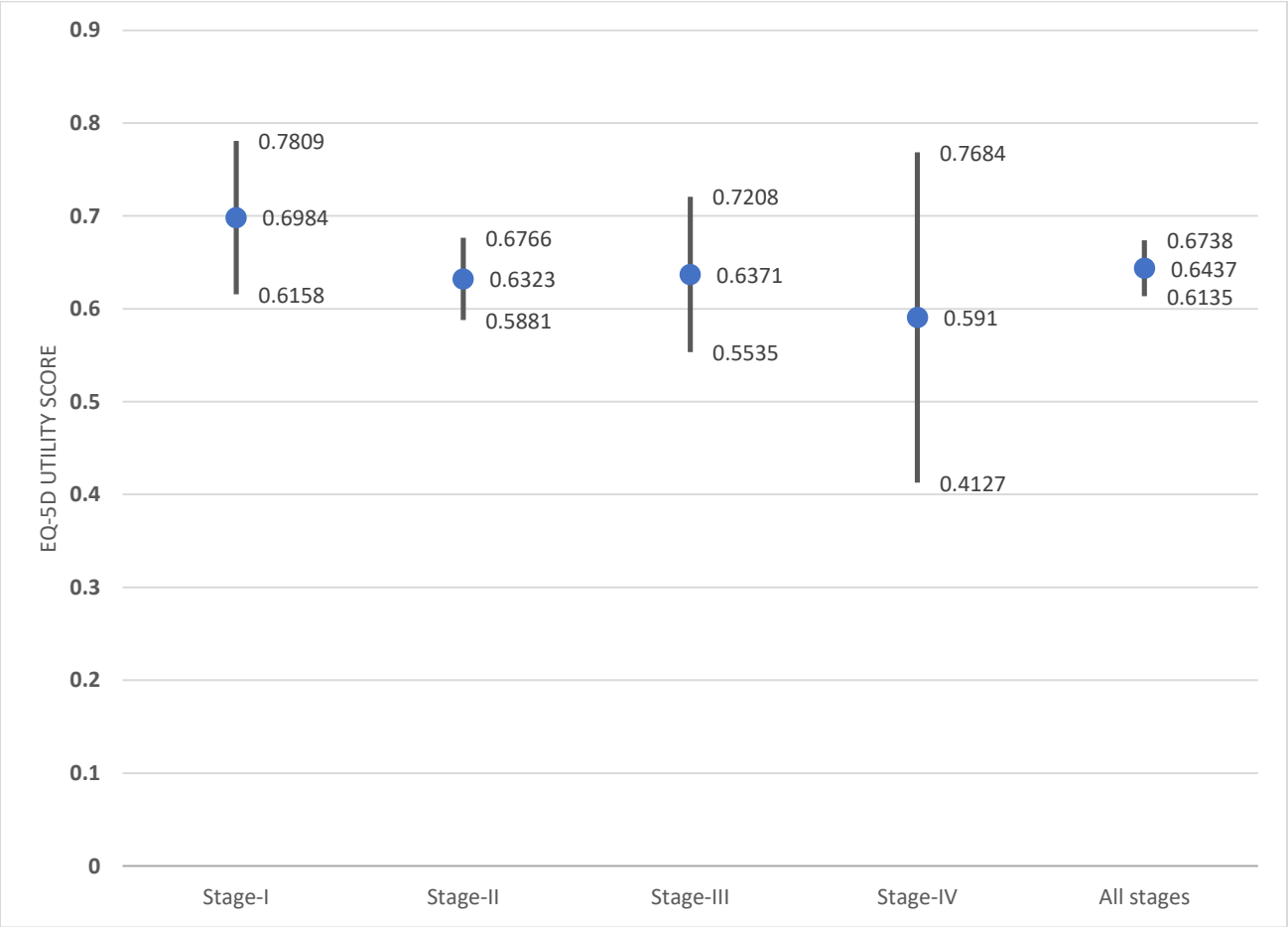
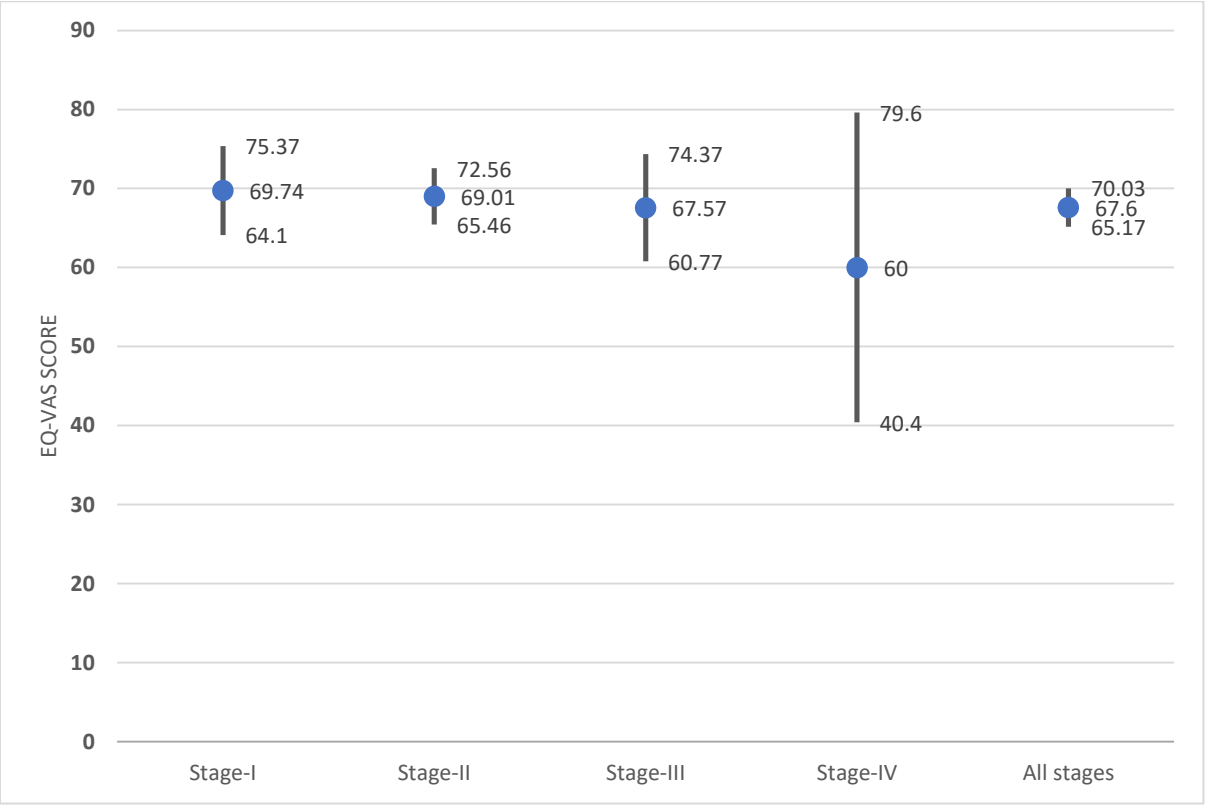


Figure 3: Stage specific EQ-VAS scores as observed in the study



Measurement of utility scores for cervical cancer patients has been attempted in various countries using Euroqol five dimensions questionnaire. Similar study conducted in Indonesia found that the mean utility score was 0.76.[18] The utility scores of cervical cancer patients was measured in China using EQ-5D-3L indicated that the mean utility scores of cervical cancer patient at 1, 3, and 6 months after therapy were 0.68, 0.75 and 0.86, respectively.[32] Meanwhile, the mean utility scores of cervical cancer patients in Taiwan was measured as 0.84.[33] The utility scores of cervical cancer patients in Italy and Argentina were observed comparatively lesser, with mean values as 0.58 and 0.40, respectively.[34, 35] These differences of utility scores may be attributed to use of EQ-5D-3L questionnaire, in contrast with the EQ-5D-5L questionnaire used

by us, and the differences of health perception across different ethnicity of population.[18, 34, 35] Previous studies reported the differences of health related quality of life scores among different ethnicities.[36, 37] Another factor that leads to the differences of utility scores might be the difference of value sets used in converting health states into utility scores in those studies.[34] A comparison of stage specific utility scores as observed in various regional studies has been presented in the Table-3.

Table 3: Comparison of utility scores of cervical cancer stages across various regional studies

FIGO staging	Present study	Endarti[18]	Goldie[31]	Praditsitthi-korn[17]	Khemapech[38]
Stage- I	0.6984	0.85	0.65	0.74	0.784
Stage- II	0.6323	0.76	0.56	0.76	0.788
Stage- III	0.6371	0.71	0.56	0.72	0.776
Stage- IV	0.591	0.77	0.48	0.63	0.814

A pertinent strength of the present analysis is that all the study participants were cervical cancer patients, in contrast to some other earlier studies in which general population was asked to perceive hypothesized health states of cervical cancer.[34, 39] Literature shows that the general population is more likely to over-emphasize the health perceived status of such disease scenario.[40, 41] Consequently, the utility scores of hypothesized sample tended to be lower than that of the real cervical cancer patient.[18] Therefore, results of the present study depicts comparatively more accurate representation of health related quality of life of cervical cancer patients.

We would like to acknowledge that there are certain limitations in the study. Firstly, given the time- limitation, the sample size was kept relatively small and it was based on convenient sampling of cervical cancer patients rather than on random sampling. All the participants recruited in the study were having access to tertiary care health facility located in the urban area. Therefore, generalization to the results to the rural population may be argued. However, sample characteristics show that two- third of the study participants were from rural area, making the results acceptable for generalization. Although it is advisable that further studies should be conducted using a larger sample size with using random sampling method, yet there have been similar studies from other countries using same methodology and equal sample size.[18] Secondly, utility scores were calculated using value set from other country which might not represent actual perception of Indian population. However, it is worthwhile to mention here that value set for Indian population has not been prepared so far[26-28, 42], necessitating the use of value set from another country. Value- set for Thailand was used in the analysis, as among the countries for which the EQ-5D-5L tariff value sets have been generated, Thailand has geographic proximity and shares similarity in social-cultural values of Asian population.[28] These considerations are recommended in selecting other country value set to be used for converting local health states to utility scores.[43, 44] Moreover, the draft Indian reference case for undertaking economic evaluation for undertaking HTA in India recommends using the Thailand value-set to calculate quality of life index scores, until the Indian value- set for the same is prepared.[29]

As the study generated utility scores for cervical cancer patients in local population, its results may be used for conducting India specific economic evaluations. However, further studies are needed to develop a local EQ-5D tariff value- set in order to facilitate the use of EQ-5D in India.

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Annexure-4: Supplementary Material

Fig 1: Dominance and extended dominance

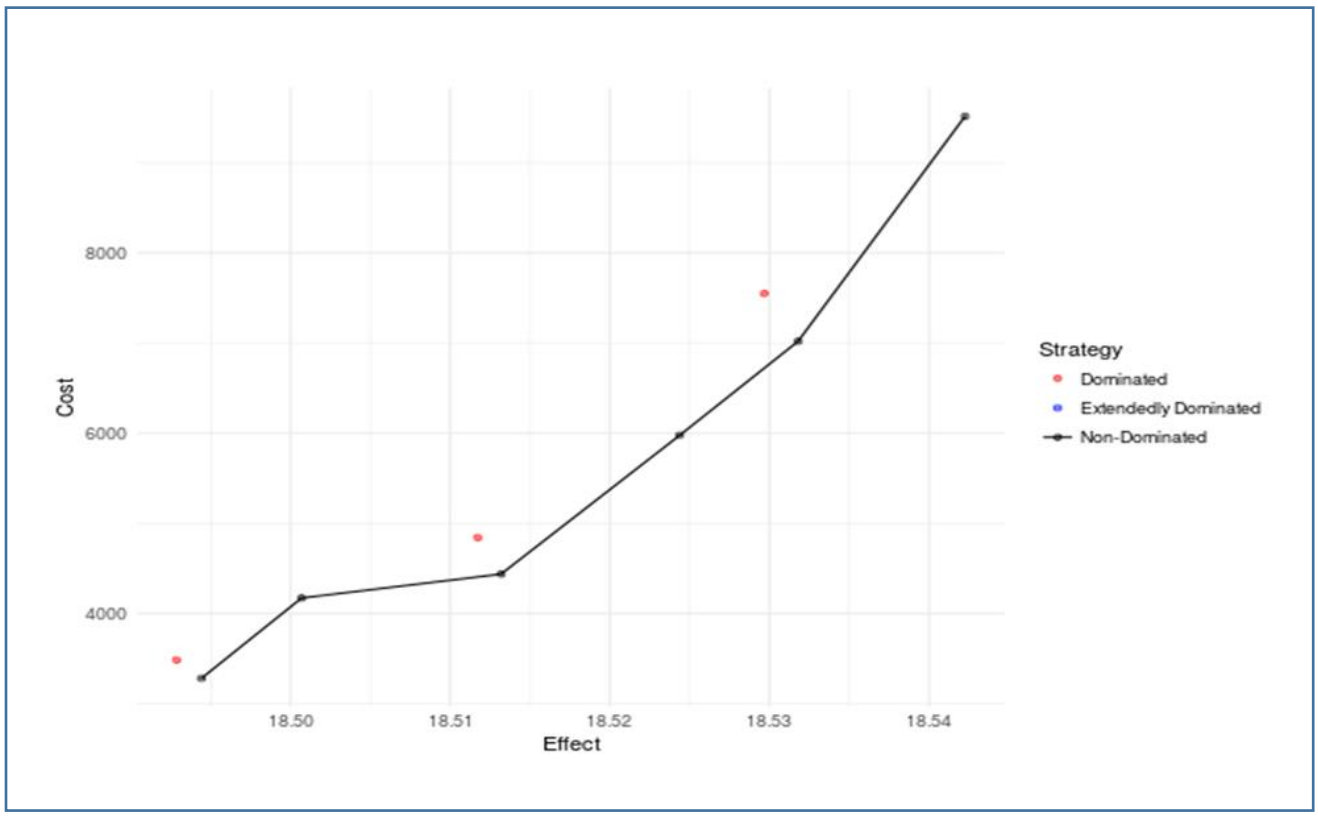

Fig 2: Per capita life time reduction in out of pocket expenditure (INR) with screening strategy of visual inspection with acetic acid every 5 years among income groups

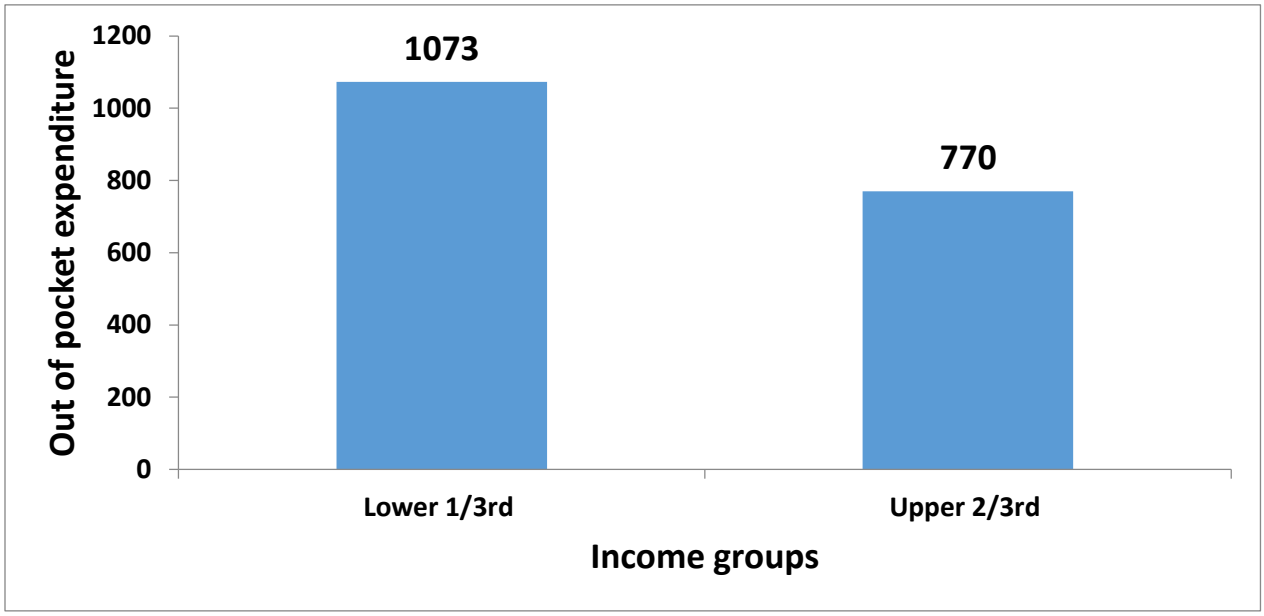

Fig3: Episodes of catastrophic health expenditure averted per I lakh households among different income groups screened with VIA every 5 years

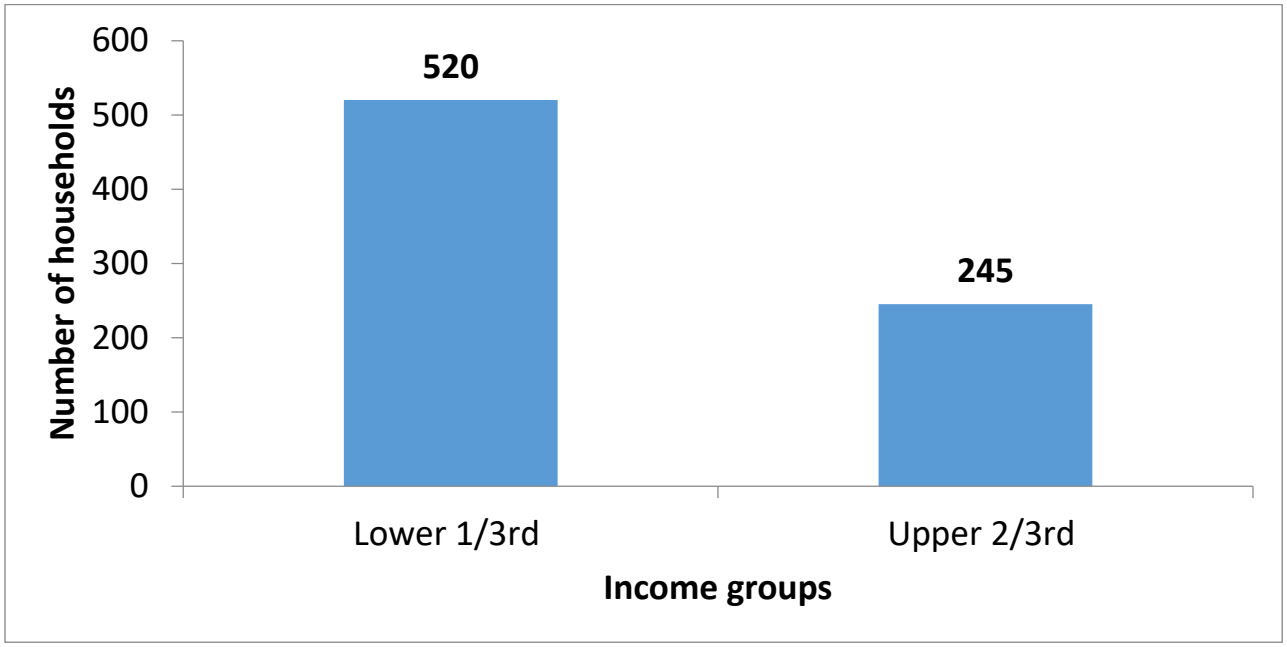

Fig 4: Cancer cases and death averted in a cohort of 1 lakh women (among income groups) screened with visual inspection with acetic acid every 5 years

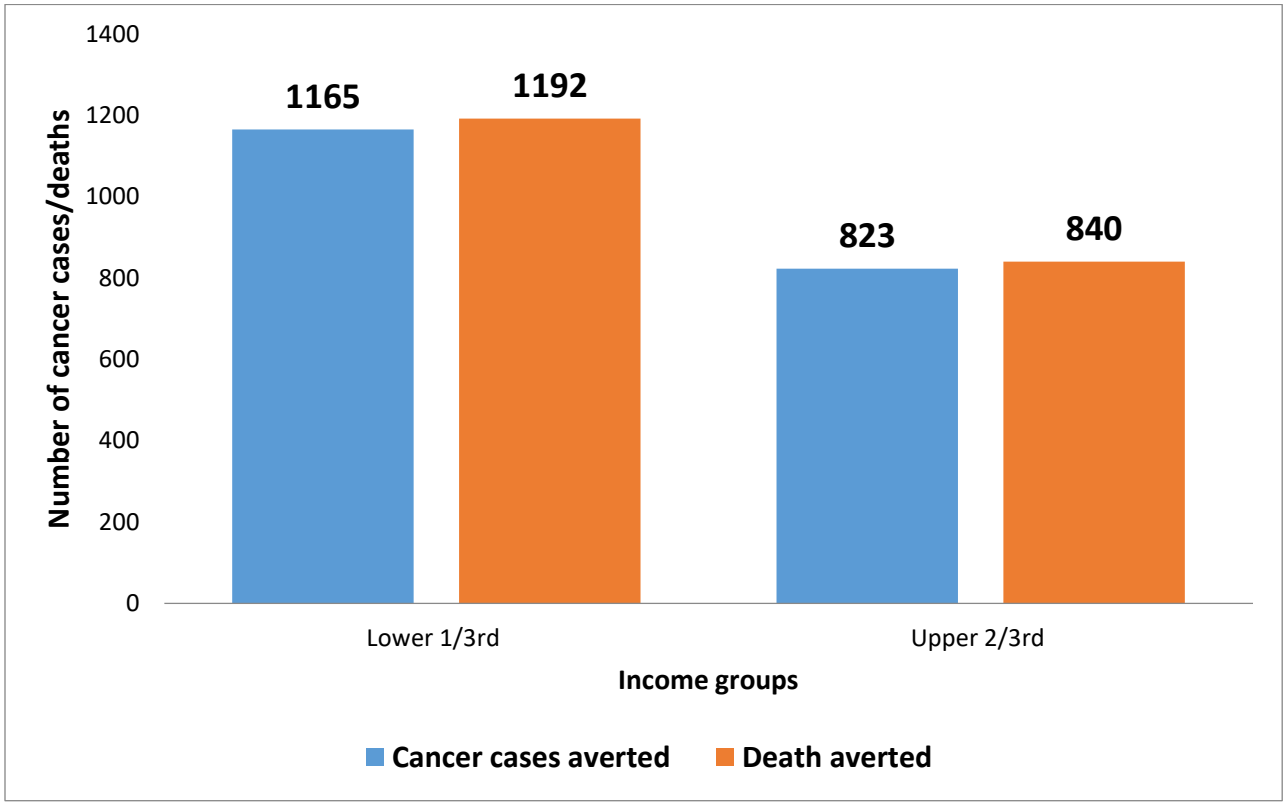

Table 1: Comparison of HPV incidence rates as derived in the present model with that of the mathematical model by Myers et al.

Age groups	HPV infection incidence rate derived in the present model	HPV infection incidence rate by Myers et al
30-34 years	0.06	0.01
35-39 years	0.047	0.01
40-44 years	0.047	0.01
44-49 years	0.046	0.01
50-54 years	0.0125	0.005
55-59 years	0.0125	0.005
60-64 years	0.0125	0.005

Table 2: Model parameters

Parameter		Value
Age specific all-cause mortality in India	30-34 years	0.00757
	35-39 years	0.00966
	40-44 years	0.01341
	45-49 years	0.01874
	50-54 years	0.03415
	55-59 years	0.04838
	60-64 years	0.08088
	65-69 years	0.12392
	70-74 years	0.18615
	75-79 years	0.27283
Coverage rates	Opportunistic screening	0.01
	Screening with VIA	0.8
	Screening with Pap smear	0.8
	Screening with HPV DNA	0.8
	Colposcopy following screening	0.9
	Treatment for precancerous lesions following colposcopy and biopsy	0.9
	Treatment for invasive cancer following colposcopy and biopsy	0.9
Treatment pattern for precancerous lesions	Proportion of women with CIN 1 lesion treated with cryotherapy	0.6875
	Proportion of women with CIN 1 lesion treated with LEEP	0.3125
	Proportion of women with CIN 2 lesion treated with cryotherapy	0.2427

	Proportion of women with CIN 2 lesion treated with LEEP	0.5317
	Proportion of women with CIN 2 lesion treated with surgery	0.2254
Treatment pattern for invasive cancer	Proportion of stage I patients getting surgical treatment only	0.33
	Proportion of stage I patients getting radiotherapy followed by brachytherapy and chemotherapy	0.33
	Proportion of stage I patients getting radiotherapy and brachytherapy preceded by surgery	0.34
	Proportion of stage II patients getting radiotherapy followed by brachytherapy and chemotherapy	0.67
	Proportion of stage II patients getting radiotherapy and brachytherapy preceded by surgery	0.33
	Proportion of stage III patients getting radiotherapy followed by brachytherapy and chemotherapy	1
	Proportion of stage IV patients getting radiotherapy only	0.25
	Proportion of stage IV patients getting radiotherapy followed by brachytherapy and chemotherapy	0.5
	Proportion of stage IV patients getting radiotherapy followed by Chemotherapy	0.25
Stage specific recurrence rates following treatment for	Stage 1	0.1
	Stage 2	0.25
	Stage 3	0.42

cervical cancer	Stage 4	0.76
Treatment pattern for recurrence	Proportion of patient with recurrence treated with radiotherapy	0.3
	Proportion of patient with recurrence treated with chemotherapy	0.3
	Proportion of patient with recurrence treated with basic support only	0.4