ORIGINAL ARTICLE

Received: August 2020
Accepted: December 2020

Major Risk Factors for Cervical Cancer in Northeast of Iran: Evidence from a Case-Control Study

Fatemeh Homaei Shandiz[1], Alireza Pasdar[2,3], Fahimeh Afzaljavan[2,4], Zohre Takalluo[5], Malihe Hasanzadeh Mofrad[5]*

1. Cancer Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
2. Department of Medical Genetics and Molecular Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
3. Division of Applied Medicine, Medical School, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK.
4. Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
5. Department of Obstetrics and Gynecology, School of Medicine, Ghaem Hospital, Mashhad University of Medical Sciences.

***Corresponding Authors:**
Malihe Hasanzadeh Mofrad, Department of Obstetrics and Gynecology, School of Medicine, Ghaem Hospital, Mashhad University of Medical Sciences.
Phone: (+98)5138400000-9
Email: hasanzademofradm@mums.ac.ir

BCCR
2020; 12(2): 91-97
www.bccrjournal.com

ABSTRACT

Background: Cervical cancer is a preventable cancer with various risk factors. In this study, we assessed different risk factors involved in invasive cervical cancer in the Northeast of Iran.

Methods: In a case-control study, 99 patients with advanced cervical cancer were compared to 102 healthy, normal women. Cervical cancer risk factors were documented for these groups using a questionnaire and available medical notes. Univariate analysis was done for each risk factor, followed by multivariate regression analysis, to evaluate the most powerful risk factors after adjustment.

Results: Multivariate model indicated that sexual transmitted diseases (STD) [p<0.001; OR=7.88, 95% CI (2.59-23.93)], age at first intercourse ≤16 [p=0.048; OR=6.22, 95% CI (1.06-36.51)] and age [p=0.001; OR= 1.11, 95% CI (1.04-1.18)] were independently significant risk factors for cervical cancer.

Conclusion: According to this survey, the significant influence of major risk factors, including STD, age at first intercourse, and age itself, has been underlined. Moreover, increasing the social knowledge and educating people to prevent high-risk sexual behaviors, HPV testing, and routine use of HPV vaccine, which is nowadays regarded as a preventive measure in cervical cancer, may also be needed to be implemented in our prevention program.

Keywords: Cervical Cancer, Sexually Transmitted Diseases, Risk Factors, Sexual Behavior

INTRODUCTION:

Cervical cancer is one of the most common cancer diagnosed in women. The worldwide incidence of cervical cancer was estimated 570 000 new cases, of which 311 000 women died of the disease in 2018 (1). The distribution of this cancer is different among societies. The most common prevalent societies are developing countries with poor screening strategies, including the lack of regular Pap smear tests (2). Also, the unprotected sexual relationship may significantly increase the distribution of (human papillomavirus) HPV among the at-risk population (3, 4). Almost 87% of cervical cancer deaths occur in less developed countries (5). However, new researches have indicated a low incidence of the disease in Iran. Conversely, there are many risk factors for cervical cancer that may cause the health care system to meet the disease's increasing rate in the future (6, 7).

There are several risk factors for cervical cancer, without any of which women rarely develop the disease. Marriage at age below 16, being multi-partner, multiparity, low social status, the coexistence of immune-compromised conditions, oral contraceptive pill (OCP) consumption, sexually transmitted diseases (STD), and HPV are among suggested risk factors in Iran and around the world (6, 8, 9). Despite the killer nature of cervical cancer, it is known as a preventable disease, mainly because it has a long pre-invasive duration. Furthermore, screening for this cancer by Pap smear is available for everyone, and owing to the effective treatment of pre-invasive lesions, it can be controlled (10).

While cervical cancer is not common in Iran, patients mostly refer to the physician in advanced stages (11). According to the cultural, economic, and social status, most Iranian women are not aware of the screening tests and Pap smear (12). Furthermore, previous studies in several parts of the country have reported different causes for the disease (4, 13, 14). Therefore, it is necessary to evaluate the disease-related risk factors in different sub-populations in line with cultural properties. Since there have been no documented studies about risk factors of cervical cancer in Khorasan province, we evaluated these factors in a case-control study for the first time in the northeast of Iran.

METHODS:

Study population

In this hospital-based, case-control study, data of 99 patients with cervical squamous cell carcinoma (SCC) referred to Ghaem Hospital for treatment and follow up, from Jan 2007 to Jan 2010, were assessed and compared to 102 outpatient women with normal Pap smear and pelvic examination referred to Ghaem clinic, as the control group. Women with no history of drug abuse with two normal Pap smear tests during a year were selected as control. A history of abnormal Pap smear or cervical cancer was considered exclusion criteria in the control group. Demographic data, obstetric and fertility history, family history of cervical cancer, smoking, and history of STD were assessed in both groups. The study was approved by the ethics committee of Mashhad University of Medical sciences. Written informed consent was obtained from all participants before recruitment.

Statistical analysis

Data analysis was performed using SPSS software version 16. Depending on the assessment of normality with the Kolmogorov-Smirnov test, the normally distributed continuous variables were examined using an independent sample t-test. Mann-Whitney test was used to compare non-normally distributed variables between the two groups. The categorical variables were compared using the chi-square or Fisher's exact tests, accordingly.

Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) in a univariate model. A multivariate model was then applied to identify the variables with an independent effect on

cervical cancer risk. P-values less than 0.05 were considered significant.

RESULTS:

Characteristics of cases and controls have been shown in **Table 1**. The mean age for patients and controls was 52.7±12.5 and 36.1±11.0 years, respectively. The result showed a significant difference in the mean age of participants in the two groups (p<001). Furthermore, such a significant difference was observed for the mean age at first intercourse (15.9±3.1 and 18.3±3.8 in case and control groups, respectively, p<001) and mean age at first pregnancy (17.5±3.3 and 20.1±3.9 in case and control groups, respectively, p<001). However, menarche's mean age did not indicate any significant difference between the groups (p=0.382).

Similarly, the rate of abortion was significantly different between groups with a higher proportion in patients than the controls (p=0.001). Furthermore, the number of marriages was also assessed, and the frequency of women with more than one marriage in cases (16.2%) was shown to be higher than the percentage in the control group (2%) (p<0.001). Moreover, the percentage of women with cervical cancer whose husband had more than one marriage was 27.9%, which had a significant difference from the control group (5.9%) (p<0.001).

Pregnancy evaluation indicated a significant difference between groups in the mean of parity number (p<001) and the frequency of parity equal or more than three (p<001) as the rate of multiparous females was 92% and 46% in cancer and healthy groups, respectively. The OCP use assessment indicated no significant difference between OCP consumption in controls and cervical cancer (p=0.171). However, among OCP takers, the average time of OCP use was significantly different (p=008). Moreover, there was also an increased risk of cervical cancer in women with long term use of OCP (OCP use ≥3 years) compared to OCP use less than three years or lack of OCP use (p=0.001). Besides, STDs were also strongly related to cervical cancer, which was 78.1% in patients and 29.3 % in control groups (p<0.001).

In this study, the mean BMI was 27.3±5.9 and 25.8±4.1 for cancer patients and healthy individuals, respectively, which indicated a marginally significant difference (p=0.043). However, there was no association between BMI≥ 25 and cervical cancer (p=0.091). Furthermore, the frequency of women with a low level of education and smoking and passive smoking status was more in cervical cancer than in the control group (p=0.001, p=0.002, and p=0.016, respectively). Conversely, a positive family history of cervical cancer did not significantly differ between the two groups (p=0.295).

Risk factors associated with cervical cancer in multivariate analysis included STD [p<0.001; OR=7.88, 95% CI (2.59-23.93)], age at first intercourse ≤16 [p=0.048; OR=6.22, 95% CI (1.06-36.51)] and age [p=0.001; OR= 1.11, 95% CI (1.04-1.18)]. Results have been shown in **Table 2**.

DISCUSSION:

Cervical cancer, as an important public health issue, is the fourth-ranked cancer in women. However, cervical cancer development and mortality can be avoided using the identification and limitation of its risk factors. In this regard, previous studies in different parts of Iran have reported marriage at a young age, multiparity, and low age at first pregnancy as significant risk factors for cervical cancer (4, 6). Our findings indicated that age, early age at first sexual intercourse, and STDs were independent factors associated with the risk of cervical cancer significantly. Other factors, such as age at menarche and the use of OCP, were not significantly related to the increased risk of cervical cancer.

Some researchers claimed that early age at first intercourse due to the higher chance of infection with HPV

Table 1. The characteristics of patients and healthy individuals and crude odds ratio (OR)

Risk factors	Case (99)	Healthy (102)	P-value	OR (95% CI)
Age	52.7±12.5	36.1±11.0	<001	1.13 (1.09-1.17)
Age at menarche	13.72±1.50	13.51±1.84	0.382	1.09 (0.91-127)
Age at first intercourse	15.9±3.1	18.3±3.8	<001	1.24 (1.13-1.36)
Age at first pregnancy	17.5±3.3	20.1±3.9	<001	1.25 (1.14-1.37)
BMI Mean (kg/m2)	27.3± 5.9	25.8± 4.1	0.043	1.06 (1.00-1.13)
Parity	6.1±2.6	2.9±2.1	<001	1.77 (1.50-2.09)
Average time of OCP use	6.4±4.3	3.4±2.7	0.008	1.29 (1.07-1.56)
BMI (kg/m2):				
<25	34 (34.3%)	47 (46.1%)		
≥25	65 (65.7%)	55 (53.9%)	0.091	1.63 (0.93-2.89)
Age at first intercourse:				
≤16	67 (67.7%)	34 (33.3%)		
>16	32 (32.3%)	68 (66.7%)	<001	4.19 (2.32-7.55)
Age at first pregnancy:				
≤17	55 (55.6%)	25 (24.5%)		
>17	44 (44.4%)	77 (75.5%)	<001	4.19 (2.32-7.55)
Parity:				
<3	7 (7.1%)	56 (54.9%)		
≥3	92 (92.9%)	46 (45.1%)	<001	16.00 (6.76-37.87)
History of abortion:				
No	49 (50.5%)	74 (74.0%)		
Yes	48 (49.5%)	26 (26.0%)	0.001	2.79 (1.53-5.07)
Use of OCP:				
No	58 (59.2%)	50 (49.5%)		
Yes	40 (40.8%)	51 (50.5%)	0.171	1.47 (0.84-2.59)
Use of OCP:				
0-3	16 (40%)	13 (25.5%)		
≥3	24 (60%)	38 (74.5%)	0.001	4.38 (1.80-10.70)
Family history of cervical cancer:				
No	93 (93.9%)	99 (97.1%)		
Yes	6 (6.1%)	3 (2.9%)	0.295	2.13 (0.52-8.76)
Marriage ≥2:				
No	83 (83.8%)	100 (98%)		
Yes	16 (16.2%)	2 (2%)	0.003	9.64 (2.15-43.13)
Husband's marriage ≥2:				
No	62 (72.1%)	95 (94.1%)		
Yes	24 (27.9%)	6 (5.90%)	<001	6.13 (2.37-15.85)
History of STD:				
No	16 (21.9%)	70 (70.7%)		
Yes	57 (78.1%)	29 (29.3%)	<001	8.60 (4.26-17.38)
Smoking:				
No	82(82.8%)	100 (98.1%)		
Yes	17 (17.2%)	2 (1.9%)	0.002	10.37 (2.33-46.17)
Passive smoking:				
No	35 (59.3%)	79 (77.5%)		
Yes	24 (40.70%)	23 (22.50%)	0.016	2.35 (1.17-4.73)
Level of education:				
≥diploma	12 (12.1%)	33 (32.4%)		
<diploma	87 (87.9%)	69 (67.6%)	0.001	3.47 (1.67-7.21)

Table 2. Association between different risk factors and occurrence of cervical cancer (multivariable analysis)

Risk factors	P-value	OR (95% CI)
Age	0.001	1.11 (1.04-1.18)
Age at first intercourse (≤16 vs. >16)	0.043	6.22 (1.06-36.51)
Age at first pregnancy (≤17 vs. >17)	0.309	2.40 (0.44-13.03)
BMI	0.700	1.02 (0.92-4.10)
Marriage ≥2 (Yes vs. No)	0.383	5.64 (0.12- 275.00)
Husband's marriage ≥2 (Yes vs. No)	0.074	4.10 (0.87-19.30)
STD (Yes vs. No)	0.000	7.88 (2.59-23.93)
Parity (≥3 vs. <3)	0.580	1.61 (0.30-8.61)
History of abortion (Yes vs. No)	0.146	2.37 (0.74-7.62)
Use of OCP (≥3 vs. 0-3)	0.158	2.53 (0.70-9.13)
Smoking (Yes vs. No)	0.472	2.30 (0.24-22.18)
Passive smoking (Yes vs. No)	0.139	2.46 (0.75-8.14)
Level of education (<diploma vs. ≥diploma)	0.861	1.15 (.24-5.41)

could be a principal risk factor for cervical cancer (15-17). Besides, the number of sexual partners, multiple marriages, and extramarital sex relationships of women have been associated with increasing the risk of cervical cancer due to a higher risk of infection with human papillomavirus (HPV) (4, 9). In line with these hypotheses, we found a 6-fold risk of cervical cancer for first intercourse ≤16 and an 8-fold increased risk for STDs. According to previous studies, the risk of cervical cancer has been strongly associated with OCP use. This relationship increases with duration of use (18, 19). Similarly, two studies in Iran reported the prolonged consumption of contraceptive pills as a risk factor for the disease (14, 19). However, consistent with a study conducted by Mohaghegh F. et al. (13), we did not observe a significant association after adjustment in multivariable analysis for OCP use. These findings identified complexity depending mainly on the considered population, study design, and confounders type.

In a meta-analysis, obesity was weakly associated with an increased risk of cervical cancer (20). In our study, BMI in the patients group was higher than in the control group with a marginal association. However, no significant difference was observed between BMI less and more than 25 kg/m2 even after adjustment.

Smoking has been an essential risk factor for SCC and probably for the cervix's adenocarcinoma (21). Smoking weakens the immune system and exposes the body to cancer-causing chemicals that may predispose cervical cancer (22). While we observed a direct association between active and passive smoking and cervical cancer development in univariate analysis, adjusted data did not confirm these findings.

Our results did not support the low level of education as an independent risk factor for cervical cancer. Similarly, another study reported no association between

educational level and adenocarcinoma or SCC of the cervix (9). However, yet this relation seems to be controversial. In a study by Franceschi S. et al. (23), the education level was assumed to be associated with cervical cancer risk, but no relationship emerged between education and HPV infection.

This is the first case-control study evaluating the risk factors of cervical cancer in northeast Iran to the best of our knowledge. Conversely, this study had limitations in evaluating HPV status due to financial constraints. The study was not population-based, with random sampling from the community. We, therefore, tried to choose a control group free of the risk factors. However, we acknowledge that cohort studies or population-based case-control studies may reflect a better view of the risk profile.

Furthermore, as age is a well-known risk factor for cancer development, it is better to choose age-matched groups to identify related risk factors. However, we had to work on available data that was different for this issue. On the other hand, a study with a larger sample size should be designed to confirm these findings with considerable statistical power.

In conclusion, although most of the risk factors for cervical cancer are modifiable, the significant influence of key risk factors, including age, STD, and age at first intercourse, has been underlined. Furthermore, social knowledge development and sufficient education to prevent high-risk sexual behavior may significantly decrease the risk of cervical cancer in our population. Besides, authors recommend screening guidelines for high-risk women using pelvic examination and cytology of the cervix smear samples.

ACKNOWLEDGMENT:

The authors thank all participants in this research. We would also like to thank Mashhad University of Medical Sciences and Ghaem hospital (Mashhad, Iran) for supporting the project.

CONFLICT OF INTERESTS:

The authors reported no potential conflict of interest.

FUNDING:

This work was supported by Mashhad University of Medical Sciences.

REFERENCES:

1. World Health Organization. Cervical cancer; Overview 2018. Available from: https://www.who.int/health-topics/cervical-cancer#tab=tab_1.
2. Organization WH. Global burden of disease report: Causes of death in 2004. Geneva: World Health Organization; 2004.
3. Vaccarella S, Franceschi S, Herrero R, Munoz N, Snijders PJ, Clifford GM, Smith JS, Lazcano-Ponce E, Sukvirach S, Shin HR, de Sanjosé S. Sexual behavior, condom use, and human papillomavirus: pooled analysis of the IARC human papillomavirus prevalence surveys. Cancer Epidemiology and Prevention Biomarkers. 2006 Feb 1;15(2):326-33.
4. Zarchi MK, Akhavan A, Gholami H, Dehghani A, Naghshi M, Mohseni F. Evaluation of cervical cancer risk-factors in women referred to Yazd-Iran hospitals from 2002 to 2009. Asian Pacific Journal of Cancer Prevention. 2010 Jan 1;11:537-8.
5. Ngoma M, Autier P. Cancer prevention: cervical cancer. ecancermedicalscience. 2019;13.
6. Momenimovahed Z, Salehiniya H. Cervical cancer in Iran: integrative insights of epidemiological analysis. BioMedicine. 2018 Sep;8(3).
7. Riahi S, Mokhtari AM, Vali M, Abdzadeh E, Mohseni S, Salehiniya H, Hassanipour S. Incidence and mortality rate of cervix cancer in Iran from 1990 to 2016: A systematic review and meta-analysis. Journal of Contemporary Medical Sciences. 2019;5(1):1-7.
8. Gayed M, Bernatsky S, Ramsey-Goldman R, Clarke AE, Gordon C. Lupus and cancer. Lupus. 2009 May;18(6):479-85.
9. Green J, De Gonzalez AB, Sweetland S, Beral V, Chilvers C, Crossley B, Deacon J, Hermon C, Jha P, Mant D, Peto J. Risk factors for adenocarcinoma and squamous cell carcinoma of the cervix in women aged 20–44 years: the UK National Case–Control Study of Cervical Cancer. British journal of cancer. 2003 Dec;89(11):2078-86.
10. Köse FM, Naki MM. Cervical premalignant lesions and their management. Journal of the Turkish German Gynecological Association. 2014;15(2):109.
11. Khorasanizadeh F, Hassanloo J, Khaksar N, Taheri SM, Marzaban M, Rashidi BH, Sari AA, Zendehdel K. Epidemiology of cervical cancer and human papilloma virus infection

among Iranian women—Analyses of national data and systematic review of the literature. Gynecologic oncology. 2013 Feb 1;128(2):277-81.

12. Farshbaf-Khalili A, Salehi-Pourmehr H, Shahnazi M, Yaghoubi S, Gahremani-Nasab P. Cervical cancer screening in women referred to healthcare centres in Tabriz, Iran. Nigerian medical journal: journal of the Nigeria Medical Association. 2015 Jan;56(1):28.
13. Mohaghegh F, Ahmadlou M. A Study of the Prevalence of Cervical Cancer among Married Wemon in Arak, 2013. Journal of Arak university of Medical Sciences. 2015 Jul 10;18(4):65-70.
14. Vaisy A, Lotfinejad S, Zhian F. Risk of cancer with combined oral contraceptive use among Iranian women. Asian pacific journal of cancer prevention. 2014;15(14):5517-22.
15. Rostad B, Schei B, Da Costa F. Risk factors for cervical cancer in Mozambican women. International journal of gynaecology and obstetrics. 2003;80(1):63-5.
16. Flores YN, Bishai DM, Shah KV, Lazcano-Ponce E, Lörincz A, Hernández M, Ferris D, Salmerón J. Risk factors for cervical cancer among HPV positive women in Mexico. salud pública de méxico. 2008;50:49-58.
17. Kahn JA, Lan D, Kahn RS. Sociodemographic factors associated with high-risk human papillomavirus infection. Obstetrics & gynecology. 2007 Jul 1;110(1):87-95.
18. Gierisch JM, Coeytaux RR, Urrutia RP, Havrilesky LJ, Moorman PG, Lowery WJ, Dinan M, McBroom AJ, Hasselblad V, Sanders GD, Myers ER. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer Epidemiology and Prevention Biomarkers. 2013 Nov 1;22(11):1931-43.
19. Nojomi M, Gilani M, Erfani A, Mozafari N, Mottaghi A. The study of frequency of risk factors of cervical cancer among women attending general hospitals in Tehran, 2005-2006. Razi Journal of Medical Sciences. 2007 Nov 10;14(56):189-95.
20. Poorolajal J, Jenabi E. The association between BMI and cervical cancer risk: a meta-analysis. European Journal of Cancer Prevention. 2016 May 1;25(3):232-8.
21. José Alberto FM. Smoking and cervical cancer. ISRN Obstetrics and Gynecology. 2011 Jul 14;2011.
22. Dugué PA, Rebolj M, Garred P, Lynge E. Immunosuppression and risk of cervical cancer. Expert review of anticancer therapy. 2013 Jan 1;13(1):29-42.
23. Franceschi S, Plummer M, Clifford G, De Sanjose S, Bosch X, Herrero R, Munoz N, Vaccarella S. Differences in the risk of cervical cancer and human papillomavirus infection by education level. British journal of cancer. 2009 Sep;101(5):865-70.