RESEARCH COMMUNICATION

Socio Demographic and Reproductive Risk Factors for Cervical Cancer – a Large Prospective Cohort Study from Rural India

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Abstract

Background: India shows some of the highest rates of cervical cancer worldwide, and more than 70% of the population is living in rural villages. Prospective cohort studies to determine the risk factors for cervical cancer are very rare from low and medium resource countries. The aim of this study was to quantify the effect of risk factors related to cervical cancer in a rural setting in South India. Material and methods: Sociodemographic and reproductive potential risk factors for cervical cancer were studied using the data from a cohort of 30,958 women who constituted the unscreened control group in a randomised screening trial in Dindigul district, Tamilnadu, India. The analysis was accomplished with the Cox proportional hazard regression model. Results: Women of increasing age (HR=2.4; 95% CI: 1.6, 3.8 in 50-59 vs 30-39), having many pregnancies (HR=7.1; 1.0, 52 in 4+ vs 0) and no education (HR=0.6; 0.2, 0.7 in high vs none) were found to be at significantly increased risk of cervical cancer. Conclusion: This cohort study gives very strong evidence to say that education is the fundamental factor among the sociodemographic and reproductive determinants of cervical cancer in low resource settings. Public awareness through education and improvements in living standards can play an important role in reducing the high incidence of cervical cancer in India. These findings further stress the importance of formulating public health policies aimed at increasing awareness and implementation of cervical cancer screening programmes.

Keywords: Cervical cancer - risk factors - rural population - cohort - India

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Introduction

India accounted for a quarter of both the world's estimated cervical cancer burden of 529,000 cases and 275,000 deaths in 2008 (Ferlay et al., 2010). Cervical cancer is the most frequent primary site of cancer among Indian women with the estimated age standardized cervical cancer incidence and mortality rates of 27 and 15 per 100,000 women, respectively in 2008 (Ferlay et al., 2010). The age standardized cervical cancer incidence rates range from 9 to 40 per 100,000 women in various regions of India (Sankaranarayanan et al., 2008). Furthermore, India shows some of the highest rates of cervical cancer worldwide, especially among rural populations such as the south Indian Dindigul district in Tamilnadu state (Rajkumar et al., 2000; Swaminathan et al., 2009a).

It is currently believed that the persistent infection with one of the 15 oncogenic types of Human papilloma virus (HPV) is the central and necessary cause of almost all cervical cancers and its precursors, cervical intra epithelial neoplasia (CIN). A proportion of CIN, if not detected and treated, progress to invasive cervical carcinoma over a period of 10-20 years owing to the effect of other cofactors (Bosch et al., 2002; Boyle & Levin, 2008; Wentzensen et al., 2009). Cervical cancer is a multi-etiology disease and HPV infection alone is not a sufficient cause of cervical cancer. Most HPV infections regress rapidly without causing clinically significant disease (Sankaranarayanan et al., 2009). The cofactors such as low socio economic status, tobacco smoking, sexual and reproductive factors, HIV and other sexually transmitted diseases, long term oral contraceptive use, certain micronutrient deficiencies, and genetic susceptibility have been suggested (Ferrera et al., 2000; Sellors & Sankaranarayanan, 2003; Stewart & Kleihues, 2003). Therefore the socio demographic risk quantification is warranted to acquire a better picture of the determinants of cervical carcinoma in low resource settings.

In India, case control approach was mainly used to study the risk factors of cervical cancer and the study subjects were recruited from cancer hospitals or registries because cancer is a rare event and a population based

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cohort study might not generate adequate numbers of cases in a defined time period (Juneja et al., 2003). This cohort study is based on the data from a cluster randomised controlled cervical cancer screening trial carried out between 2000-2006 in Dindigul district, Tamilnadu state, India (Sankaranarayanan et al., 2007). The present study was undertaken to identify the socio economic and reproductive potential risk factors of cervical cancer in a rural population of South India. Taking into account the socio demographic factors that affect the incidence of cervical cancer is of utmost importance in formulation of public health policies and cervical cancer control programmes.

Materials and Methods

The current study of risk factors for cervical cancer is based on a cohort of 30,958 women coming from the control arm of a previous cluster randomized screening trial (Sankaranarayanan et al., 2007). The screening trial was conducted to evaluate the efficacy of a single round of visual inspection in reducing cervical cancer incidence and mortality. The study was conducted in 113 local administrative units called panchayaths. The panchayaths were randomised into two groups such as 57 in the intervention and 56 in the control group. Eligible participants were healthy women aged 30 to 59 years with an intact uterus and no past history of cancer. Health workers interviewed all eligible women from both arms 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.

Enumeration and screening was executed from 2000 to 2003 and both groups were followed up for the next three years in one year intervals to collect information on deaths, migration, and cervical cancer. Additionally, all cervical cancer cases and deaths among the eligible population intervention and control groups were obtained from the Dindigul Ambillikai Cancer registry (DACR) and mortality registration systems as well as by active follow up of the study cohorts by house visits. Altogether 158 cervical cancer cases were identified from control group in 2000 to 2006. The details of the study have been described earlier (Sankaranarayanan et al., 2003, 2004a, 2007) .

The effect of the following household and individual socio demographic factors on the incidence of invasive cervical cancer during the study period was assessed in this analysis: type of house (thatched and tiled/concrete); household income (categorized in <2000, 2000-5000 and >5000 rupees); age in years (categorized in 30-39, 40-49 and 50-59); formal education (none, primary/middle and high school/college); occupation (house wife/others and manual labour); marital status (currently married and widowed/separated); age at marriage in years (<18 and 18+); and number of pregnancies (0, 1-3 and 4+).

Table 1. Effect of Socio Demographic Characteristics on Cervical Cancer Incidence using Cox Regression Analysis

Characteristics		Control arm				
		Cervical cancer cases	Person years of observation (PYO)	Incidence rate per 100,000 PYO	Hazard ratio (95% CI)* (bivariate model)	Hazard ratio (multivariate model) (95% CI)
Individual charateristics						
Age group:	P-value for trend				<0.001	<0.001
	30-39	45	84585	53.2	1.00	1.00
	40-49	50	54900	91.1	1.71 (1.14-2.56)	1.63 (1.06-2.49)
	50-59	63	39031	161.4	3.01 (2.05-4.41)	2.45 (1.59-3.77)
Education:	P-value for trend				0.005	0.017
	None	135	130758	103.2	1.00	1.00
	Primary/Middle	12	33829	35.5	0.42 (0.23-0.75)	0.44 (0.24-0.81)
	Highschool/College	4	9367	42.7	0.52 (0.19-1.42)	0.63 (0.23-1.74)
Occupation:	House wife and others	56	76559	73.2	1.00	1.00
	Manual	102	101807	100.2	1.38 (0.99-1.90)	1.29 (0.91-1.81)
Marital status:	Currently married	140	162422	86.2	1.00	1.00
	Widowed/separated	18	15976	112.7	0.94 (0.57-1.56)	0.87 (0.50-1.50)
Age at marriage:	<18	54	51049	105.8	1.00	1.00
	18+	100	124099	80.6	0.77 (0.56-1.08)	0.86 (0.61-1.22)
Number of pregnancies:	P-value for trend				0.001	0.002
	0	3	7306	41.1	1.00	1.00
	1-3	87	123987	70.2	1.72 (0.55-5.45)	4.63 (0.64-33.4)
	4+	68	47224	144.0	2.83 (0.89-9.04)	7.13 (0.98-51.8)
Household charateristics						
Type of house:	Thatched	27	27825	97.0	1.00	1.00
	Tiled/concrete	131	150627	87.0	0.87 (0.57-1.32)	0.93 (0.60-1.44)
Income (in rupees)**:	P-value for trend					0.83
	<2000	112	124793	89.7	1.00	1.00
	2000-5000	39	43825	89.0	0.97 (0.67-1.39)	1.06 (0.73-1.55)
	>5000	7	9835	71.2	0.78 (0.36-1.68)	0.78 (0.36-1.70)

* All characteristics except age are adjusted for age; CI, confidence interval; ** 1 US Dolar, 45 rupees

Statistical analysis

Data was entered in the study database using Access software and analyzed using Stata/IC 11.2 software package. 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 by 31st December 2006, i.e. the date of last follow up for those still alive. The incidence rates per 1000,000 person years of observation (PYO) were calculated for all individual and household characteristics. Cervical cancer incidence risk estimates of the different individual and household characteristics were assessed using Cox proportional hazard regression analysis. The overall effect of socio demographic and reproductive characteristics on the incidence of cervical cancer was adjusted for age in the bivariate analysis. Also we estimated the adjusted hazard ratios including all variables in the multivariate model. We used the data from the control arm only because selective attendance to screening and screening itself causes bias in the estimated relative risks. Such bias cannot be removed by methods of adjustment or multivariate analyses.

Results

The mean follow up time of the control group was 5.76 years (SD 1.18) with 178517 person years of observation (PYO) and the crude cervical cancer incidence rate was 88.5 per 100 000 person years. The effect of socio-demographic characteristics of the assessed women on cervical cancer incidence is showed in the Table1. The risk significantly increased with increasing age. There was a 2.5-fold (95%CI = 1.59-3.77) increase in risk among women aged 50-59 years compared to those aged 30-39, and a significant dose-response relationship (p-value<0.001) was also observed. It was further seen that the more the number of children a woman had, the higher the risk she had of getting cervical cancer (HR 7.1; 95% CI 1.0, 52) in 4+ vs nulli parous, this factor also showing a significant dose-response relationship(p-value =0.002). Compared to those with no formal education, women with some formal education had a reduced risk of cervical cancer (HR=0.44; 95% CI 0.24, 0.81) and a significant dose-response relationship was observed with increasing education level (p-value=0.017). No significant association with incidence of cervical cancer was observed with respect of occupation (HR=1.3, manual vs house wife), current marital status (HR=0.9, widowed/separated vs married), age at marriage (HR=0.9, more than 18 vs less), type of house (HR=0.9, tiled/concrete vs thatched) and household income (HR=0.8, more than 5000 vs less than 2000 RS).

Discussion

To the best of our knowledge this is the first population based prospective cohort study in India to determine the socio demographic risk factors for cervical cancer. The results are a by product from the randomised study on VIA screening (Sankaranarayanan et al., 2007). We used data on controls only, because screening affects the risk ratio estimates. Also, attendance is selective as women with high socioeconomic status are less likely to attend than women of low socioeconomic status. Screening affects the risk of cancer; the incidence of invasive disease and that of pre-invasive disease is increased by once in a life time screening. Therefore the results from the screening arm would be biased as to risk factors on cancer. Adjusting or applying multivariate methods spreads this bias evenly by exposure categories but will not remove it. Thus we used only data from the control arm in this study.

The observed peak incidence of cervical cancer in the older (50-59) age resemble with the other studies from developing countries. A recent study of education and cancer incidence in this rural population has shown that the risk of cervical cancer is inversely associated with increasing educational levels (Swaminathan et al., 2009b). The study highlights the factors which influence the causal pathway between education and cancer risk as: the reproductive factors, sexual behaviour, cancer detection and, demographic and biologic factors including smoking, nutrition, and energy balance (Swaminathan et al., 2009b) . Also HPV positivity in the rural population of Dindigul district was found to be inversely associated with education level (Franceschi et al., 2005) .Therefore our result evidently support the role of education in the determinants of cervical cancer.

Supporting the literature, having four or more children has been identified as a predominant factor for cervical cancer in our study. The results from a case control study in Chennai showed that high parity (>4 vs. ≤ 2 births) was associated with invasive cervical cancer (OR=7.3) after restricting the analysis to HPV positive women (Franceschi et al., 2003). Birth interval or the rapidity of multiple pregnancies also has an independent influence on the risk for cervical cancer (Mukherjee et al., 1994). The pregnancy induced cervical changes may predispose to malignant transformation, and multiparity may increase the risk of cervical cancer by maintaining the transformation zone on the ectocervical region for several years ,resulting direct exposure to HPV and other cofactors (Hinkula et al., 2004).

In this rural population, age at marriage is considered as a proxy measure of age at first sexual intercourse, but it did not come out as an independent risk factor for cervical cancer. Recently a pooled analysis of case control studies on cervical cancer from eight developing countries provide convincing evidence for the risk associated with early age at first sexual intercourse (Mukherjee et al., 1994). Moreover, age at first sexual intercourse, age at marriage and age at first pregnancy were highly interrelated in developing countries, where mostly there is a very short latency period between age at marriage and age at first pregnancy (Louie et al., 2009). A hospital based case control study among rural women of eastern India also confirmed the association of early age at first intercourse and it defines the role of the sexual risk factors in cervical carcinogenesis among rural Indian women (Biswas et al., 1997). Even though we did not observe a significant association between age at marriage and cervical cancer, our estimated hazard ratio is consistent with those observed from these previous studies. Also it indicates that it may be suitable to consider age at marriage as a proxy measure of age at first sexual intercourse.

Widowhood was reported to be associated with an increased risk (OR= 1.2) for cervical cancer compared to married women owing to the fact that widows are vulnerable in the society and there is a chance of sexual exploitation (Franceschi et al., 2003). A recent study from Rural west India also demonstrate that widows and separated women are at a higher risk of HPV infection (Sauvaget et al., 2011). An elevated risk for late stage diagnosis among widowed/divorced compared to married women was also reported from south India (Kaku et al., 2008). This was because widowed or divorced women did not seek medical advice for medical problems or they did not get diagnostics in time due to lack of financial resources and/or absence of family or social support. All these factors point out that there may be a high chance of under reporting of cervical cancer cases from widowed/separated women in our study and hence, we did not find widowhood/separation as a risk factor for cervical cancer.

Occupation, type of house and family income were the measures to assess the economic status of the women who participated in this study and those are interrelated. Manual workers were mainly the labourers working in the agricultural sector and housewives/others included those women who were taking care of their family and doing house works or working in public or private sectors. Thatched houses having a roof made with straw or plant leaves were the shelter for very poor people and middle or above middle class lived in tiled/concrete houses. It is possible that under reporting the family income the women expected to have free service. But majority of the rural village people are practising very poor hygienic conditions and they have no better sanitation facilities even though they are living in tiled/concrete houses or earning higher income. Hence in our study we found that occupation, type of house or family income is not determining the risk of cervical cancer in rural settings. A study in Kerala, India confirmed the role of genital hygiene in the development of cervical dysplasia and cancer (Varghese et al., 1999).

We have evaluated only some of the possible correlates of cervical cancer in our study. Persistent infection with high-risk HPV has been indicated as the necessary cause of progression to invasive cervical cancer. However, in our study, assessment of HPV infection was not done hence we could not take into consideration women HPV status in our analyses. Women smoke very rarely in this population under study, but the chances of passive smoking or women's husband's smoking history were not assessed because of lack of routinely collected information on this. Also, pan chewing with or without tobacco is common among manual workers and low educated women in the community. Poor nutritional status is a common problem among women with low socioeconomic status. The questions connected with sexual habits, number of sexual partners of women, and the sexual history of women's male partner could not be asked due to the prevailing socio-cultural norms in this population. Also we excluded religion from our study because 95% of the population were Hindus and the Christians and Muslims together contribute only 5% of the population.

It has clearly been shown that persistent infection with specific high-risk type of HPV plays a fundamental role in the development of cervical cancer. The long time frame between initial infection and evident disease indicates that other exogenous or endogenous cofactors, such as sexual reproductive factors, sexually transmitted diseases, nutritional deficiencies and fruits and genetic susceptibility, acting in conjunction with HPV may be necessary for the disease progression (Sellors & Sankaranarayanan, 2003; Stewart & Kleihues, 2003). Spontaneous regression of CIN may also signify that a lot of women may not be exposed to these cofactors. In cervical cancers among the slum dwellers of a major Indian city only 33% of the patients studied were positive for high grade HPV (Rughooputh et al., 2007). In another study from India only 67% of CIN2+ lesions (CIN2- 50.4% and CIN3 - 84.3%) were HPV positives (Sankaranarayanan et al., 2004[b]). The HPV prevalence among mild dysplasia reported by another study from Kerala was only 33.3% (Cherian Varghese, 2000).These results further pinpoint the importance of socio demographic factors and poverty in planning of cervical cancer control.

The changing socio economic profile and initiation of different screening strategies results in decline the cervical cancer incidence and mortality worldwide (Mathew and George, 2009). The DACR report shows clearly a decline in cervical cancer incidence in Dindigul district, where the crude rate of 23.1 per 100,000 observed during 2003-2006 was lesser compared to 47.7 during 1996-1998 (Swaminathan et al., 2009a) resembling the trend observed in other registries in India (Yeole, 2008) . But cervical cancer is still the leading cancer among Indian women (Ferlay et al., 2010) . Hence, like the circumstance in many other developing countries, cervical cancer continues to be an important public health problem in India. Lack of awareness about important risk factors of cervical cancer is reported even among the educated young women of India point out that the larger population of less educated women is in greater lack of awareness (Saha et al., 2010; Teresa et al., 2011). The participation of male partner of women and the male elders from the family in the awareness programmes is also important (Giftson et al., 2011). However, formal education only does not help if one does not have money for improve hygienic conditions. Public awareness through education and improvements in living standards can play an important role in reducing the high incidence of cervical cancer in India. The same factors can also ensure good participation in early detection programmes and acceptance of HPV vaccination. It is also important to consider the socio-demographic factors associated with cervical cancer while making public health policies and implementation of cervical cancer control programmes.

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