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Determinants of Cervical Cancer in Indian context

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ABSTRACT

As per the population-based Cancer registries, cervical cancer is on the declining trend in India still every year in India, 122,844 women are diagnosed with cervical cancer and 67,477 women die from the disease. India has a population of 432.2 million women aged 15 years and older who are at risk of developing cancer. India also has the highest age-standardized incidence of cervical cancer in South Asia. We have attempted to review the available scientific literature for all the potential factors that may determine the development of cervical cancer in an Indian woman. Factors such as bio-social characteristics, reproductive, sexual habits and personal habits of both female and male partners, social customs, nutrition, genital hygiene, family history of cervical cancer and history of associated co-morbid conditions have been explored. There are several reasons cited for increasing incidence of cervical cancer cases and associated mortality such as high parity, poor socio-economic status, poor genital hygiene, associated sexually transmitted infection, active and passive smoking, lack of condom usage, obesity, family history and various social factors. Certain factors role in the development of cervical cancer is still dubious such as co-infection with Chlamydia trachomatis, micronutrient deficiency and long-term oral contraceptive pills use. A multipronged approach is needed to address this problem. Timely screening especially of the women who are identified with these risk factors and risk factor prevention through behaviour changes is the need of the hour.

KEYWORDS: cervical cancer, HPV, screening, India, risk factors, epidemiology

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INTRODUCTION

As per World Health Organization (2002) 493,243 women are diagnosed with cervical cancer every year and 273,505 die from it making it as the world's most fatal cancer. In developing countries cervical cancer is the most prevalent cancer amongst women and one of the commonest cause of death.[1,2] Cervical cancer is a slow growing malignant neoplasm and the symptoms may not appear for a long time but can be only detected in early stages with regular screening methods. Late symptoms include abnormal vaginal bleeding in form of post-coital bleeding, inter-menstrual bleeding and vaginal bleeding in post menopausal women, pelvic pain, and pain during intercourse, mass in cervix, weight loss, loss of appetite, weakness, very foul smelling and or blood stained vaginal discharge.[3]

Mortality due to cervical cancer is a health inequality indicator, as 86% of all deaths due to cervical cancer are in low and middle income countries.[4, 5, 6] India constitutes a population of 432.2 million women aged 15 years and older. They are at risk of developing cancer and every year 122,844 women are diagnosed with cervical cancer and 67,477 die from this disease posing a major public health problem. India also ranks highest in age standardized incidence of cervical cancer in South Asia at 22 (19.2 in Bangladesh, 13 in Sri Lanka).[7, 8] Indian women are afflicted by it physically, psycho-socially and financially. Not just the women, but her family and the society also suffer.[1, 2] It is therefore vital to understand the determinants of cervical cancer especially in Indian perspective.

METHODOLOGY

The English language research literature published from 2000 to 2017 was exhaustively searched using the web based search engine and scientific database Google Scholar and Scopus. Searches were made using combination of key words: cervical cancer; epidemiology, determinants, risk factors development; India; developing countries. Articles were selected for inclusion if their title or on-line abstract included reference to factors contributing to development of cervical cancer in a woman especially in Indian perspective. During literature search each of the factor identified was then extensively reviewed using key words combination: cervical cancer + factor/determinant identified. This paper is divided into sub-sections having description of each of the determinant identified. The results have been discussed along with Indian studies in relation to the studies carried out in the developed world and classical papers which formed the basis of the research of cervical cancer.

RESULTS AND DISCUSSION

An exhaustive search was done through several types of original researches in form of observational, case-control, cohort and systematic reviews with or without meta-analysis. There are several reasons cited for increasing incidence of cervical cancer cases and associated mortality. The long interval between initial infection and disease indicates that there are other factors involved, such as sexual habits, reproductive factors, other sexually transmitted diseases, co-infection with HIV, smoking, nutritional deficiency, genetic susceptibility and high parity.[9] **C**ertain factors role in development of cervical cancer is still dubious such as co-infection with Chlamydia trachomatis, micronutrient deficiency and long term oral contraceptive pills use.[10, 11, 12] Following subheadings describe the factors identified for the development of cervical cancer.

3.1 Geographical determinant: Sanjosé S et al in their meta-analysis to estimate the world-wide age-specific prevalence of cervical human papilloma virus (HPV) DNA (main factor for development of cervical cancer) in women concluded that even though the studies from Asia contributed 26·0% of all study participants, of whom half were from Indian subcontinent, still the pooled estimates of prevalence of HPV infection was low (7.5%; 7.0-8.0). This finding was not in concordance with historical cervical cancer incidence data that reflected that India has very high rates of cervical cancer. They reasoned this discrepancy in findings with ineffective cervical screening programmes and management of cervical lesions may lead to very high rates of invasive disease.[13, 14] Parkin et al**.** in their historical study stated that of the nine cities the highest age standardized worldwide incidence (per 100,000) was of Chennai (30.1) followed by Delhi (25.8) and the least was of Trivandrum (10.9). [15]

***3.2 Age factor*:** Cervical cancer is worldwide the second most frequent cancer amongst women aged between 15 to 44 year. Globally in unscreened populations, the peak risk of invasive cervical cancer occurs from about 35-55 years.[2] In India the peak age for cervical cancer incidence is 55–59 years.[16] Study by Bobdey et al (2016) revealed that in India more than 85% of patients were from aged ≥ 40 years.[17] Maximum numbers of cases were reported in 50–59 years of age group amounting to 27.37% of all cervical carcinoma cases as revealed in a three year report Population based Cancer Registries.[18] Similarly, a hospital-based susceptibility study in North India found an increase in cytopathological abnormalities with increasing age and parity. [19]

3.3 Literacy and Socio-Economic factor: **Vedantham et al**. stated that VIA (visual-inspection on Acetic Acid; a screening method for Cervical cancer) positivity was significantly

associated with less education, age (>60 years); Christian or Hindu religion; being divorced, widowed, or separated.[20] Evidence suggests that cervical cancer incidence is greater amongst women of lower classes, less educated, and with high parity.[5] A meta-analysis of social inequality and the risk of cervical cancer showed a 100% increased risk in the low–social-class categories for the development of invasive cervical cancer. Although this difference was observed in all countries, it was stronger in low-and middle-income countries.[21]

***3.4 Personal habit factors*:** Tobacco smoking is a well-known risk factor for cervical cancer. [22]. Direct carcinogenic action of cigarette smoking on the cervix has been upheld on the grounds that nicotine metabolites were found in the cervical mucus of women who smoke. [23] Smoking is associated with sexual behavior, hence it is difficult to determine whether this association is spurious, as it is impossible to eliminate the confounding through adjustment for measures of sexual activity.[24] Cornelia et al. in their cohort study revealed that smoking whether active or passive has been found to be a high risk factor. A strong co-relation exists between smoking and risky sexual behavior. The adjusted relative risk and 95% C.I for passive smoking was 2.1 (1.3, 3.3). and for current active smoking was 2.6 (1.7, 4.1).Chemical substances in the cigarettes detected in cervical mucosa aids in development of cervical cancer through DNA damages.[25] Harris et al. found that alcohol consumption did not appear to be related to cervical abnormality.[26]

***3.5 Sexual habits and sexual partners related factors*:** Brinton and Fraumeni stated that age independent, a woman's risk is strongly associated with the number of partners, and age at first intercourse.[27] Buckley et al.[28], Harris et al.[29] have reported strong correlation between the numbers of sexual partners that a woman's husband has had with development of cervical cancer. S Franceschi et al. in their multicenter case-control study in Chennai stated that with respect to a woman's report of her husband's extramarital sexual relationships and sexual intercourse with prostitutes, ORs were 4.3 and 5.8 for women who were uncertain and 8.7 and 10.5, respectively, for those who positively confirmed and were significant risk factors for cervical cancer.[30] Several studies have reported that woman with multiple sexual partners puts herself at higher risk of acquiring the HPV infection.[24, 31, 32] Evidence for sexual transmission of an infectious agent comes from studies showing that wives of patients with penile cancer are at an increased risk of cervical cancer.[33, 34, 35] Study from Madras showed statistically significant ratios for cervical cancer amongst Hindus (2.5 times) and Christians (1.9 times) compared to Muslim women. The incidence rate for penile cancer was 2.2 per 100000 among Hindus , 0.8 among Christians and nil among Muslims.[36]

3.6 Reproductive health factors: American Cancer Society in 2010 pointed out that women that have had three or more full term pregnancies are high risk patients as due to the hormonal changes during pregnancy women are more susceptible to HPV infection. Women who have had their first full term pregnancy before the age of 17 are twice at risk of having cervical cancer later in the life compared with women who conceived 25 years or over.[37] There is a linear trend between parity and risk, as seen in many studies.[38] A hospital-based study in North India found an increase in cytopathological abnormalities with increasing age and parity.[19] High parity and deficient diets of women in developing nations may contribute for the high incidence rates of cervical cancer.[24]

3.7 Associated Infections: Chan et al in their study in 2003 pointed out that a woman with multiple sexual partners puts her higher risk of acquiring the HPV infection.[31] The high burden of cervical cancer in Southeast Asian countries is due to a high prevalence of HPV (more than 10% in women aged more than 30 years) and due to lack of screening.[39] The WHO's International Agency for Research on Cancer (IARC) classified HPV infection as "carcinogenic" to humans (HPV types 16 and 18), "probably" carcinogenic (HPV types 31 and 33) and "possibly" carcinogenic (other HPV types except 6 and 11).[40]

Clinical and subclinical HPV infections are the most common STDs today. They may be seen in asymptomatic cases (detected in 5%-40% of women of reproductive age).[41] HPV infection is a transient phenomenon thus only a small percentage of women positive for a given HPV type is found to have the same type in subsequent specimens.[42, 43] Risk of subsequent cervical intraepithelial neoplasia (CIN) is proportional to the number of specimens testing positive for HPV, which also suggests that carcinogenic development results from persistent infections.[44] Hence it is well established that HPV infection is the central causal factor in cervical cancer. [45, 46] HPV prevalence among cervical cancer patients in India has varied from 87.8% to 96.67%.[24-27] Molecular studies have shown that HPV-16 and 18 are the two most common highly oncogenic types found in invasive cervical cancer, and out of these two HPV-16 has been found more abundantly.[47]

Several co-infections apart from HPV have been linked with development of cervical cancer such as bacterial vaginosis, *Chlamydia trachomatis* (*C. trachomatis*), herpes simplex virus, and human immunodeficiency virus.[48] The role of chronic inflammation, especially due to co-infection with Chlamydia trachomatis, is controversial.[12] However a case-control study of 1,238 cases of ICC (Invasive Cervical Carcinoma) and 1,100 control women from 7 countries shows an association of C. trachomatis with squamous cell ICC amongst all cases and control women with or without

adjustment for HPV. However, no significant association was seen with adenocarcinoma variant of cervical cancer.[49] In a recent meta-analysis by Zhu et al (2016) reported that *C. trachomatis* infection significantly doubled the risk of cervical cancer risk in both the prospective studies and retrospective studies: and even after adjusting for HPV and age, *C. trachomatis* infection was identified as an independent predictor of cervical cancer Co-infection of HPV and *C. trachomatis* raises the risk significantly to four-fold and also they found that *C. trachomatis* have a higher risk of cervical cancer in both squamous and adeno variants [50]

3.8 Associated co-morbid conditions: Several studies have indicated that Obesity is an important independent risk factor for mortality due to cervical cancer.[51-56] Maruthur et al. have revealed in their systematic review and meta-analysis an association of obesity and cervical cancer and have pointed out several possible patient- and physician-related barriers to cervical screening for overweight and obese women. Postponing medical care because of negative body image, embarrassment, a perceived lack of respect from health care providers, or because they want to avoid weight loss advice, obesity-related co-morbid conditions such as Diabetes Mellitus obstructing preventive services, technical difficulty in providing care for obese women by care givers, reluctance by physicians to perform pelvic exams on reluctant and obese women. Also associated Diabetes Mellitus, through hormonal actions, may play a role in the pathogenesis of cervical adenocarcinoma and has been found to be associated with adenocarcinoma of the cervix in some observational studies.[57-59].Similarly a population based survey done in US on 11,435 women aged between 18-75 years found that overweight and obese women were less likely to be screened for cervical and breast cancer with Pap smears and mammography, even after adjustment for other known barriers to care.[60] In Indian context there is lack of evidence for role of obesity and Diabetes in cervical cancer development and associated morbidity and mortality.

3.9 Nutrition related factors: In absence of confirmed role of any one micronutrient through supplementation trials, there is some evidence of a possible protective association between higher folate and the risk of precancer.[2, 19, 20] Evidence is gathering for high intake of foods containing known anti-oxidants such as beta carotene, vitamin C, E and A in reducing the risk of cervical cancer. These results from studies using diet recall methods have generally been supported by laboratory surveys assaying dietary constituents in plasma.[61-66]

***3.10 Method of contraception related factors*:** Several studies have reported that usage of condom helps in prevention of HPV infection and thereby has a protective effect on cervical cancer[26, 29] Winer et al**.** in their longitudinal study amongst women in reproductive age group revealed that

the incidence of genital HPV infection was 37.8 per 100 patient-years at risk among women whose partners used condoms for all instances of intercourse, as compared with 89.3 per 100 patient-years at risk in women whose partners used condoms less than 5 percent of the time (adjusted hazard ratio, 0.3; 95% CI: 0.1 to 0.6, adjusted for the number of new partners and the number of previous partners of the male partner). [67] In a survey conducted in urban and rural areas of North Bengal for evaluation of prevalence of risk factors for cervical cancer it was found that 94.6 % of the women were not using condom.[68]

Risk of cervical cancer, especially for adeno carcinoma variant, is seen with long-term use (12 years or more) of oral contraceptives.[69] However, Franco EL in his study has reasoned that the association with oral contraceptive use with cervical cancer observed may have been due to detection bias, since women using oral contraceptives are more likely to visit for gynecological examinations, thereby more likely to have disease detected early than those who do not use them. The difficulty in correctly assessing the effect of oral contraceptive use arises because of high association with other risk factors, such as sexual activity and history of Pap smear screening.[24, 70] Several studies have indicated that long term usage of OCPs was an important risk factor for development of cervical cancer but after adjusting it with smoking and HPV infection the significance was lost.[71, 72]

3.11 Family history of Cervical Cancer: Brinton et al in their classical multi-centre case-control study revealed that a family history of cervical cancer in a first degree relative was associated with significant high risk of squamous cell cancer (RR = 3.1) and adenosquamous tumors (RR = 9.9).[73]

3.12 Other related cancers: Amundadottir et al in their study found that, patients who are diagnosed with stomach, esophagus and lung cancer are at higher risk of developing cervical cancer owing to direct relation with tobacco intake**.** Both lung and cervical cancers have strong environmental and familial risks mostly because of shared tobacco intake habit. Patients with Fanconi anemia, a rare genetic syndrome, have a greater risk of acute myeloid leukemia and squamous cell cancers of the head and neck, vulva, cervix, esophagus, liver and brain.[74-84]

3.13 Poor Genital hygiene: Franceschi et al. in case-control study from Chennai revealed that ORs for lack of a toilet (OR = 4.8) , running water (OR = 2.0) inside the house and not washing genitals after sexual intercourse (OR = 4.5) were significantly associated with cervical cancer. Similarly Varghese et al in their study from Trivandrum found that poor sexual hygiene was a risk factor for cervical dysplasia. They stated that poor women did not have the facilities needed for

practicing genital hygiene. Sanitary pads were expensive for women of lower socioeconomic strata and were not used by over 90% of the women in the study, who had an excess risk of cervical dysplasia.[30, 85]

Several studies have set different criteria for poor genital hygiene such as using home-pads for menstruation instead of sanitary napkins, no vaginal douching during menstruation, not using condom, not taking treatment for foul smelling vaginal or penile discharge respectively and being sexually active during such periods of infection etc. All these variables showed association with cervical cancer in the age-adjusted analyses. Zhang et al. in their population based case-control study reported that the use of home-made pads during menstruation showed a 3- to 4-fold increased risk of cervical cancer. Use of commercial (cleaner) pads had a protective effect. Lack of washing the genital area during menstruation also had a significant 4-fold increased risk in the adjusted analyses. Brinton et al. found that poor genital hygiene amongst male was far more important than the number of sexual partners the male has in developing HPV infection.[27,30,86,87]

***3.14 Social determinants; barriers of cervical screening*:** Specific religious practices also modify the risk of developing cervical cancer in women following HPV infection. [88] Asian women are the most important group of women who avoid screening because of cultural and social restrictions.[31] Child marriage, early age of marriage and conception, polygamy, high parity, lack of empowerment and decisions making for health seeking in women, fear of social stigma are important social factors. Sexual hygiene, use of barrier contraceptives and ritual circumcision can undoubtedly reduce cervical cancer incidence.[89-92]

CONCLUSION: There are some modifiable risk factors such as poor genital hygiene, poor sexual habits, smoking, social restrictions and obesity which adds to the risk and mortality from cervical cancer or act as barrier in screening. They need to be addressed through behavior change modifications. Some factors warrants regular screening such as increasing age, family history, long term OCP usage, *C. trachomatis* infection and other cancers. Some nutritional factors have protective effect and further confirmatory research needs to be done. A multi-pronged approach is the need of the hour for reduction of prevalence of these determinants of cervical cancer and ensuring early screening.

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