RESEARCH ARTICLE

Effect of Screening on the Risk Estimates of Socio Demographic Factors on Cervical Cancer - A Large Cohort Study from Rural India

Jissa Vinoda Thulaseedharan[1,2]*, Nea Malila[2,3], Matti Hakama[2,3], Pulikottil Okuru Esmy[4], Mary Cherian[4], Rajaraman Swaminathan[5], Richard Muwonge[6], Rengaswami Sankaranarayanan[6]

Abstract

Background: Prospective cohort studies to determine cofactors with oncogenic HPV- infections for cervical cancer are very rare from developing countries and such data are limited to the few screening trials. Large screening trials provide such data as a by product. Some of the cases are prevented by screening and do not surface as invasive cancers at all. Also, pre-invasive lesions are detected almost entirely by screening. Screening causes selection bias if attendance in or effectiveness of screening is correlated with the risk factors. The aim of this study was to quantify the influence of screening on risk factors for cervical cancer. Materials and Methods: Our material stems from a rural cohort of 80,000 women subjected to a randomised screening trial. The effect of screening on the incidence of cervix cancer was estimated with reference to socio-demographic and reproductive risk factors of cervical cancer. We compared these risks with the incidence of cancer in the randomised control population by the same determinants of risk. Results: The results in the screening arm compared to the control arm showed that the women of low SES and young age were benefitting more than those of high SES and old age. The relative risk by age (30-39 vs 50-59) was 0.33 in the control arm and 0.24 in the screening arm. The relative risk by education (not educated vs educated) was 2.8 in the control arm and 1.8 in the screening arm. The previously married women did not benefit (incidence 113 and 115 per 100,000 women years in control vs screening arms) whereas the effect was substantial in those married (86 vs 54). Conclusions: The results in controls were consistent with the general evidence, but results in attenders and nonattenders of the screening arm showed that screening itself and self-selection in attendance and effectiveness can influence the effect estimates of risk factors. The effect of cervical cancer screening programmes on the estimates of incidence of cervical cancer causes bias in the studies on etiology and, therefore, they should be interpreted with caution.

Keywords: Cervical cancer - risk factors - screening - bias - rural population - cohort

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Introduction

Cervical cancer is the leading cancer among Indian women with the estimated age standardized incidence and mortality rates around 2008 of 27 and 15 per 100,000 woman years, respectively (Ferlay et al., 2012). The age standardized cervical cancer incidence rates range from 9-40 per 100,000 woman years in various regions of India (Sankaranarayanan et al., 2008). Persistent infection with specific high-risk types of human papilloma virus (HPV) is the central and necessary cause of almost all cervical cancers and their precursors, cervical intra epithelial neoplasia (CIN). The long time frame between initial infection and evident disease indicates that other exogenous or endogenous cofactors, such as sexual habits, reproductive factors, other sexually transmitted diseases, smoking, nutritional deficiencies and genetic susceptibility, acting in conjunction with HPV may be necessary for the disease progression (Ferrera et al., 2000; Sellors and Sankaranarayanan, 2003; Stewart and Kleihues, 2003).

It has been established that different socio demographic and reproductive factors can influence the participation in screening programmes. Some of them are age, education, marital status, income, number of children, use of contraception, region, lack of knowledge about screening of cervical cancer and its prevention, personal and life style factors, attitudes, ease of access and lack of

*[1]Achutha Menon Centre for Health Science Studies, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, [4]Christian Fellowship Community Health Centre, Ambillikai, Tamilnadu, [5]Cancer Institute (WIA), Chennai, India, [2]School of Health Sciences, University of Tampere, Tampere, [3]Finnish Cancer Registry, Helsinki, Finland, [6]International Agency for Research on Cancer (IARC/WHO), Lyon, France *For correspondence: jissa@sctimst.ac.in, jissavinoda@yahoo.co.in*

patient friendly health services (Sankaranarayanan et al., 2003; Nene et al., 2007; Frida et al., 2012; Laurie et al., 2012; Sarah et al., 2012; Singh et al., 2012). Because the risk factors of cervix cancer and determinants to attend the screening are much the same, it is important to know whether data from screening studies provide unbiased information in studies on etiology i.e. on the effects of risk factors on cervical cancer risk.

Our data stems from a cohort study based on a cluster randomised controlled cervical cancer screening trial carried out from 2000-2006 in a rural population in Dindigul district, Tamilnadu state, South India. The present study was undertaken to quantify the bias due to screening on the estimates of risk by socio economic and reproductive risk factors of cervical cancer. Also we wanted to see the effect of screening on risk of cancer, ie in which strata the effect of screening is large and where it is small.

Materials and Methods

The screening trial was conducted to evaluate the efficacy of a single round of visual inspection with 3-5% acetic acid (VIA) in reducing cervical cancer incidence and mortality. The details of the study have been described earlier (Sankaranarayanan et al., 2003; 2004; 2007). The study was conducted in 113 local administrative units called panchayaths .The panchayaths were randomised into two groups 57 in the intervention arm and 56 in the control arm. Eligible participants were healthy women aged 30-59 years with an intact uterus and no past history of cancer. Also, all eligible women in the study were ever married. Health workers interviewed the women using a structured questionnaire to collect information on socio demographic and reproductive variables after educating them about prevention, early detection and treatment of cervical cancer. The intervention group received screening over a three and half year period during 2000-2003. Screening and treatment of pre cancerous lesions and invasive cancer were free of cost. Along with health education, the women in the control group were also advised how to avail themselves of cervical cancer prevention services from the base hospital and other sources and they received the usual care and treatment facilities from the hospitals. Both study groups were followed up for next three years in one year intervals to collect information on deaths, migration, and cervical cancer both by active follow up consisting of household visits and passive follow up linked with the mortality register system and the population based cancer registry.

Data on risk factors of cervical cancer were based on the full cohort of 80,269 eligible women from both the screening and control groups of the cluster randomized trial. The effect of the following individual and household socio demographic factors on the incidence of invasive cervical cancer during the study period were assessed: age in years (categorized in 30-39, 40-49 and 50-59); formal education (some education, no education); occupation (house wife/others and manual labour); marital status (currently married and widowed/separated); age at marriage in years (18+ and <18); number of pregnancies (<4 and 4+); type of house (tiled/concrete, thatched); household income (categorized in ≥2000 and <2000 rupees, 1 US Dollar is approximately equal to 50 rupees); The effect of these risk factors was assessed based on hazard ratios of invasive cervix cancer.

Altogether 325 cervical cancer cases were identified during 2000-2006 (Figure 1). Of these cases, 158 cases were in the control arm and 167 in the intervention arm. The cancer cases from the intervention arm comprised of 67 screen detected cancers, 29 cancer cases which developed among screen negatives, 10 cases among screen positives who had been treated for precursors, and 61 cases diagnosed among unscreened women (Figure 1).

Statistical analysis

The analyses were stratified by study group (screening and control) and by screening status (participated and not participated in screening). Follow up time was calculated for each individual by taking their first date of interview during enumeration as starting date, and the end date as; diagnosis date for those who were diagnosed with cervical cancer; date of death for those who died without cervical cancer; date of migration or last seen for migrated or lost to follow up; or date of last follow up of 31st December 2006 for those still alive. The person years of observation (PYO) and the incidence rate per 100,000 PYO were calculated for all individual and household characteristics. The cervical cancer incidence risk estimates by the different socio demographic characteristics were assessed by relative risks with the low risk category as reference. Data was entered in the study database using Access software and analyzed using Stata/IC 11.2 software.

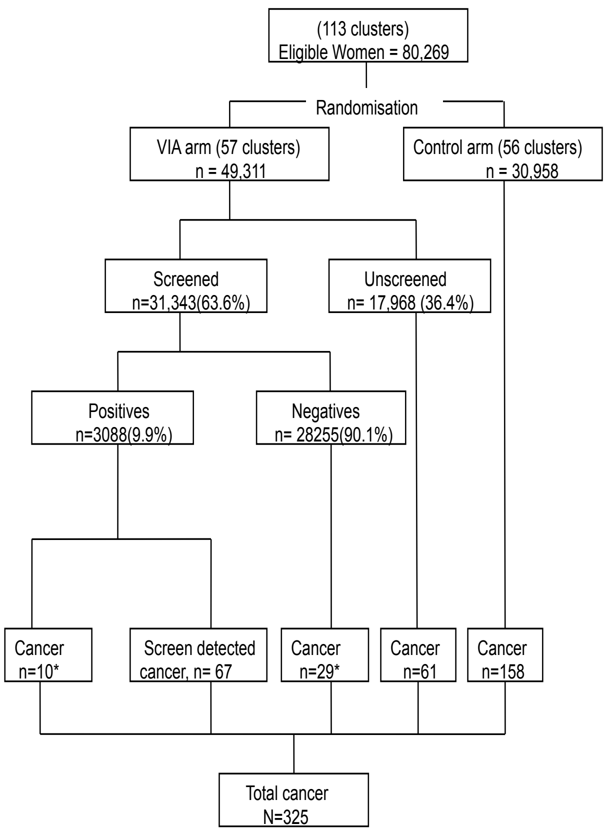

Figure 1. Flow Chart Illustrating the Base Population and the Study Outcomes. *Later diagnosed with cancer

Results

Overall, 452775 person-years of observation (PYO) were accrued during the study period with a mean follow-up time of 5.64 years (SD: 1.09 years) as a sum of the person years contributed by screening group (274258 PYO, mean follow up time: 5.56, SD: 1.02) and control group (178517 PYO, mean follow up time: 5.76, SD: 1.18). A total of 168210 PYO were accumulated in the screening group participants and 106048 PYO in the nonparticipants.

As expected, the overall incidence in the screening group was lower than in the control group (screening arm: 61, control arm: 89 per 100,000 PYO). The cervical cancer incidences among educated, and previously married (widowed/separated) in the screening and control arm were found to be approximately equal (educated: 40 vs 37; previously married: 115 vs 113 per 100,000 PYO in screening vs control arm) but the incidences among uneducated and currently married in the screening and control arm were different (uneducated: 71 and 103; currently married: 54 and 86 per 100,000 PYO in screening vs control arm) (Table.1). In all other exposure categories, incidence in the screening group was lower than in the control group. The estimated hazard ratios for occupation, age at marriage and household income were similar in screening and control arm. But we observed a difference in the estimates of hazard ratios for age, education, marital status, number of pregnancies and type of house.

Table 2 shows the comparison between participants and nonparticipants of screening arm. The observed cervical cancer incidence rates in the younger, currently married, having less than 4 children and low income were similar in both groups. But in contrast, the incidence rates among older, previously married, having 4 or more children and high income were more in the participants than in the non-participants. The cervical cancer incidence among manual workers, married at younger than 18 years, and lived in thatched houses were high in the participants while the incidence among housewives/others, married at 18 years or above, and those who lived in tiled/concrete houses were high in the non-participants. In educated and uneducated the incidence was higher among participants compared to non-participants.

Overall, the cervical cancer incidence was inversely associated with education. The estimate of risk among uneducated compared to educated women was low in the participants and non-participants compared to control (HRs: 1.73, 1.89 and 2.79). The cervical cancer risk in the older age groups compared to younger age group was found to be the same in non-participants and control, but the risk was high in the participants. Among middle-aged similar incidence rate was observed in participants and in control but a low incidence observed in the nonparticipants (for 40-49 years: 90, 91 and 61 per 100,000 PYO). A similar pattern was observed among those who lived in thatched houses also (94, 97 and 46 per 100,000 PYO). We found a low incidence of cervical cancer among the manual workers in the participants and non participants compared with control (76, 61 and 100 per 100000 PYO respectively) but the estimated hazard ratios showed a 60% higher risk for manual workers among the participants, 37% higher risk among the control and no increased risk in the non participants (HR=1.11) compared to the group of other occupations.

The incidence rate observed among widowed/separated women in the participants was high compared to non-participants and control (141, 88 and 113per 100,000 PYO), and the observed hazard ratio was

Table 1. Effect of Socio Demographic Characteristics on Cervical Cancer Incidence-comparison between Screening and Control Arm

Characteristics		Screening arm				Control arm			
		Cervical cancer cases	Person-years of observation (PYO)	Incidence rate per 100000 PYO	Incidence Rate Ratio (IRR)	Cervical cancer cases	Person-years of observation (PYO)	Incidence rate per 100000 PYO	Incidence Rate Ratio (IRR)
Individual characteristics									
Age group	30-39	44	147318	29.9	1.00	45	84585	53.2	1.00
	40-49	59	76320	77.3	2.59	50	54900	91.1	1.71
	50-59	64	50620	126.4	4.23	63	39031	161.4	3.03
Education	Some education	38	94521	40.2	1.00	16	43195	37.0	1.00
	No education	125	175307	71.3	1.77	135	130758	103.2	2.79
Occupation	House wife/others	69	136423	50.6	1.00	56	76559	73.2	1.00
	Manual	97	137413	70.6	1.40	102	101807	100.2	1.37
Marital status	Currently married	132	243231	54.3	1.00	140	162422	86.2	1.00
	Widowed/separated	35	30360	115.3	2.12	18	15976	112.7	1.31
Age at marriage	18+	87	167403	52.0	1.00	100	124099	80.6	1.00
	<18	73	98015	74.5	1.43	54	51049	105.8	1.31
Number of pregnancies	<4	95	193959	49.0	1.00	90	131293	68.6	1.00
	4+	72	80012	90.0	1.84	68	47224	144.0	2.10
Household characteristics									
Type of house	Tiled/Concrete	116	207428	55.9	1.00	131	150627	87.0	1.00
	Thatched	51	66831	76.3	1.36	27	27825	97.0	1.12
Income (in rupees)	2000 +	45	76460	58.9	1.00	46	53659	89.8	1.00
	<2000	122	197666	61.7	1.05	112	124793	89.7	1.00

Table 2. Effect of Socio Demographic Characteristics on Cervical Cancer Incidence-comparison between Participants and Non Participants in the Screening Arm

Characteristics		Participants				Non participants			
		Cervical cancer cases	Person-years of observation (PYO)	Incidence rate per 100000 PYO	Incidence Rate Ratio (IRR)	Cervical cancer cases	Person-years of observation (PYO)	Incidence rate per 100000 PYO	Incidence Rate Ratio (IRR)
Individual characteristics									
Age group	30-39	29	100241	28.9	1.00	15	47077	31.9	1.00
	40-49	39	43560	89.5	3.09	20	32760	61.1	1.92
	50-59	38	24409	155.7	5.38	26	26211	99.2	3.11
Education	Some education	26	60662	42.9	1	12	33858	35.4	1
	No education	78	105153	74.2	1.73	47	70154	67.0	1.89
Occupation	House wife/Others	39	81541	47.8	1.00	30	54882	54.7	1.00
	Manual	66	86367	76.4	1.60	31	51046	60.7	1.11
Marital status	Currently married	84	152332	55.1	1.00	48	90899	52.8	1.00
	Widowed/separated	22	15579	141.2	2.56	13	14781	88.0	1.67
Age at marriage	18+	48	102253	46.9	1.00	39	65150	59.9	1.00
	<18	53	61693	85.9	1.83	20	36322	55.1	0.92
No. of pregnancies	<4	57	118388	48.2	1.00	38	75571	50.3	1.00
	4+	49	49674	98.6	2.05	23	30338	75.8	1.51
Household characteristics									
Type of house	Tiled/Concrete	66	125503	52.6	1.00	50	81924	61.0	1.00
	Thatched	40	42707	93.7	1.78	11	24124	45.6	0.75
Income (in rupees)	2000 +	30	44638	67.2	1.00	15	31822	47.1	1.00
	< 2000	76	123542	61.5	0.92	46	74124	62.1	1.32

2.56 in participants while the risk was 1.67 and 1.37 in nonparticipants and control group. Women married younger than 18 years of age showed high risk of cervical cancer among the screening participants (HR= 1.83) and in the control group (HR=1.31), and no increased risk in the non participants (HR=0.92) compared to women married at an age 18 or above. The estimated hazard ratios for four or more pregnancies compared to less than four pregnancies in the participants and in the control women were similar (HR=2), but the risk was 1.5 in the nonparticipants. The risk of cervical cancer for those who lived in thatched houses was high in the participant group (HR=1.78) but a low risk observed in the nonparticipants (HR=0.75) and no effect (HR=1.12) was estimated in the control group compared to those living in tiled/concrete houses. No increased risk was observed among the low-income group of control women and in the participants but a high risk was observed in the non-participants (HR=1.32).

Discussion

Screening for cervical cancer aims at the detection of preinvasive lesions, and hence preventing the diagnosis of invasive cancer. The screening history can affect the study on risk factors if the introduction of screening has an effect on the actual or reported incidence of cancer selectively, i.e. when the particular exposure correlates with the acceptance or efficacy of screening (Weiss, 2003). Therefore we stratified the analysis by screening and control to verify if the estimates from the screening arm were different from those of the control arm and whether screening influenced the hazard ratio estimates. We observed some differences in the magnitudes of the estimates in the screening and control arm. This was due to the fact that women with low SES attended more than women with high SES and, furthermore, selectively within a socio-demographic stratum. With this in background, we were interested to see whether screening and self-selection can influence the estimates of hazard ratios in the screening arm. Therefore we again stratified the analysis by participants and non-participants of the screening arm and we found that the estimates were different for participants and non-participants. Consequently, with the comparison between participants, non-participants and control arm, we propose that screening and self-selection can influence the hazard ratio estimates and, hence, will make the results on etiology biased.

The effect of screening on the estimates of hazard ratios for risk factors depends on the length of follow-up in a cohort study. If there is a short follow-up, the prevalent preclinical invasive cancers detected at the first screen will dominate. With a longer follow-up the interval cancers that were not detected at screen at the detectable preinvasive phase will dominate. The former are slow growing and the latter fast growing ones. In fact our intervention trial was to assess the effect of one time screening by visual inspection with acetic acid, and the screening completed in three and half years followed by a follow-up of three years in one year intervals. Due to the relatively short follow-up period of the trial, the screen detected cancers dominated the effect estimates of the screening arm participants.

In addition this selection by tumour characteristics there is selection by patient characteristics: attendance is related to awareness and empowerment and - as a consequence – to SES and many other risk factors of cancer. In our study there was a higher participation of young (age 30-39), currently married, educated and low income women with screening. Moreover there is a possibility that many of the women who attended screening were already suspected /suffering from some cervical problems and they decided to acquire the advantage of free screening and treatment. Hence they were different from those who did not attend screening and from the control group. Therefore in the participants there was the effect due to screening and self selection and in the non participants there was the effect due to self selection only. Hence we suggest considering participants, non participants and controls as three distinct groups.

The purpose of our paper was to empirically quantify whether screening affects the estimated hazard ratios of cervical cancer due to risk factors. We were able to demonstrate this by utilization of a limited set of socio-demographic variables. There were variations in the hazard ratios by screening status. It is irrelevant if the effects were formally significant. We were studying bias and relevant indicator is variation in the magnitude (point estimates) in the hazard ratios. Statistical significance is an indicator of random variation and a measure of it (confidence limits or tests) is not a measure of bias. The bias will not be removed by adjusting by applying multivariate or other methods, but it spreads evenly over the strata compared.

We observed from our study, for instance; had we a screened population, there was a 2 fold risk of cervical cancer among the previously married compared to married women; had we a population not subject to screening, the risk was only 30% increased and not 100%. If we study the etiology, then the first result is wrong, that is biased and the second result within random variation is correct. If we study where the screening effect on incidence stems from, then we compare the incidences: among previously married the incidence was about the same (115) but there was a difference between married (54 vs 86) and from that we can make out that married were of low risk and benefitted by screening whereas previously married were of high risk and did not benefit at all. The observed high incidence among previously married in the participants compared to non participants (141 vs 88) adds more evidence to the effect attributed by self selection on the screen detected cancers. It points out the helplessness and limitations of widowed/separated women in the society to afford and access health services due to the lack of financial resources and supporting system. The high incidence among previously married in the participants might be due to the participation of more number of women who were already suffering from some cervical problems and they utilised the advantage of seeking screening. Along with that the high attendance proportion of younger and married women exaggerated the risk of previously married. The distance of the screening facility is an important determinant of women accessing cervical cancer screening (Frida et al., 2012). This is the more important the more the women suffered from lack of financial resources and supporting systems, which, furthermore, supports our result by marital status.

In the same way, we could observe that screening benefited the women in all age groups but due to the higher participation of younger women with screening, the risk of older age groups was exaggerated in screening participants. However, In the case of education, the risk of uneducated was reduced in the screening arm compared to control arm (1.8 vs 2.8) showing the advantage of uneducated women who received screening, while the incidence among educated were more or less similar in all comparing groups meaning they were not actually gained as with uneducated. Though manual workers and housewives benefited by screening, the elevated risk among manual workers in the participants (HR=1.60) compared to non participants (HR=1.11) might be due to self selection ie utilisation of free screening and treatment by economically backward people as in the case of previously married women. Similarly the risk among women who married early in the participants was exaggerated by the higher participation of younger women with screening in such a way that more number of older women was married when they were very young and more number of younger women was married after 18 years of age. The women with <4 or ≥ 4 pregnancies were equally benefitted by screening so that the risk was around 2 in all groups.

The difference in the attitudes of women in different socio economic status is reflected in the estimates of thatched houses (HR: 1.78 Vs HR: 0.75) as well as low income (HR: 0.92 vs HR: 1.32) in participants and in non participants. Type of house and income were probably correlated with the screening effectiveness because the women who lived in thatched houses and participated were subjected to an increased participation of low income group with screening. Women with high socioeconomic status are less likely to attend screening than women of low socioeconomic status because the high income group rarely use free public health services and predominantly seek private care. Moreover the follow up of low income women with abnormal or inadequate test results is often very poor (Laurie et al., 2012). That could be the reason why the incidence among high income group was low in the nonparticipants (47.1) compared to participants (67.21) and control (90). In low resource settings, the common factor shared by widowed/separated or having many pregnancies or having no education is the financial constraint and it can influence their health seeking behaviour (Crispin et al., 2012).

There were a lot of studies in India to determine the socio demographic factors affecting the acceptance or practise of cervical cancer screening (Sankaranarayanan et al., 2003; Nene et al., 2007; Aswathy et al., 2012; Ekta et al., 2012; Singh et al., 2012). However to the best of our knowledge this is the first population based prospective cohort study in India to determine the effect of screening in study on socio demographic risk factors not only for cervical cancer but also in general, and it provides very strong evidence to prove that screening material is not fit for etiological research. So, for the purpose of evaluating risk factors only the control women provide a valid basis.

Also our study showed the public health impact of screening. We found that young, currently married, uneducated and poor women benefitted most due to screening. And this was mainly because the benefiters had a high attendance proportion. Cervical cancer continues to be an important public health problem especially in low and medium resource countries. From the point of view of equity it was encouraging that the benefiters were those at high background risk and with poor resources. Therefore, screening is important component when making public health policies and implementation of cervical cancer control programmes.

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