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Factors associated with cervical cancer among women in northeastern Iran: a population-based case–control study

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Abstract

Background

Cervical cancer remains an important public health problem among women worldwide. Although several demographic, reproductive, lifestyle, and clinical characteristics have been associated with cervical cancer, population-based evidence from Iran remains limited. This study aimed to investigate factors associated with cervical cancer in a population-based case–control study conducted in northeastern Iran.

Methods

This population-based retrospective case–control study included women covered by Mashhad University of Medical Sciences between March 21, 2017, and March 19, 2021. Cases comprised 74 women with histopathologically confirmed cervical cancer identified from the regional Population-Based Cancer Registry, while 148 controls without cervical cancer were randomly selected from the Primary Health Care Family Physician Information System. Univariable and multivariable logistic regression analyses were performed to estimate crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Model performance was evaluated using the area under the receiver operating characteristic curve (AUC), Hosmer–Lemeshow goodness-of-fit test, Brier score, and Nagelkerke R^2. Internal validation was performed using bootstrap resampling.

Results

A total of 222 women (74 cases and 148 controls) were included in the analysis. After adjustment for potential confounders, increasing age (adjusted OR [aOR] = 1.043, 95% CI: 1.004–1.083; *P* = 0.030) and earlier age at first pregnancy (aOR = 0.918 per one-year increase in age at first pregnancy, 95% CI: 0.850–0.992; *P* = 0.030) were independently associated with cervical cancer. No independent associations were observed for body mass index, parity, age at menarche, smoking, or hypertension. The final multivariable model demonstrated modest discriminatory ability (AUC = 0.666, 95% CI: 0.586–0.746), satisfactory calibration (Hosmer–Lemeshow *P* = 0.847), a Brier score of 0.218, and a Nagelkerke R^2 of 0.100. Bootstrap internal validation demonstrated stable model performance (mean bootstrap AUC = 0.640; SD = 0.023).

Conclusions

Increasing age and earlier age at first pregnancy were independently associated with cervical cancer among women in northeastern Iran. Although the predictive performance of the model was modest, the findings provide population-based evidence that may contribute to cervical cancer risk assessment and

targeted prevention strategies. Future prospective studies incorporating additional demographic, reproductive, behavioral, and socioeconomic factors are warranted to improve cervical cancer risk prediction.

Introduction

Cervical cancer remains a major public health concern and is one of the leading causes of cancer-related morbidity and mortality among women worldwide. According to the World Health Organization (WHO) and the Global Cancer Observatory (GLOBOCAN), cervical cancer was the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related death among women in 2022, accounting for more than 660,000 new cases and approximately 350,000 deaths globally (1–3). Although the burden of cervical cancer has declined substantially in many high-income countries through the implementation of organized screening programs and widespread human papillomavirus (HPV) vaccination, the disease continues to disproportionately affect women in low- and middle-income countries, where nearly 90% of cervical cancer deaths occur (1–6). In response to this global disparity, the WHO has launched a strategy to eliminate cervical cancer as a public health problem by expanding HPV vaccination, high-quality screening, and timely treatment of precancerous lesions and invasive disease (1).

Persistent infection with high-risk HPV genotypes is the necessary cause of nearly all cervical cancers. However, HPV infection alone is insufficient for malignant transformation because most infections are transient and are cleared spontaneously by the immune system (3–6). The progression from persistent HPV infection to cervical intraepithelial neoplasia and invasive cervical cancer is influenced by a complex interaction of demographic, reproductive, behavioral, biological, and socioeconomic factors. Increasing age, early age at first pregnancy or marriage, high parity, cigarette smoking, prolonged oral contraceptive use, immunosuppression, obesity, and inequalities in access to preventive healthcare have all been associated with cervical cancer risk, although the strength and independence of these associations vary across populations (5–7,13–20).

Previous epidemiological studies have reported inconsistent findings regarding several established and suspected risk factors for cervical cancer. While some investigations have demonstrated independent associations between reproductive characteristics, obesity, and cervical cancer, others have shown that these relationships become attenuated after adjustment for HPV infection, socioeconomic status, and healthcare utilization (11,13–16). Likewise, studies from both high-income and low- and middle-income countries have highlighted the substantial influence of screening inequalities, geographic disparities, and barriers to preventive healthcare on cervical cancer incidence and outcomes (12,13,17–19). These inconsistencies emphasize the need for population-specific evidence because demographic characteristics, reproductive patterns, healthcare accessibility, and screening practices differ considerably between countries and regions.

In Iran, cervical cancer has a lower incidence than in many developing countries; however, national registry data indicate considerable regional variation and changing epidemiological patterns (7, 8, 10). Although cervical cancer screening has expanded in recent years, participation remains suboptimal and is strongly influenced by socioeconomic status, educational attainment, health literacy, cultural beliefs, and access to healthcare services (9,11,12,20). Most Iranian studies have been hospital-based, conducted in limited geographic areas, or included relatively small sample sizes, thereby limiting their generalizability to the broader population (7–12). Consequently, robust population-based evidence from northeastern Iran remains limited.

To address this knowledge gap, the present study was designed as a population-based retrospective case–control study among women residing in Mashhad and surrounding areas covered by Mashhad University of Medical Sciences. Histopathologically confirmed cervical cancer cases were identified through the regional Population-Based Cancer Registry, while controls were randomly selected from the Primary Health Care (PHC) Family Physician Information System. Because both cases and controls originated from the same underlying source population, this design minimizes selection bias and improves the validity and generalizability of the estimated associations. To our knowledge, few population-based case–control studies in Iran have combined registry-confirmed cervical cancer cases with population-derived controls to investigate demographic, reproductive, lifestyle, and clinical factors associated with cervical cancer.

Therefore, the aim of this study was to evaluate the independent associations between demographic, reproductive, lifestyle, and clinical characteristics and cervical cancer using multivariable logistic regression analysis. In addition, the predictive performance and internal validity of the final model were assessed using receiver operating characteristic analysis, model performance indices, and bootstrap internal validation. The findings are expected to provide population-based evidence to improve cervical cancer risk assessment, inform targeted prevention strategies, and support evidence-based public health planning in northeastern Iran.

Materials and Methods

Study design

This population-based retrospective case–control study was conducted among women residing in Mashhad and the surrounding areas covered by Mashhad University of Medical Sciences (MUMS), northeastern Iran. The study aimed to investigate demographic, reproductive, lifestyle, and clinical factors associated with cervical cancer. Eligible participants were identified between **March 21, 2017, and March 19, 2021**. The study was designed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.

Study population

Cases

The case group comprised all eligible women with histopathologically confirmed primary cervical cancer who were registered in the Population-Based Cancer Registry of Mashhad University of Medical Sciences during the study period. Histopathological confirmation was considered the reference standard for case ascertainment. To minimize selection bias, all consecutive eligible cases recorded during the study period were included.

Controls

Controls were randomly selected from the Primary Health Care (PHC) Family Physician Information System, which routinely collects demographic and health-related information for women covered by the PHC network in Mashhad and surrounding areas. Eligible controls had no recorded diagnosis of cervical cancer and originated from the same underlying source population as the cases. Controls were selected using simple random sampling at an approximate ratio of 2:1 relative to cases to improve statistical efficiency while maintaining comparability between study groups.

Data collection

Demographic, reproductive, lifestyle, and clinical information was extracted from the Population-Based Cancer Registry and the PHC Family Physician Information System using standardized data collection procedures. The evaluated variables included age, body mass index (BMI), parity, age at menarche, age at first pregnancy, age at last pregnancy, age at first sexual intercourse, smoking status, hypertension, diabetes mellitus, oral contraceptive use, abortion history, marital status, live birth history, and other available reproductive and clinical characteristics. Data quality was assessed before analysis, and records with incomplete information for variables required in the regression analyses were excluded from the corresponding analyses.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation (SD) or median (interquartile range [IQR]), according to their distribution. Categorical variables were presented as frequencies and percentages. Baseline characteristics were compared between cases and controls using the independent-samples *t* test or the Mann–Whitney *U* test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

Univariable logistic regression analysis was performed to estimate crude odds ratios (ORs) and 95% confidence intervals (CIs) for each candidate predictor. Variables with a *P* value < 0.20 in the univariable analysis or considered clinically relevant based on previous literature were entered into the multivariable logistic regression model to estimate adjusted odds ratios (aORs) and corresponding 95% CIs. Variables

exhibiting sparse data or complete/quasi-complete separation that resulted in unstable parameter estimates were excluded from the final multivariable model.

Model discrimination was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC). Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test, overall prediction accuracy was evaluated using the Brier score, and explanatory performance was quantified using the Nagelkerke R^2 statistic. Internal validation was performed using bootstrap resampling with 100 iterations to assess model stability. One hundred bootstrap resamples were used to provide an initial assessment of internal model stability while maintaining computational efficiency. Successful convergence of the multivariable model across all bootstrap samples was considered evidence of model robustness.

All statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant.

Results

Participant characteristics

A total of 222 women were included in the final analysis, comprising 74 women with histopathologically confirmed cervical cancer (cases) identified from the regional cancer registry and 148 population-based controls randomly selected from the Primary Health Care (PHC) Family Physician Information System. The baseline demographic, reproductive, lifestyle, and clinical characteristics of the study participants are presented in Table 1.

Compared with controls, women with cervical cancer were significantly older (47.72 ± 9.72 vs. 42.30 ± 12.41 years, P = 0.001), had higher parity (3.35 ± 1.79 vs. 2.70 ± 1.74, P = 0.010), and were more likely to report oral contraceptive use (5.4% vs. 0.7%, P = 0.043). No statistically significant differences were observed between cases and controls with respect to body mass index (BMI), smoking status, hypertension, diabetes mellitus, or history of abortion (Table 1).

Univariable logistic regression analysis

The associations between individual variables and cervical cancer were initially evaluated using univariable logistic regression analysis (Table 2). Increasing age (OR = 1.041, 95% CI: 1.015–1.067, P = 0.002) and parity (OR = 1.228, 95% CI: 1.046–1.443, P = 0.012) were associated with higher odds of cervical cancer, whereas increasing age at first pregnancy was associated with lower odds of cervical cancer (OR = 0.925, 95% CI: 0.866–0.989, P = 0.022).

No statistically significant associations were observed for BMI, abortion history, age at menarche, age at last pregnancy, age at first sexual intercourse, smoking, oral contraceptive use, hypertension, diabetes mellitus, or marital status. Oral contraceptive use and marital status demonstrated sparse data with

unstable parameter estimates and were therefore not included in the final multivariable model despite their potential clinical relevance.

Multivariable logistic regression analysis

Variables with a *P* value <0.20 in the univariable analysis or considered clinically relevant based on previous evidence were entered into the multivariable logistic regression model, including age, BMI, parity, age at menarche, age at first pregnancy, smoking status, and hypertension (Table 3).

After adjustment for potential confounders, increasing age remained independently associated with higher odds of cervical cancer (adjusted OR [aOR] = 1.043, 95% CI: 1.004–1.083, *P* = 0.030). Likewise, increasing age at first pregnancy remained independently associated with lower odds of cervical cancer (aOR = 0.918, 95% CI: 0.850–0.992, *P* = 0.030).

No statistically significant independent associations were identified for BMI (aOR = 0.978, 95% CI: 0.918–1.043, *P* = 0.501), parity (aOR = 0.893, 95% CI: 0.706–1.129, *P* = 0.343), age at menarche (aOR = 1.118, 95% CI: 0.862–1.450, *P* = 0.401), smoking (aOR = 1.336, 95% CI: 0.494–3.611, *P* = 0.568), or hypertension (aOR = 1.312, 95% CI: 0.486–3.545, *P* = 0.592).

Model performance

The performance of the final multivariable logistic regression model is summarized in Table 4. The model demonstrated modest discriminatory ability, with an area under the receiver operating characteristic (ROC) curve (AUC) of 0.666 (95% CI: 0.586–0.746). Model calibration was satisfactory, as indicated by the non-significant Hosmer–Lemeshow goodness-of-fit test (χ^2 = 4.116, *P* = 0.847). The Brier score was 0.218, indicating acceptable overall prediction accuracy. The model demonstrated modest explanatory performance (Nagelkerke R^2 = 0.100), indicating that approximately 10% of the variation in cervical cancer status was accounted for by the variables included in the final model.

Internal validation

Bootstrap internal validation was performed using 100 resamples to evaluate model stability (Table 5). The multivariable logistic regression model converged successfully in all bootstrap samples (100/100). The mean bootstrap AUC was 0.640 (standard deviation = 0.023), indicating acceptable model stability with only modest optimism following internal validation.

Overall, after adjustment for potential confounders, increasing age and earlier age at first pregnancy remained independently associated with cervical cancer in this population-based study of women covered by Mashhad University of Medical Sciences.

Table 1. Baseline characteristics of the study participants

Characteristic	Controls (n = 148)	Cases (n = 74)	*P* value
Age (years), mean ± SD	42.30 ± 12.41	47.72 ± 9.72	**0.001**
BMI (kg/m²), mean ± SD	27.16 ± 5.28	27.89 ± 5.37	0.337
Parity, mean ± SD	2.70 ± 1.74	3.35 ± 1.79	**0.010**
Smoking, n (%)	11 (7.4%)	9 (12.2%)	0.320
Hypertension, n (%)	14 (9.5%)	12 (16.2%)	0.183
Diabetes mellitus, n (%)	16 (10.8%)	7 (9.5%)	0.820
Oral contraceptive use, n (%)	1 (0.7%)	4 (5.4%)	**0.043**
History of abortion, n (%)	33 (22.3%)	13 (17.6%)	0.484

Table 2. Univariable logistic regression analysis of factors associated with cervical cancer

Variable	Crude OR	95% CI	P value
Age (years)	**1.041**	**1.015–1.067**	**0.002**
Parity	**1.228**	**1.046–1.443**	**0.012**
Abortion	0.723	0.354–1.476	0.374
Age at menarche	1.095	0.858–1.398	0.466
Age at first pregnancy	**0.925**	**0.866–0.989**	**0.022**
Age at last pregnancy	0.971	0.912–1.035	0.370
Age at first sexual intercourse	0.945	0.854–1.044	0.265
BMI (kg/m²)	1.026	0.974–1.081	0.337
Smoking	1.674	0.661–4.241	0.277
Oral contraceptive use	8.171	0.896–74.482	0.062
Hypertension	1.839	0.803–4.208	0.149
Diabetes mellitus	0.855	0.336–2.180	0.744
Marital status	6.489	0.827–50.902	0.075

Abbreviations: OR, odds ratio; CI, confidence interval.

Table 3. Multivariable logistic regression analysis of factors associated with cervical cancer

Variable	Adjusted OR (aOR)	95% CI	*P* value
Age (years)	**1.043**	**1.004–1.083**	**0.030**
BMI (kg/m²)	0.978	0.918–1.043	0.501
Parity	0.893	0.706–1.129	0.343
Age at menarche (years)	1.118	0.862–1.450	0.401
Age at first pregnancy (years)	**0.918**	**0.850–0.992**	**0.030**
Smoking	1.336	0.494–3.611	0.568
Hypertension	1.312	0.486–3.545	0.592

Abbreviations: aor, adjusted odds ratio; CI, confidence interval.

Footnote: The final multivariable model included age, body mass index, parity, age at menarche, age at first pregnancy, smoking status, and hypertension. Cases were coded as 1 and controls as **0**.

Table 4. Performance of the final multivariable logistic regression model

Performance metric	Value
Area under the ROC curve (AUC)	**0.666**
95% CI for AUC	0.586–0.746
Hosmer–Lemeshow χ^2	**4.116**
Hosmer–Lemeshow *P* value	**0.847**
Brier score	**0.218**
Nagelkerke R^2	**0.100**

Table 5. Internal validation of the final multivariable logistic regression model

Validation metric	Value
Bootstrap resamples	**100**
Successful model fits	**100 (100%)**
Mean bootstrap AUC	**0.640**
Bootstrap AUC standard deviation	**0.023**

Discussion

In this population-based case–control study, increasing age and earlier age at first pregnancy were independently associated with cervical cancer after adjustment for potential confounders. In contrast, body mass index (BMI), parity, age at menarche, smoking, and hypertension were not independently associated with cervical cancer. These findings support the multifactorial etiology of cervical cancer, in which demographic and reproductive characteristics interact with persistent high-risk human papillomavirus (HPV) infection, host susceptibility, access to cervical cancer screening, and broader social determinants of health (1–7).

Increasing age remained independently associated with higher odds of cervical cancer in the present study. This finding is consistent with national and international evidence demonstrating that cervical cancer incidence increases with advancing age because of the cumulative effects of persistent HPV infection, prolonged exposure to carcinogenic cofactors, and the long natural history of cervical carcinogenesis (2,3,5,8,10,13,16). Our findings are also consistent with recent epidemiological studies from Iran reporting that increasing age is among the strongest demographic factors associated with cervical cancer incidence and reflects cumulative exposure to persistent HPV infection together with delayed diagnosis (2,5,9). Although organized screening has substantially reduced cervical cancer incidence in many high-income countries, delayed diagnosis among older women remains an important public health concern in many low- and middle-income settings, including Iran (1,5,8).

Age at first pregnancy was also independently associated with cervical cancer. Women with an earlier age at first pregnancy had higher odds of cervical cancer, which is biologically plausible because the cervical transformation zone is more susceptible to persistent HPV infection and neoplastic change during adolescence and early reproductive life (3,5). Similar associations have been reported in recent population-based studies from the Middle East and other regions, although the magnitude of the association varies after adjustment for socioeconomic characteristics, reproductive history, and access to screening services (13,15). These findings suggest that reproductive characteristics may serve as markers of cumulative biological and social exposures rather than acting as independent causal factors.

BMI was not independently associated with cervical cancer after adjustment for potential confounders. Although obesity has been associated with lower participation in cervical cancer screening and may reduce the detection of precancerous lesions, recent nationwide cohort studies have reported inconsistent evidence regarding a direct association between excess body weight and invasive cervical cancer after accounting for reproductive and behavioral factors (14). Likewise, parity, smoking, hypertension, and age at menarche were not independently associated with cervical cancer in our study. Previous investigations have also reported heterogeneous findings for these variables, suggesting that their observed associations may reflect residual confounding by HPV infection, screening behavior, socioeconomic status, and healthcare utilization rather than independent biological effects (5,7,11–15). Because HPV infection status was unavailable in the present study, residual confounding by persistent HPV infection cannot be excluded. Therefore, the absence of statistically significant associations should not be interpreted as evidence that these factors play no role in cervical carcinogenesis but rather that their effects may be mediated through pathways not captured in the available data.

The predictive performance of the final multivariable model was modest, with an area under the receiver operating characteristic curve (AUC) of 0.666 and a Nagelkerke R^2 of 0.100. These findings suggest that the model had limited ability to distinguish women with and without cervical cancer and that additional biological, behavioral, and socioeconomic predictors are needed to improve prediction. Variables such as HPV infection status, cervical cancer screening history, sexual behavior, educational attainment, socioeconomic status, and immunosuppression were unavailable for analysis and therefore could not be incorporated into the prediction model. Recent epidemiological studies have consistently demonstrated that integrating biological, behavioral, and social determinants substantially improves cervical cancer risk prediction (6,13,17,18).

A major strength of this study is its population-based design. All histopathologically confirmed cervical cancer cases diagnosed during the study period were identified through the regional cancer registry, while controls were randomly selected from the Primary Health Care (PHC) Family Physician Information System. Because both cases and controls originated from the same underlying source population covered by Mashhad University of Medical Sciences, selection bias was minimized and the generalizability of the findings within the study population was strengthened. The use of population-based controls also reduced the likelihood of Berkson's bias, which is commonly encountered in hospital-based case–control studies. In addition, internal validation using bootstrap resampling demonstrated stable model performance, supporting the robustness of the estimated associations.

Several limitations should be acknowledged. First, because of the retrospective case–control design, causal inferences cannot be established. Second, information on HPV infection, cervical cancer screening history, sexual behavior, educational level, household income, and immunosuppressive conditions was unavailable, and residual confounding by these important determinants cannot be excluded. Third, several reproductive and lifestyle variables were obtained from routinely collected health records and may be subject to measurement error, incomplete documentation, or misclassification. Fourth, the relatively small sample size may have limited the statistical power to detect modest associations for some variables. Finally, although internal validation demonstrated satisfactory model stability, external validation in independent populations is necessary before the model can be considered for broader application.

The present findings have important implications for cervical cancer prevention in Iran. Strengthening HPV vaccination, improving participation in organized cervical cancer screening, reducing socioeconomic inequalities in access to preventive services, and enhancing health literacy remain essential components of the World Health Organization strategy for cervical cancer elimination (1,4,5). Recent evidence from Iran and other countries demonstrates that screening participation is strongly influenced by educational attainment, socioeconomic status, cultural beliefs, and accessibility of healthcare services (9,11,12,17,19,20). Integrating cervical cancer prevention within the Primary Health Care system and implementing targeted interventions for women at increased risk may improve screening uptake, facilitate earlier diagnosis, and ultimately reduce cervical cancer morbidity and mortality.

Conclusion

This population-based case–control study identified increasing age and earlier age at first pregnancy as independent factors associated with cervical cancer among women covered by Mashhad University of Medical Sciences. In contrast, BMI, parity, age at menarche, smoking, and hypertension were not independently associated with cervical cancer after adjustment for potential confounding variables. These findings provide population-based evidence that may contribute to cervical cancer risk assessment and support targeted prevention strategies in northeastern Iran. Future prospective studies incorporating HPV infection status, cervical cancer screening history, socioeconomic determinants, and external validation are warranted to improve cervical cancer prediction models and to inform evidence-based cervical cancer prevention policies.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences (Approval No. **IR.MUMS.MEDICAL.REC.1403.249**) and was conducted in accordance with the ethical principles of the Declaration of Helsinki. Histopathologically confirmed cervical cancer cases were identified from the regional cancer registry using anonymized secondary data; therefore, the requirement for individual informed consent was waived by the Ethics Committee. Population-based controls were selected from the Primary Health Care (PHC) Family Physician Information System. All personal identifiers were removed before analysis to ensure participant confidentiality and privacy. Data were securely stored and were accessible only to authorized members of the research team.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available because they contain confidential patient information and are subject to institutional and ethical restrictions. De-identified data may be available from the corresponding author on reasonable request and with permission from Mashhad University of Medical Sciences.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MZ conceived and designed the study. MZ and ME collected, curated, and analyzed the data. SP contributed to the study design, interpretation of the findings, and critical revision of the manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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