Secondhand Smoke Exposure, Diabetes, Elevated Glucose Level Are Risk Factors for Uterine Cervical Cancer: A Cross-Sectional Study From the Korea National Health and Nutrition Examination Survey (2010-2018)

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Research Article

Keywords: KNHANES (Korea National Health and Nutrition Examination Survey), Cervical cancer, Diabetes, Secondhand cigarette smoke

Posted Date: January 21st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-145552/v1

Version of Record: A version of this preprint was published at BMC Cancer on July 31st, 2021. See the published version at https://doi.org/10.1186/s12885-021-08580-3.

Abstract

Background: Human papilloma virus infection and tobacco smoking are the major risk factors for cervical cancer. There are limited studies searching other risk factors for cervical cancer and the results are not consistent. This study investigated the relations between cervical cancer and possible risk factors, including secondhand cigarette smoke exposure, diabetes, work schedule.

Methods: In this cross-sectional study, 29,557 women completed a cervical cancer questionnaire and were selected using 2010–2018 data from the Korea National Health and Nutrition Examination Survey. Details in secondhand smoke exposure, diabetes, work schedule were assessed from participants' health interviews and blood test results were used for fasting glucose level and hemoglobin A1c (HbA1c) level.

Results: Two hundred sixty-two women (0.89%) in the sample were diagnosed with cervical cancer. Domestic secondhand smoke exposure, diabetes, high fasting glucose level, and high HbA1c significantly increased cervical cancer risk. The respective odd ratios and 95% confidence intervals were: 1.488 (1.002–2.207), 2.369 (1.713–3.274), 1.008 (1.005–1.009), and 1.304 (1.193–1.425). Weekly work hours and work schedule were not significantly related to cervical cancer incidence.

Conclusion: Among Korean women, passive exposure to cigarette smoke at home, diabetes, elevated fasting glucose level, and high HbA1c level all increase risk for cervical cancer.

Background

Cervical cancer is the fourth most common and the third most lethal female malignancy worldwide [1]. Cervical cancer is caused by human papilloma virus (HPV) infection, which is one of the most powerful human carcinogens and has been implicated in several cancers, including uterine cervix, anorectum and oropharynx [2]. In addition to HPV infection, young age at first intercourse, multiple sexual partners, cigarette smoking, race, high parity, low socioeconomic status, and chronic immune suppression are also risk factors for cervical cancer [3].

Tobacco smoking is a strong risk factor for cervical neoplasia. Smoking status, duration, and intensity are associated with twofold increase in risk for high-grade cervical dysplasia and invasive carcinoma, independent of HPV infection [4]. Passive cigarette smoking, or secondhand smoke exposure is also considered a risk factor for cervical carcinogenesis, although related study results have been inconsistent. Su et al. reported a 1.7-fold increase in cervical cancer risk among those exposed to secondhand smoke, whereas Louie et al. concluded that passive smoking is not an independent risk factor for invasive cervical cancer in the absence of active smoking [5, 6].

Diabetes mellitus (DM), especially type 2 diabetes, is a major risk factor for many cancers. The association between endometrial cancer and diabetes is well-established, and some have shown weak correlations between ovarian cancer and diabetes [7, 8]. However, the relationship between cervical cancer incidence and type 2 diabetes remains unclear and relevant studies have been limited.

Socioeconomic disparities among women also affect cervical cancer occurrence. Cervical cancer incidence and mortality are much higher in low- and middle-income countries compared with high-income countries [9]. In Korea, women with lower education levels and lower household income have significantly lower cervical cancer screening rates than do highly educated and high-earning females [10, 11]. Regarding occupation, service and sales workers appear to have a higher risk of cervical cancer compared with those in other fields. [12]. To our knowledge, the relationship between work schedule and cervical neoplasm has not been addressed.

To better prevent cervical cancer, and raise public health awareness, risk factors other than HPV infection and smoking must be identified. Thus, the study purpose was to determine the relationships between cervical cancer and potential risk factors, including passive cigarette smoking, diabetes-related factors and work schedule, using data from the Korea National Health and Nutrition Examination Survey (KNHANES).

Methods

The analyses presented herein are based on data collected during the 2010–2018 KNHANES, which began in 1998 and is administered by the Division of Health and Nutrition Survey under the Korea Disease Control and Prevention Agency. KNHANES is an ongoing population-based cross-sectional survey designed to assess the health and nutritional status of Koreans. The study monitors trends in health risk factors, assesses the prevalence of major chronic diseases, and provides data for the development and evaluation of health policies and programs in Korea [13].

The health interviews and examinations were conducted in mobile examination centers, while the nutritional surveys were performed by trained physicians or nurses who visited each household. Participants were asked to complete the cervical cancer, diabetes, smoking, and working conditions questionnaire during their health interviews. Fasting glucose and hemoglobin A1c (HbA1c) levels were assessed via blood samples. Written informed consent was acquired from all participants before the survey was administered. Institutional Review Board of the Catholic University of Korea, Bucheon, Republic of Korea approved this study (HC20ZASI0107).

Table 1
Sample distribution by study year

Year	Without cervical cancer (n)	Cervical cancer (n)	Cervical cancer (%)
2010	3,555	30	0.84
2011	3,478	23	0.66
2012	3,313	16	0.48
2013	3,103	33	1.06
2014	2,942	31	1.05
2015	2,921	27	0.92
2016	3,337	38	1.14
2017	3,252	36	1.11
2018	3,394	28	0.82
total	29,295	262	0.89

During the 2010–2018 KNHANES, 32,485 women aged 18 years or older participated. The annual participant distribution is shown in Table 1. Among the 29,557 women who completed the cervical cancer questionnaire, 262 (0.89%) were diagnosed with cervical cancer. Among the sample with cervical cancer, there were 45 women with diabetes, who were cassified into three groups according to treatment method: insulin injection, medication, or nonpharmacological treatment. Participants who reported secondhand smoke exposure were asked to identify whether this occurred in their workplace, home, or public places. Work schedule was categorized as: day shift, evening shift, night shift, regular 12-hour shift, 24-hour shift, split shift, irregular shift, or other. Having cervical cancer or diabetes at the health interview was defined based on a diagnosis by a qualified physician.

Statistical analyses conducted using Stata (v. 16.1; StataCorp LLC, College Station, TX, USA), reflect the complex sampling design and sampling weights of the KNHANES, and were chosen to provide nationally representative prevalence estimates. Fisher's exact probability tests were performed to identify distribution patterns by cervical cancer occurrence and odds ratios (OR), along with 95% confidence intervals (CI), were calculated using logistic regression models with respective independent variables. To compare mean fasting glucose, HbA1c, and weekly work hours, independent samples t-test were applied.

Results

Distribution patterns by categories are shown in Table 2. To investigate the relations between passive smoke exposure and cervical cancer occurrence, secondhand smoke in the workplace, home, and public places were analyzed separately. Passive smoke exposure at work was negatively related to cervical cancer risk. Incidence of cervical cancer among women exposed to secondhand smoking at work was 0.57%, whereas 0.95% of unexposed women ha

d cervical cancer ($\chi 2 = 6.835$, $p = 0.009$). Domestic passive smoke exposure was related with increased cervical cancer incidence. Cervical cancer was present among 1.26% of women exposed domestic secondhand smoke, but only 0.85% of those living in a smoke-free home ($\chi 2 = 4.017$, $p = 0.045$). Among women exposed to secondhand smoke in public places, 0.84% had cervical cancer, which did not differ significantly from the rate of 1.01% among those who were unexposed ($\chi 2 = 0.569$, $p > 0.05$).

Table 2
Sample distribution by passive smoking, diabetes, DM treatments, and work schedule

Variables			n	Cervical cancer (%)	p^*
Passive smoking	Workplace	Unexposed	24,044	228 (0.95)	0.009
		Exposed	5,081	29 (0.57)	
	Domestic	Unexposed	27,142	230 (0.85)	0.045
		Exposed	2,222	28 (1.26)	
	Public place	Unexposed	10,680	108 (1.01)	0.451
		Exposed	2,264	19 (0.84)	
Diabetes		Nondiabetic	27,175	217 (0.80)	0.000
		Diabetic	2,380	45 (1.89)	
DM treatment	Insulin injection.	No	29,340	258 (0.88)	0.124
		Yes	214	4 (1.87)	
	Medication	No	27,427	219 (0.80)	0.000
		Yes	2,127	43 (2.02)	
	Nonpharmacologic	No	29,247	256 (0.88)	0.045
		Yes	307	6 (1.95)	
Work schedule		Day shift	13,973	100 (0.72)	0.354
		Evening shift	2,102	16 (0.76)	
		Night shift	278	0 (0.00)	
		12-hr regular shift	297	0 (0.00)	0.438
		24-hr regular shift	43	0 (0.00)	
		Split shift	133	1 (0.75)	
		Irregular shift	93	1 (1.08)	
		Other	64	0 (0.00)	

*p value calculated by Fisher's exact test

DM, diabetes mellitus

Using pooled data, cervical cancer prevalence among women with diabetes was 1.89%, significantly higher than 0.80% among women without diabetes ($\chi2 = 29.712$, $p < 0.001$). However, insulin usage for diabetes treatment was not meaningfully related to cervical cancer occurrence ($\chi2 = 2.369$, $p > 0.05$). Nonpharmacologic DM treatment ($\chi2 = 4.026$, $p = 0.045$) and medication prescribed for diabetes ($\chi2 = 33.610$, $p < 0.001$) were significantly related to cervical cancer. On the other hand, mean fasting glucose among those with cervical cancer (103.31 ± 25.17) was substantially higher than among those without cervical cancer (97.39 ± 21.58; $t = -4.147$, $p < 0.001$). Average HbA1c among women with cervical cancer (5.99 ± 0.95) was also elevated compared with those without cervical cancer (5.73 ± 0.79; $t = -4.793$, $p < 0.001$).

Mean weekly work hours among women with cervical cancer (34.74 ± 16.69) did not differ significantly from women without cervical cancer (37.21 ± 18.35; $t = 1.460$, $p > 0.05$). Nor were there difference between those working the day, evening, or night shifts ($\chi2 = 2.074$, $p > 0.05$) or between those working regular 12-hour, 24-hour, split, irregular, or another shift type ($\chi2 = 3.767$, $p > 0.05$).

The relationships between cervical cancer and passive smoking, diabetes, fasting glucose, HbA1c, weekly work hours, and work schedule are shown in Table 3. The OR for cervical cancer based on exposure to secondhand smoke at home was 1.488 (95% CI: 1.002–2.207, $p < 0.001$). For exposure to secondhand smoke in the workplace, the OR for cervical cancer was 0.595 (95% CI: 0.404–0.876, $p = 0.009$).

The relation between diabetes and cervical cancer was significant (OR: 2.369, 95% CI: 1.713–3.274, $p = 0.008$). Fasting glucose level (OR: 1.008, 95% CI: 1.005–1.009, $p = 0.003$) and HbA1c level (OR: 1.304, 95% CI: 1.193–1.425, $p = 0.007$) were also related to cervical cancer incidence. However, diabetes treatment methods and cervical cancer risk were discrepant; while the ORs for cervical cancer were 2.126 (95% CI: 0.784–5.760, $p = 0.001$) and 2.235 (95% CI: 0.987–5.061, $p = 0.001$) for women taking insulin injections and nonpharmacologic treatments, respectively, in any case, the results were not statistically significant. In contrast, OR for cervical cancer among whose taking antidiabetic drugs was 2.536 (95% CI: 1.823–3.527, $p = 0.008$).

Regarding weekly work hours and work schedule, there were fewer than expected participants in many cells, which thus failed to meet the analysis criteria. Consequently, the omnibus analyses for these factors were not statistically meaningful.

Discussion

This study investigated whether secondhand smoke exposure, diabetes-related factors, or work schedule are risk factors for cervical carcinogenesis.

The role of passive cigarette smoking in cervical neoplasia is controversial. Herein, secondhand smoke exposure at home was meaningfully related to cervical cancer. This finding is consistent with most studies, which have shown that secondhand smoke exposure is positively correlated with cervical cancer [5, 14–16]. Some studies have also reported passive smoking as an independent risk factor for abnormal cervical cytology or cervical intraepithelial neoplasm (CIN) [17–19]. However, most reports did not adjust for covariates like dose of tobacco exposure, sexual behavior, socioeconomic conditions, and (especially important) HPV infection status. A few investigators have proposed that passive smoking is statistically unrelated to CIN or cervical cancer after accounting for HPV infection status [6, 20, 21]. Interestingly, we identified that workplace secondhand smoke exposure is associated with lower cervical cancer risk. Considering the KNHANES data characteristics, it is possible that women diagnosed with cervical cancer may seek out smoke-free work environment and move to such jobs.

Table 3
Relations between risk factors and cervical cancer

Variables		OR	95% CI	P*
Passive smoking	Workplace	0.595	0.404–0.876	0.009
	Domestic	1.488	1.002–2.207	0.049
	Public place	0.836	0.513–1.365	0.475
Diabetes		2.369	1.713–3.274	0.000
DM treatment	Insulin injection	2.126	0.784–5.76	0.138
	Medication	2.536	1.823–3.527	0.000
	Nonpharmacologic	2.235	0.987–5.061	0.054
Fasting glucose		1.008	1.005–1.009	0.000
HbA1C		1.304	1.193–1.425	0.000
Weekly work hours		0.992	0.983–1.002	0.100
Work schedule	Night shift	1.093	0.644–1.857	0.741
	Split shift	0.689	0.042–11.234	0.794
*OR with CI calculated using logistic regression test				

CI, confidence interval; DM, diabetes mellitus; HbA1c, hemoglobin A1c; OR, odd ratio

There was a substantial connection between diabetes and cervical cancer. Several studies have reported increased risk for and mortality from many cancer types among patients with diabetes, especially type 2 DM [7, 8, 22–24]. Some characteristics of diabetes may explain this carcinogenic tendency, including hyperinsulinemia, hyperglycemia, and chronic inflammatory status. These conditions all encourage cellular proliferative, angiogenetic, antiapoptotic, and metastatic activities [7, 25]. This too is consistent with our findings that elevated fasting glucose and HbA1c levels increase cervical cancer risk. Some researchers have reported that exogenous insulin treatment for DM increases overall cancer risk [26, 27]. Although statistically nonsignificant and based on low case numbers, our results also show that injected insulin is related to cervical cancer incidence. Since insulin treatment is used in response to poorly controlled glucose levels, this may explain the connection between higher fasting glucose and cervical cancer. Regarding oral antidiabetic agent, researchers have suggested that metformin therapy lowers cancer risk, while sulfonylureas increase carcinogenesis risk [26, 28, 29]. Herein, use of antidiabetic drugs increased cervical cancer risk. Because these data did not include which diabetic drugs were used, it is difficult to either determine the effects of individual drugs or interpret these findings more generally.

No notable results were found regarding work hours and schedule. Few studies have explored the potential connections between night shift work and cancer risk, reporting lack of evidence or few correlations [30, 31]. Since our data were cross-sectional, it is difficult to suggest causal relations. For example, women who were diagnosed with cervical cancer may have reduced their work hours or moved to a shift that carried fewer burdens. Further prospective studies are needed to assess a broad range of occupations and various socioeconomic characteristics.

A major strength of this study is that it was based on extensive nationwide survey data, including 29,557 women in Korea. Furthermore, relatively recent data (2010–2018) were used, reflecting current disease patterns and trends. There are also several limitations. The study was cross-sectional; thus, exposure and outcomes were assessed simultaneously and deductions about interrelated courses are difficult. Finally, most of these data were derived from self-report questionnaires based on participant recall.

Conclusion

Several factors, including passive cigarette smoking at home, diabetes, high fasting glucose level, and elevated HbA1c, are related to increased risk of cervical cancer among women in South Korea.

Abbreviations

HbA1c
hemoglobin A1c; OR:odd ratios; CI:confidence intervals; HPV:human papilloma virus; DM:Diabetes mellitus; KNHANES:Korea National Health and Nutrition Examination Survey; CIN:cervical intraepithelial neoplasm

Declarations

Ethics approval and consent to participate

Written informed consent was acquired from all participants before the survey was administered. Institutional Review Board of the Catholic University of Korea, Bucheon, Republic of Korea approved this study (HC20ZASI0107). All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available in website of The Korea Disease Control and Prevention Agency; Korea National Health and Nutrition Examination Survey repository, [https://knhanes.cdc.go.kr/knhanes/sub03/sub03_02_05.do]

Competing interests

None.

Funding

None.

Authors' contributions

All authors contributed to the study design and execution. JY, HN collected the data and wrote the manuscript. DW, MJ, and JE analyzed the data. YJ reviewed the data and wrote manuscript. All authors have read and approved the final manuscript.

Acknowledgements

None.

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