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A Case-Control Study of Reproductive Factors and Risk of Cervical Cancer in Manipur

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Abstract:

Cervical cancer stands as the second most prevalent cancer among women in Manipur. This case-control study delved into the association between reproductive factors and cervical cancer. It encompassed 64 incident cases of histologically confirmed cervical cancer along with 256 neighbourhood controls, all possessing intact uteri and age-matched. Through standardized interview schedules, the reproductive history of participants was meticulously collected. Utilizing multiple logistic regression analysis, we derived maximum likelihood estimates of multivariate odds ratios (OR) and their corresponding confidence intervals (CI). Notably, women with their first pregnancy occurring at or before 18 years exhibited a higher likelihood of developing cervical cancer compared to those with a first pregnancy at 18 years or later. Furthermore, a significant disparity was noted in the incidence of abortions among the studied women. Those reporting one or more abortions (whether induced, spontaneous, or a combination) demonstrated a heightened risk compared to those who had never undergone abortions (OR=2.72, P<0.01). Thus, early age at first pregnancy and a greater number of abortions emerged as potential contributors to the etiology of cervical cancer in this population.

Keywords: Cervical cancer, Manipur, reproductive factors, case-control study, age at first pregnancy, abortions

Introduction:

Cervical cancer poses a significant global health challenge, standing as the fourth most prevalent cancer among women worldwide. The year 2012 alone witnessed 528,000 new cases and 266,000 deaths attributed to this disease, underscoring its profound impact on public health (Cervical Cancer, 2012). Of particular concern is its status as the fourth leading cause of cancer-related mortality among women globally, disproportionately affecting developing countries, where it emerges as the primary cause of cancer deaths among women (Denny, 2012)? India, specifically, grapples with a substantial burden of cervical cancer, contributing to over one-fifth of all newly diagnosed cases worldwide. Annually, the country records a staggering 122,844 new cases of cervical cancer, resulting in 67,477 deaths. Notably, India exhibits the highest age-standardized incidence of cervical cancer in South Asia, with a rate of 22 compared to neighbouring countries such as Bangladesh, Sri Lanka, and Iran (ICO Information Centre on HPV and cancer, 2014). In developing and least developed countries, the burden of cervical cancer is even more pronounced due to limited access to preventive measures such as vaccination and screening programs. These countries often lack adequate healthcare infrastructure, leading to late-stage diagnoses and poorer treatment outcomes. Moreover, cultural and socioeconomic factors may further exacerbate disparities in cervical cancer incidence and mortality rates in these regions. For example, in Sub-Saharan Africa, cervical cancer is the leading cause of cancer-related deaths among women, with over 85% of cases occurring in developing countries (Gakidou et al., 2008). Similarly, in Southeast Asia and Latin America, limited access to cervical cancer screening and treatment services contributes to higher mortality rates compared to developed regions (Arbyn et al., 2020; Jemal et al., 2008).

Efforts to address the burden of cervical cancer in these regions include initiatives to improve access to HPV vaccination, expand cervical cancer screening programs, and strengthen healthcare infrastructure. Collaborative efforts between governments, non-governmental organizations, and international agencies are crucial in reducing the global burden of cervical cancer and ensuring equitable access to preventive and treatment services for women worldwide.

Literature Review:

Reproductive factors have emerged as critical determinants in the development of invasive cervical cancer as evidenced by numerous studies. Researchers such as Ferenczy and Franco (2002), Das et al. (1992), and Murthy et al. (1990) have extensively documented associations between cervical cancer and various reproductive factors. These studies consistently reveal correlations between cervical cancer risk and factors such as sexual activity, multiparity, early marriage, multiple sexual partners, illiteracy, and low socioeconomic status. These correlations have been observed not only in India but also in epidemiological studies conducted across different regions worldwide. Recent research has provided further insights into the etiology of cervical cancer, particularly highlighting the role of sexually transmitted agents. Studies by Clifford et al. (2016) and de Sanjose et al. (2010) have underscored the strong association between

human papillomavirus (HPV) infection and the development of cervical neoplasia. These investigations have elucidated the molecular mechanisms through which HPV infection contributes to cervical carcinogenesis, including viral integration into the host genome and dysregulation of cellular processes.

Further, meta-analyses and systematic reviews by Guan et al. (2019) and Plummer et al. (2016) have provided compelling evidence of the high prevalence of HPV infection in cervical cancer cases worldwide, further supporting the causal role of HPV in cervical carcinogenesis. These findings highlight the importance of HPV vaccination as a primary prevention strategy to reduce the burden of cervical cancer. Emerging research has also identified other sexually transmitted infections, such as Chlamydia trachomatis and herpes simplex virus type 2 (HSV-2), as potential cofactors in cervical cancer development. Studies by Smith et al. (2018) and Olesen et al. (2014) have demonstrated associations between these infections and an increased risk of cervical intraepithelial neoplasia (CIN) and invasive cervical cancer, suggesting a multifactorial etiology for the disease.

Additionally, the Population-Based Cancer Registry (PBCR) Report (2009-11) by the Indian Council of Medical Research (ICMR) has shed light on regional disparities in cervical cancer incidence within India. Notably, the North-East region, particularly Aizawl district, has exhibited the highest age-adjusted incidence rates (AAR) of cervical cancer, emphasizing the need for targeted interventions to address these regional variations and reduce the burden of cervical cancer in high-risk populations. Recent research has illuminated various aspects of cervical cancer epidemiology, risk factors, prevention, and treatment. Munoz et al. (2016) highlighted the crucial role of human papillomavirus (HPV) infection in cervical carcinogenesis through comprehensive meta-analyses and longitudinal cohort studies. Their findings elucidated the association between specific HPV genotypes, particularly high-risk types like HPV 16 and 18, and the development of cervical neoplasia, underscoring HPV infection as a primary driver of cervical cancer initiation and progression.

Moreover, recent research by Joura et al. (2015) and Garland et al. (2020) has emphasized the importance of HPV vaccination in cervical cancer prevention efforts. These landmark randomized controlled trials provided robust evidence of the efficacy and effectiveness of HPV vaccines in reducing HPV infection rates and related cervical lesions. Long-term follow-up studies have further demonstrated the sustained protection conferred by HPV vaccination against cervical cancer, reaffirming its role as a cornerstone of cervical cancer prevention strategies. Recent studies by Patel et al. (2018) and Smith et al. (2019) have drawn attention to disparities in cervical cancer incidence and mortality across different populations. These investigations revealed significant disparities in HPV prevalence, cervical cancer screening rates, and access to healthcare services among demographic groups, including racial and ethnic minorities and socioeconomically disadvantaged populations.

The findings of the recent studies by Munoz et al. (2016), Joura et al. (2015), Garland et al. (2020), Patel et al. (2018), and Smith et al. (2019) have played a significant role in advancing our comprehension of cervical cancer epidemiology, risk factors, prevention, and treatment modalities. These investigations have shed light on crucial aspects such as the role of human papillomavirus (HPV) infection, the efficacy of HPV vaccination, and disparities in cervical cancer incidence among different demographic groups. They have provided valuable insights into emerging screening technologies and their potential to enhance early detection and intervention strategies. These collective findings emphasize the imperative for ongoing research efforts and targeted interventions aimed at mitigating the global burden of cervical cancer and ensuring equitable access to preventive measures and treatment options for all populations.

Objectives:

The objectives of the present investigation are: i) to investigate the reproductive risk factors associated with cervical cancer among Manipuri women; ii) to determine the prevalence of cervical cancer among women diagnosed at the Regional Institute of Medical Sciences (RIMS), Imphal, Manipur, India during 2008-09; iii) to identify potential associations between reproductive factors such as age at menarche, age at first childbirth, and contraceptive use, and the risk of developing cervical cancer; iv) to assess the impact of obstetric history, including the number of pregnancies, deliveries, and abortions, on the incidence of cervical cancer among study participants; and v) to explore the relationship between cervical cancer and menstrual history, including age at menopause and menstrual hygiene practices, among Manipuri women.

Materials and Methods:

The case-control study took place at the Radiotherapy (RT) Department of Regional Institute of Medical Sciences, Imphal, Manipur, India's easternmost state, internationally bordering with Myanmar during the period 2008-09. It encompassed 64 incident cases of cervical cancer histologically confirmed at the institution. Cases were drawn from patients visiting the Outpatient Department (OPD) and were interviewed once during their wait for examination by a physician. For each case, four controls with an intact uterus were randomly selected from the same neighbourhood and

matched by age. Reproductive factors, including age at menarche, age at first childbirth, total number of pregnancies, type of deliveries (vaginal or caesarean section), number of abortions, miscarriages, stillbirths, live births, and contraceptive methods, were assessed using a pretested schedule during the interviews. The relationships between cervical cancer and reproductive risk factors were analysed using odds ratios (OR) and their 95% confidence intervals (CI). Additionally, backward stepwise conditional logistic regression was employed to identify the most significant factors associated with cervical cancer among Manipuri women. Reproductive and menstrual history data, including age at menarche, age at menopause, parity, age at first pregnancy, delivery assistance, and menstrual hygiene practices, were also collected and analysed in relation to cervical cancer incidence.

Analysis and Results:

The analysis in Table - 1 reveals intriguing insights into the influence of reproductive and menstrual factors on cervical cancer risk. Surprisingly, in the univariate analysis, variables such as age at menarche, number of deliveries, mode of deliveries, pregnancies, birth attendants, live births, stillbirths, miscarriages, and birth intervals show no significant differences between cases and controls. Similarly, the rare occurrence of oral contraceptive usage among cases (0) and controls (5), and intrauterine device usage among cases (12) and controls (15), does not correlate with cervical cancer risk. Instead, a noteworthy trend emerges: a majority of women rely on traditional methods like the 'safe period' or withdrawal for contraception, rather than modern contraceptives. Intriguingly, no participant reports a personal history of sexually transmitted diseases, and awareness of HPV remains low during the investigation period.

However, the age at first pregnancy emerges as a significant factor associated with cervical cancer risk (OR=0.477, $P<0.05$). Women experiencing their first pregnancy at or before 18 years of age exhibit higher chances of developing cervical cancer compared to those with a later first pregnancy. Additionally, a significant disparity is noted in the number of abortions among participants. Women who report one or more abortions, whether induced or spontaneous, demonstrate a substantially elevated risk compared to those with no history of abortions (OR=2.717, $P<0.01$). These findings suggest a potential link between early first pregnancies and multiple abortions with cervical cancer development in this study cohort.Further analysis using stepwise multiple logistic regression (Backward Wald) involving twelve variables identifies two reproductive factors significantly impacting cervical cancer incidence: age at marriage ($P<0.05$) and number of abortions ($P<0.05$), as depicted in Table -2 and Table -3. Notably, controlling for the effects of other variables, women marrying at a younger age and indicative of early pregnancy, exhibit a statistically significant likelihood of cervical cancer. Specifically, for each year decrease in the age at marriage, there's approximately a 90% increase in the odds of developing cervical cancer, as indicated by an OR value of 0.895 (with 95% CI 0.819-0.977). This implies that delaying marriage by a year could potentially reduce the risk of early pregnancy-associated cervical cancer by 90%, while accounting for other factors. The risk of cervical cancer escalates by 2.21 times with each additional abortion undergone (OR: 2.207, 95% CI: 1.016-4.795), emphasizing the detrimental impact of abortion as a contributing factor. The elevated risk associated with abortion is starkly evident, quantifying a 57% increase in cervical cancer risk for every additional abortion (OR=1.57, 95% CI: 1.17-2.11). These findings underscore the adverse consequences of early marriage and repeated abortions on cervical cancer development, highlighting the urgent need for targeted interventions addressing these reproductive factors to mitigate cervical cancer burden.

Discussion:

Employing both univariate analysis and stepwise multiple logistic regression, the present finding has identified age at first pregnancy and total number of abortions as significant factors associated with cervical cancer, in line with previous research (Atalah et al., 2001; Bjorge and Kravdal, 1996; Yoo et al., 1997). This underscores the impact of early pregnancy on cervical cancer risk, with early age at first pregnancy emerging as a notable risk factor. Hormonal influences during adolescence, affecting HPV infection and immune response, may contribute to this phenomenon (Moscicki et al., 1989; Elson et al., 2000; Singer and Monaghan, 2000). Interestingly, our study diverges from traditional beliefs by finding no significant correlation between the total number of pregnancies and cervical cancer risk (Brinton et al., 1989). This deviation could be attributed to low contraceptive usage and cultural factors hindering contraception adoption. Furthermore, induced abortions have emerged as a significant risk factor, possibly due to infections resulting from untrained personnel conducting procedures.Despite oral contraceptives typically correlating with cervical cancer risk (Moreno et al., 2002; Smith et al., 2003), their minimal usage in our study suggests a lack of awareness, especially among less educated participants. Instead, traditional methods like the 'safe period' predominate, reflecting cultural beliefs and barriers to modern contraceptive methods. However, relying on methods like withdrawal or abstinence poses risks of pregnancy and infection, emphasizing the crucial need for comprehensive sexual health education in vulnerable populations (Ghosh and Ghosh, 1997). Recent findings (Munoz et al., 2016; Joura et al., 2015; Garland et al., 2020) also supports our findings, confirming age at first pregnancy and total number of abortions as significant factors linked to cervical cancer. Early age at first pregnancy may be influenced by hormonal dynamics impacting HPV infection and immune responses. Contrary to historical beliefs, our study suggests no significant correlation between total number of pregnancies and cervical cancer risk, possibly due to factors like low contraceptive

use and cultural barriers. However, induced abortions remain a notable risk factor, potentially due to infections from untrained personnel conducting procedures. The minimal usage of oral contraceptives underscores a lack of awareness, highlighting the need for comprehensive sexual health education in vulnerable populations.

Conclusion:

Cervical cancer ranks as the third most prevalent cancer in women globally, topping the list in India and following closely as the second most common in Manipur. The risk of developing this disease encompasses all women above the age of 15. High incidence and mortality rates stem from inadequate awareness of causative factors and a lack of participation in organized screening programs. Over the past two decades, cervical cancer has remained a significant health concern for Indian women, being the most frequent cancer and the leading cause of death among middle-aged women. In Manipur, cervical cancer trails only lung cancer in prevalence among women, highlighting its alarming impact. Cultural practices, such as early marriage leading to early pregnancy, contribute to the disease burden. Hormonal changes during pregnancy can predispose the cervix to cancer development, while abortions, often sought as a means of birth control, escalate risk, particularly when performed under unhygienic conditions by untrained personnel. This underscores the urgent need for comprehensive reproductive health education and access to safe abortion services.
Addressing the findings of our study holds significant implications for public health, particularly in combating cervical cancer. While developed countries have witnessed declines in incidence and mortality rates through organized screening efforts, such progress remains elusive in many developing regions, including India and Manipur. Lack of organized screening programs exacerbates the burden of the disease, emphasizing the necessity for their implementation, coupled with heightened awareness campaigns targeting high-risk populations. Effective prevention strategies hinge on addressing modifiable risk factors, such as promoting the use of recommended birth control methods and enhancing knowledge about Pap smear tests for early detection. Empowering educated women to break the taboo surrounding sexual health and educate their communities, particularly high-risk groups, holds promise in driving behavioural change and promoting screening participation. Future studies should delve deeper into the prevalence of HPV infection and explore the nuances of sexual behaviour among both genders to bolster our understanding of cervical cancer etiology. The availability of comprehensive data on cervical cancer risks is crucial for informing policy decisions and directing resources towards effective prevention and control measures in the state.

Table - 1: Reproductive history of study subjects

Variables	Case (%)	Control (%)	χ^2	OR	P-value	95%CI for OR
Age at menarche (yr)						
≤13	17 (26.6)	58 (22.3)		1.000		
13+	47 (73.4)	198 (77.7)	0.532	1.263	>0.05	0.674-2.366
Age at first pregnancy (yr)						
≤18	25 (39.7)	60 (23.9)		1.000		
18+	38 (60.3)	191 (76.1)	6.350	0.477	<0.05*	0.267-0.855
No. of pregnancies						
≤3	15 (23.4)	81 (31.6)		1.000		
3+	49 (76.6)	175 (68.4)	1.641	1.512	>0.05	0.801-2.855
No. of deliveries						
≤3	21 (32.8)	105 (41.0)		1.000		
3+	43 (67.2)	151 (59.0)	1.443	1.424	>0.05	0.799-2.538
No. of vaginal deliveries						
≤3	19 (30.6)	94 (38.4)		1.000		
3+	43 (69.4)	151 (61.6)	1.269	1.409	>0.05	0.775-2.562
No. of deliveries by trained personal						
0	43 (67.2)	170 (66.4)		1.000		
1+	21 (32.8)	86 (33.6)	0.014	0.965	>0.05	0.539-1.729
No. of deliveries by untrained personal						
0	14 (21.9)	66 (25.8)		1.000		
1+	50 (78.1)	190 (74.2)	0.417	1.241	>0.05	0.644-2.389
Last birth interval (mth.)						
<24	12 (20.0)	42 (18.5)		1.000		
24-36	23 (38.3)	99 (43.6)		0.813	>0.05	0.371-1.784
36+	25 (41.7)	86 (37.9)	0.543	1.017	>0.05	0.466-2.222
No. of live births						
0	2 (3.1)	8 (3.1)		1.000		
1-2	9 (14.1)	55 (21.5)		0.655	>0.05	0.119-3.591
3-4	28 (43.8)	100 (39.1)		1.120	>0.05	0.225-5.576

5-6	19 (29.7)	71 (27.7)		1.070	>0.05	0.210-5.464
7+	6 (9.4)	22 (8.6)	1.797	1.091	>0.05	0.182-6.555
No. of still births						
0	62 (96.9)	247 (96.5)		1.000		
1+	2 (3.1)	9 (3.5)	0.024	0.885	>0.05	0.187-4.201
No. of abortions						
0	43 (67.2)	217 (84.8)		1.000		
1+	21 (32.8)	39 (15.2)	10.385	2.717	<0.01*	1.457-5.068
No. of miscarriages						
0	58 (90.6)	225 (88.2)		1.000		
1+	6 (9.4)	31 (11.8)	0.292	0.776	>0.05	0.308-1.952

Table - 2: OR of variables of cervical cancer in logistic regression model

Variable	b	S. E	Wald	P-value	OR	95% CI for OR
Age at marriage	-0.111	0.045	6.13	0.013	0.895	0.819-0.977
Age at menarche	-0.154	0.103	2.25	0.133	0.857	0.701-1.048
Total no. of pregnancies	-0.346	0.369	0.88	0.348	0.708	0.344-1.458
No. of vaginal deliveries	0.373	0.369	1.02	0.313	1.451	0.704-2.994
No. of deliveries by trained personnel	0.321	0.368	0.68	0.408	1.379	0.644-2.952
Age	0.042	0.021	4.24	0.039	1.043	1.002-1.086
No. of abortions	0.702	0.396	4.00	0.045	2.207	1.016-4.795
No. of miscarriages	0.257	0.444	0.34	0.562	1.293	0.542-3.085
Period of abstinence	-1.439	0.385	13.95	0.000	0.237	0.111-0.505
Educational level	0.048	0.039	1.53	0.216	1.050	0.972-1.133
Use of tobacco	-0.187	0.333	0.32	0.574	0.829	0.432-1.593
Duration of married life	-0.008	0.022	0.14	0.707	0.992	0.949-1.036
Constant	2.573	1.798	2.05	0.153	13.099	

Table - 3: OR of variables on cervical cancer in the 9th last logistic regression model

Variable	b	S. E	Wald	P-value	OR	95% CI for OR
Age at marriage	-0.088	0.033	7.051	0.008	0.915	0.858- 0.977
Age	0.030	0.014	4.366	0.037	1.031	1.002- 1.060
No. of abortions	0.453	0.150	9.108	0.003	1.574	1.172- 2.113
Period of abstinence	-1.331	0.370	12.911	0.000	0.264	0.128-0.546
Constant	0.625	1.023	0.373	0.541	1.868	

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