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ORIGINAL RESEARCH

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Dyslipidemia is positively associated with cervical cancer in Korea: Korean national health and nutrition examination survey 2010—2020

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Abstract

Several previous papers have reported that hypoxic environments induced by hypertension, Insulin like growth factor-1 (IGF-1) overexpressed by hyperinsulinemia, hyperactivity of fatty acid metabolism, stimulation of cell growth signaling factors, and formation of carcinogen by dyslipidemia contribute to tumor cell proliferation.Therefore, we hypothesized that hypertension, diabetes, and dyslipidemia are positively correlated with cervical cancer; the purpose of this study was to evaluate this correlation. We included 25,055 participants from the Korean National Health and Nutrition Examination Survey between 2010 and 2020. The participants were divided into the non-cervical cancer and cervical cancer groups. For comparisons between the two groups, continuous variables were analyzed using Student's *t*-test, and categorical variables were analyzed using the chi-squared test or Fisher's exact test. The odds ratios (OR) in the non-cervical cancer group, and 311 females were included in the cervical cancer group. In the cervical cancer group, dyslipidemia had an adjusted OR (AOR) of 2.88 compared with that of the non-cervical cancer group (AOR: 2.88, confidence interval (CI): 1.785–4.654, $p < 0.001$) after adjusting for confounding variables such as age, education level, waist circumference, body mass index (BMI), and number of pregnancies in the multivariate logistic regression analysis. Among the three major chronic diseases, dyslipidemia was positively correlated with cervical cancer. Therefore, Encouraging gynecologists to get proper treatment for dyslipidemia in gynecological patients with dyslipidemia is believed to help lower the potential risk of cervical cancer in the future.

Keywords

Cervical cancer; Dyslipidemia; Korean females; Chronic diseases

1. Introduction

In the 1980s, cervical cancer was one of the most common cancers in Korean females [1]. Since then, the prevalence of cervical cancer has gradually decreased with the introduction of cervical cancer screening tests and vaccines. However, according to the 2020 Korean statistics, 3218 patients are diagnosed with cervical cancer every year, making it the ninth most common type of cancer in females [2]. As such, much effort is needed to lower the incidence of cervical cancer. Further, understanding the risk factors for cervical cancer and making efforts to lower its risk are important.

Several studies have explored the relationship between cancer and chronic diseases. The three major chronic diseases in Korea are hypertension, diabetes, and dyslipidemia. Dyslipidemia is defined as an elevated plasma cholesterol level or an elevated triglyceride level [3]. Similarly, in this paper, dyslipidemia was defined as plasma cholesterol level $\geq$240 mg/dL or triglyceride level $\geq$200 mg/dL. According to the incidence of these diseases reported by the Korea Centers for Disease Control and Prevention (KCDC), the incidence of hypertension slightly decreased from 49.3% in 2008 to 38.5% in 2020. Likewise, the incidence of diabetes slightly decreased from 39.3% in 2008 to 33.8% in 2020. However, the incidence of dyslipidemia increased from 10.8% in 2008 to 22.3% in 2020 [4]. Considering these aforementioned rates, as well as the high proportion of patients with hypertension, diabetes, and dyslipidemia in Korea, we selected hypertension, diabetes, and dyslipidemia as the chronic diseases to be included in our study.

According to previous studies, a hypoxic environment induced by hypertension promotes angiogenesis; a hyperinsulinemic environment in diabetes increases not only insulin-like growth factor-1 (IGF-1) but also the expression of glucose transport proteins, such as glucose transporter-1, causing tumor cell proliferation and anaerobic glycolysis [5–8]; an environment of high blood cholesterol and triglyceride in dyslipidemia decreases adenosine diphosphate in the mitochon-

dria, inhibiting adenosine triphosphate energy generation and increasing reactive oxygen species (ROS) production in the liver or muscle. Aldehydes, products of the reaction between ROS and lipids, act as carcinogens that cause gene mutations and upregulate cyclooxygenase-2 (COX-2) to inhibit apoptosis of cancer cells, aiding cancer cell proliferation and invasion [9, 10].

Applying these principles, studies have identified the risk factors for chronic diseases in gynecologic cancers. In 2015, a large population-based case-control study reported that hypertension, elevated fasting glucose, and dyslipidemia are positively correlated with increased endometrial cancer incidence [11]. Another study reported that diabetes is closely related to mortality and ovarian cancer recurrence [11]. Several papers on cervical cancer found that hypertension, diabetes, and dyslipidemia are associated with the development of cervical cancer [12, 13]. However, compared to that of endometrial cancer, information on cervical cancer is insufficient to determine the association between chronic diseases and cervical cancer.

We hypothesized that hypertension, diabetes, and dyslipidemia, the three major chronic diseases in Korea, are positively correlated with cervical cancer incidence, and effective treatment of these chronic diseases may aid the treatment of cervical cancer as well. To evaluate this hypothesis, we used data from the Korean National Health and Nutrition Examination Survey (KNHANES), which includes information from a health examination questionnaire, as well as information on the age, height, weight, and chronic diseases, among others, of Koreans. This study aimed to investigate the relationship between cervical cancer and chronic diseases, such as hypertension, diabetes, and dyslipidemia, in Korea.

2. Materials and methods

2.1 Study participants and design

This cross-sectional study used the KNHANES data from 2010 to 2020. Since 1998, KNHANES has been conducted every three years to understand the health level, health behavior, food habits, and nutrition of Koreans. The steps in the questionnaire, such as height, weight, waist circumference, body mass index (BMI), and a health questionnaire, are conducted by well-trained medical staff.

The inclusion criteria for this study were females $>$20 years of age who answered the cervical cancer health questionnaire. The exclusion criteria were males, females $<$20 years of age, and cases with missing values (*e.g.*, unfilled, missing system). In total, 25,055 of 88,220 participants were selected for this study (Fig. 1). The participants were divided into two groups: non-cervical cancer and cervical cancer.

2.2 Study variables

KNHANES includes health survey results on taking medications, health examination results, education, economic activities, obesity, weight control, drinking, smoking, mental health, physical activity, and female health; examination surveys; blood pressure measurements, blood tests, and body measurements; and nutrition surveys on dietary habits and nutritional information.

In this study, personal income was categorized into four quartiles based on average monthly household income ((monthly overall household income) (household size)$^{-0.5}$): the first quarter was low; the second quarter, low intermediate; third quarter, upper intermediate; and fourth quarter, high. The degree of education was classified into less than elementary school, middle school, high school, and college or higher. In adult females, drinking was divided into five categories based on frequency: not drinking at all, less than once a month, approximately once a month, approximately once a week, and almost every day. Based on a questionnaire surveying the lifetime smoking pattern of adults, smoking was classified into a non-smoker, less than 100 cigarettes, and 100 or more cigarettes. Waist circumference was measured at the narrowest part between the rib cage and iliac crest after normal expiration. Body mass index (BMI) (weight in kg/height in m^2) was not only treated as a continuous variable and compared, but also categorized and compared as follows; underweight (BMI $<$18.5 kg/m^2), normal weight (18.5 kg/m^2 $\leq$ BMI $<$ 23 kg/m^2), pre-obese (23 kg/m^2 $\leq$ BMI $<$ 25 kg/m^2), and obese (BMI $\geq$25 kg/m^2).

Those who had a spouse but did not live with one, including those who were divorced and widowed, were included in the not living together group, and those living with a spouse were included in the living together group. Based on their responses, those who were still menstruating were included in the menstruation group, and those who were naturally or artificially menopausal were included in the menopause group. Age at first childbirth and the number of pregnancies were also included in the questionnaire. Those who were taking oral contraceptives (OC) were included in the yes group, and those who were not were included in the no group. In a questionnaire on physical activity, walking exercise frequency (number of days per week) was classified into not at all, one day, two days, three days, four days, five days, six days, and seven days (daily). For comparisons, we further grouped the participants into those who walked less than one day a week, three days a week, and four to seven days a week.

Blood samples were collected from the antecubital vein in the morning after overnight fasting. Total cholesterol, triglyceride, and plasma glucose levels were measured using Labospect 008AS (Biochemical Analyzer, Hitachi, Tokyo, Japan). Hemoglobin A1c (HbA1c) levels were measured using Tosoh G8 (Glycohemoglobin Analyzer, Tosoh, Tokyo, Japan).

According to hypertension status, the participants were divided into three groups: normal, prehypertension, and hypertension. Normal was defined as a systolic blood pressure (SBP) $<$120 mmHg and diastolic blood pressure (DBP) $<$80 mmHg; prehypertension was defined as an SBP of 120–140 mmHg or a DBP of 80–90 mmHg; and hypertension was defined as an SBP $\geq$140 mmHg or a DBP $\geq$90 mmHg. Hypertension was also defined as an answer of "yes" to the question "Have you been diagnosed with hypertension by a doctor?" or "Do you currently suffer from hypertension?". According to diabetes status, participants were classified into three groups: normal, impaired fasting glucose, and diabetes. Normal was defined as a fasting glucose level $<$100 mg/dL or an HbA1c level $<$5.7%; impaired fasting glucose was defined as a fasting glucose level of 100–125 mg/dL or an HbA1c level of 5.7–

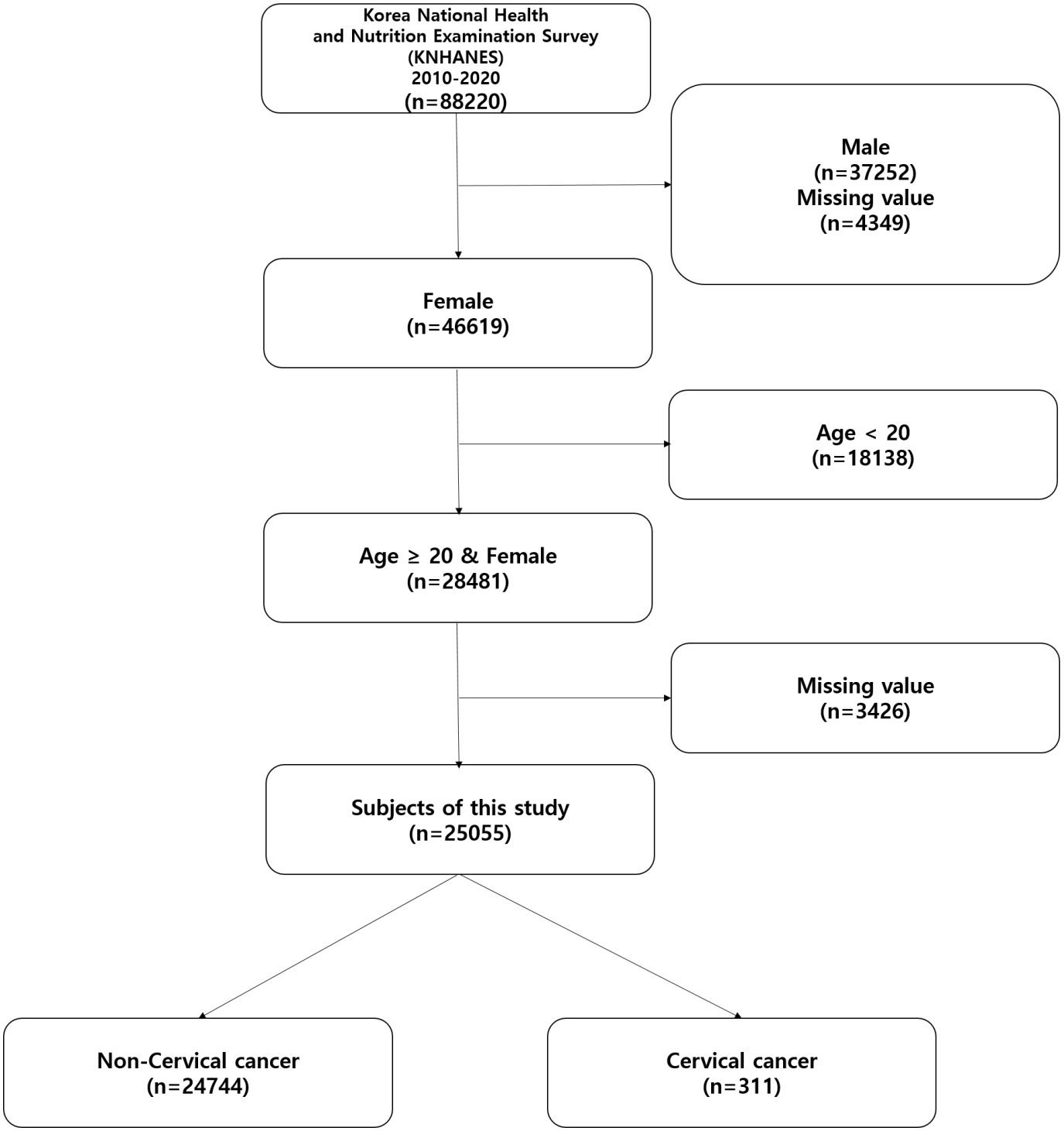

FIGURE 1. A diagram of participants for final analysis. KNHANES: Korean National Health and Nutrition Examination Survey.

6.4%; and diabetes was defined a fasting glucose level ≥126 mg/dL or an HbA1c level ≥6.5%. Diabetes was also defined as an answer of "yes" to the question "Have you been diagnosed with diabetes by doctor?" or "Do you currently suffer from diabetes?". According to dyslipidemia status, the participants were classified into two groups: normal and dyslipidemia. Normal was defined as a cholesterol level <240 mg/dL and triglyceride level <200 mg/dL. Normal was also defined as an answer of "no" to the question "Have you been diagnosed with dyslipidemia by doctor?" or "Do you currently suffer from dyslipidemia?". Dyslipidemia was defined as a cholesterol level ≥240 mg/dL or triglyceride level ≥200 mg/dL. Dyslipidemia was also defined as an answer of "yes" to the question "Have you been diagnosed with dyslipidemia by doctor?" or "Do you currently suffer from dyslipidemia?".

2.3 Statistical analysis

The KNHANES data were extracted by two-stage stratified cluster sampling instead of simple random sampling. Statistical analysis was conducted based on this complex sampling

method. Student's *t*-test was used to compare the continuous variables of the two groups according to cervical cancer status. Chi-squared test or Fisher's exact test was used to analyze categorical variables. Univariate analysis was performed for each investigated variable to compare the risk of the cervical cancer group with that of the non-cervical cancer group. Multivariate logistic regression analysis was performed to evaluate the risk of cervical cancer according to the status of chronic diseases such as hypertension, diabetes, and dyslipidemia. We identified five confounding variables (*i.e.*, age, educational attainment, waist circumference, BMI, and number of pregnancies), which were adjusted for the multivariate logistic regression analysis. All analyses were performed using SPSS Statistics for Windows (version 25.0; SPSS Inc., Chicago, IL, USA). For all analyses, p-values < 0.05 were considered statistically significant.

3. Results

The mean age of the study population was 48.35 ± 0.17 years; participants without cervical cancer, 48.23 ± 0.15 years; and preposition to be for participants with cervical cancer, 58.59 ± 0.88 years. In total, 24,744 participants did not have cervical cancer, and 311 had cervical cancer. As shown in Table 1, statistically significant differences were observed between non-cervical cancer and cervical cancer groups for age (48.23 ± 0.17 *vs.* 58.59 ± 0.88, $p < 0.001$) education status ($p < 0.001$), body measurements (*i.e.*, waist circumference (78.72 ± 0.10 *vs.* 81.36 ± 0.61, $p < 0.001$), BMI (23.33 ± 0.03 *vs.* 24.18 ± 0.25, $p < 0.001$), living status with spouse ($p < 0.001$), menstrual status ($p < 0.001$), age at first childbirth (25.65 ± 0.04 *vs.* 24.10 ± 0.21, $p < 0.001$), number of pregnancies (3.61 ± 0.02 *vs.* 4.15 ± 0.12, $p < 0.001$), frequency of walking exercise ($p = 0.013$), hypertension status ($p < 0.001$), diabetes status ($p < 0.001$), and dyslipidemia status ($p < 0.001$). The higher the level of education, the lower the proportion of the cervical cancer group compared to the non-cervical cancer group. And, in the cervical cancer group, the proportion of people who did not live with their spouse, menopausal state, and frequency of walking exercise (less than 3 days a week) was relatively higher than in the non-cervical cancer group. Further, participants with cervical cancer had a higher waist circumference, BMI (especially in overweight and obese classifications), and a number of pregnancies than non-cervical cancer group. And, the age of first childbirth in cervical cancer patients was younger than non-cervical cancer group. The prevalence of chronic diseases, including hypertension, diabetes, and dyslipidemia, significantly differed between the non-cervical cancer and cervical cancer groups (Table 1).

Table 2 shows the results of the univariate analysis comparing the risks in the cervical cancer and non-cervical cancer groups. The factors significantly associated with the risk of cervical cancer included old age (Crude odds ratio (COR), 1.04; 95% CI, 1.031, 1.047; $p < 0.001$), low educational attainment (Middle school COR, 0.80; 95% CI, 0.536, 1.182; $p < 0.001$) (High school COR, 0.43; 95% CI, 0.312, 0.581; $p < 0.001$) (College or higher COR, 0.19; 95% CI, 0.125, 0.279; $p < 0.001$), high waist circumference (COR, 1.03; 95% CI, 1.013, 1.036; $p < 0.001$), high BMI (COR, 1.06; 95% CI, 1.027, 1.036; $p < 0.001$), living without a spouse (living together COR, 0.53; 95% CI, 0.405, 0.692; $p < 0.001$), menopausal status (COR, 4.45; 95% CI, 2.995, 6.624; $p < 0.001$), young age at first childbirth (age at first childbirth COR, 0.91; 95% CI, 0.874, 0.940; $p < 0.001$), high numbers of pregnancies (COR, 1.12; 95% CI, 1.069, 1.164; $p < 0.001$), prehypertension status (COR, 1.80; 95% CI, 1.263, 2.562; $p < 0.001$), impaired fasting glucose (COR, 1.48; 95% CI, 1.093, 2.003; $p < 0.001$), diabetes (COR, 2.71; 95% CI, 1.903, 3.871; $p = 0.001$), and dyslipidemia (COR, 4.32; 95% CI, 2.959, 6.293; $p < 0.001$).

In the results of univariate logistic regression analysis, multivariate logistic regression analysis was performed by adjusting age, education level, waist circumference, BMI, and number of pregnancies. Table 3 shows the risk of cervical cancer according to chronic disease status. The risk of cervical cancer was significantly higher in patients with dyslipidemia (adjusted odds ratio (AOR), 2.88; 95% CI, 1.785, 4.654; $p < 0.001$). Prehypertension (AOR, 1.14; 95% CI, 0.832, 1.547; $p = 0.112$), hypertension (AOR, 0.74; 95% CI, 0.440, 1.254; $p = 0.156$), impaired fasting glucose (AOR, 0.96; 95% CI, 0.661, 1.395; $p = 0.662$), and diabetes (AOR, 1.11; 95% CI, 0.617, 1.979; $p = 0.674$) were not associated with cervical cancer risk.In addition, the results of the multivariate logistic regression analysis were expressed as a graph in the for of a Forest plot to make it easy to see at a glace, which was presented as Fig. 2.

4. Discussion

In this retrospective study, we found that females with dyslipidemia had a significantly higher risk of developing cervical cancer. However, contrary to our assumption, hypertension and diabetes were not associated with this risk. To the best of our knowledge, this study is one of the first to determine the association between the risk of cervical cancer and presence of chronic diseases, such as hypertension, diabetes, and dyslipidemia.

Among the variables, old age, low educational attainment, high BMI, living without a spouse, menopause, young age at first childbirth, and multiparity were associated with an increased risk of cervical cancer. Smoking and OC use are previously known as risk factors for cervical cancer; however, the results of our study showed that these variables were not associated with cervical cancer risk.

Several studies have reported that OC use increases the risk of cervical cancer or cervical intraepithelial neoplasia (CIN) [14, 15]. The estrogen and progesterone components of OCs stimulate the expression of human papillomavirus (HPV)-16 E6 and E7 oncogenes, inhibiting tumor protein 53 (p53), known as a tumor suppressor. The viral DNA induces carcinogenesis, increasing cervical cancer risk [15–17]. However, the relationship between cervical cancer and OC use has been inconsistent. Some studies have reported no association between OC use and cervical cancer [18, 19]. Through several previously published papers, we explored the reason for the results that OC was not a risk factor for cervical cancer. Since the KNHANES data did not contain information on type of OC and duration of OC use, we simply analyzed

TABLE 1. Characteristics of the study participants by cervical cancer status.

	Total (N = 25,055)	Non-Cervical Cancer group (N = 24,744)	Cervical Cancer group (N = 311)	*p*-value
Age (years), M ± SE	48.35 ± 0.17	48.23 ± 0.17	58.59 ± 0.88	<0.001
Income, N (%)				
Q1	6136	6043 (24.7%)	93 (30.9%)	0.067
Q2	6307	6225 (25.0%)	82 (25.7%)	
Q3	6309	6234 (25.1%)	75 (24.5%)	
Q4	6303	6242 (25.2%)	61 (18.9%)	
Education, N (%)				
Less than Elementary school	5965	5837 (18.1%)	128 (36.2%)	<0.001
Middle school	2801	2750 (9.5%)	51 (18.0%)	
High school	6723	6637 (28.3%)	86 (29.5%)	
College or higher	9566	9520 (44.1%)	46 (16.3%)	
Alcohol consumption, N (%)				
Not drinking at all	9545	9420 (45.0%)	125 (56.2%)	0.084
Less than once a month	5487	5424 (24.3%)	63 (20.3%)	
Approximately once a month	4181	4136 (16.5%)	45 (11.2%)	
Approximately once a week	3556	3509 (11.6%)	47 (11.4%)	
Almost everyday	2286	2255 (2.8%)	31 (0.9%)	
Smoking, N (%)				
Non-smoker	22,184	21,910 (87.8%)	274 (88.2%)	0.883
Smoker, less than 100 cigarettes	444	437 (1.9%)	7 (2.2%)	
Smoker,100 or more cigarettes	2427	2397 (10.3%)	30 (9.6%)	
Waist circumference, M ± SE	78.75 ± 0.10	78.72 ± 0.10	81.36 ± 0.61	<0.001
BMI, M ± SE	23.34 ± 0.03	23.33 ± 0.03	24.18 ± 0.25	<0.001
BMI (categorical), N (%)				
<18.5	1261	1255 (5.8%)	6 (2.5%)	0.011
18.5–23	10,985	10,873 (46.0%)	112 (35.4%)	
23–25	5303	5227 (20.1%)	76 (22.5%)	
≥25	7506	7389 (28.1%)	117 (39.6%)	
Living status with spouse, N (%)				
Not living together	6639	6530 (19.8%)	109 (31.8%)	<0.001
Living together	18,416	18,214 (80.2%)	202 (68.2%)	
Menstrual status, N (%)				
Menstruating	12,470	12,373 (58.7%)	97 (24.2%)	<0.001
Menopausal	12,585	12,371 (41.3%)	214 (75.8%)	
Age at first childbirth, M ± SE	25.63 ± 0.04	25.65 ± 0.04	24.10 ± 0.21	<0.001
Number of pregnancies, M ± SE	3.62 ± 0.02	3.61 ± 0.02	4.15 ± 0.12	<0.001
Oral contraceptive use, N (%)				
Yes	4371	4303 (16.3%)	68 (18.9%)	0.275
No	20,684	20,441 (83.7%)	243 (81.1)	
Frequency of walking exercise, N (%)				
0 days a week	6368	6282 (23.6%)	86 (24.6%)	0.013
1–3 days a week	5778	5691 (23.0%)	87 (30.4%)	
4–7 days a week	12,909	12,771 (53.4%)	138 (45.0%)	

TABLE 1. Continued.

	Total (N = 25,055)	Non-Cervical Cancer group (N = 24,744)	Cervical Cancer group (N = 311)	*p*-value
Hypertension status, N (%)				
Normal	12,509	12,403 (56.2%)	106 (37.4%)	<0.001
Prehypertension	4874	4811 (18.8%)	63 (23.5%)	
Hypertension	7672	7530 (25.0%)	142 (39.1%)	
Diabetes status, N (%)				
Normal	12,249	12,132 (55.1%)	117 (37.0%)	<0.001
Impaired fasting glucose	9133	9114 (33.8%)	119 (40.8%)	
Diabetes	3573	3498 (11.1%)	75 (22.2%)	
Dyslipidemia status, N (%)				
Normal	24,027	23,759 (96.7%)	268 (87.3%)	<0.001
Dyslipidemia	1028	985 (3.3%)	43 (12.7%)	

Note: Values are presented as mean ± standard deviation or non-weighted N (weighted %).
M ± SE, mean ± standard error; Q, quarter; BMI, body mass index; OC, oral contraceptive.

TABLE 2. Univariate logistic regression analysis comparing the risks in the cervical cancer and non-cervical cancer groups.

	Risk in the cervical cancer group compared to that of the non-cervical cancer group		
	COR	95% CI	*p*-value
Age	1.04	(1.031, 1.047)	<0.001
Income			
Q1	1.00	Reference	
Q2	0.82	(0.575, 1.177)	0.006
Q3	0.50	(0.385, 0.661)	0.113
Q4	0.21	(0.145, 0.297)	0.193
Education			
Elementary school or lower	1.00	Reference	
Middle school	0.80	(0.536, 1.182)	<0.001
High school	0.43	(0.312, 0.581)	<0.001
College or higher	0.19	(0.125, 0.279)	<0.001
Alcohol consumption			
Not drinking at all	1.00	Reference	
Less than once a month	0.67	(0.418, 1.072)	0.084
Approximately once a month	0.55	(0.306, 0.974)	0.242
Approximately once a week	0.79	(0.431, 1.432)	0.377
Almost everyday	0.27	(0.061, 1.195)	0.182
Smoking			
Non smoker	1.00	Reference	
Smoker, less than 100 cigarettes	1.18	(0.506, 2.730)	0.753
Smoker, 100 or more cigarettes	0.93	(0.582, 1.479)	0.623
Waist circumference	1.03	(1.013, 1.036)	<0.001

TABLE 2. Continued.

	Risk in the cervical cancer group compared to that of the non-cervical cancer group		
	COR	95% CI	*p*-value
BMI	1.06	(1.027, 1.089)	<0.001
BMI (categorical)			
<18.5	1.00	Reference	
18.5–23	1.76	(0.710, 4.348)	0.034
23–25	2.41	(0.963, 6.028)	0.008
≥25	2.68	(1.076, 6.680)	0.531
Living status with spouse			
Not living together	1.00	Reference	
Living together	0.53	(0.405, 0.692)	<0.001
Menstrual status			
Menstruating	1.00	Reference	
Menopausal	4.45	(2.995, 6.624)	<0.001
Age at first childbirth	0.91	(0.874, 0.940)	<0.001
Number of pregnancies	1.12	(1.069, 1.164)	<0.001
OC use			
Yes	1.19	(0.873, 1.629)	0.268
No	1.00	Reference	
Frequency of walking exercise			
0 days a week	1.00	Reference	
1–3 days a week	1.26	(0.875, 1.816)	0.325
4–7 days a week	0.84	(0.586, 1.193)	0.004
Hypertension status			
Normal	1.00	Reference	
Prehypertension	1.80	(1.263, 2.562)	<0.001
Hypertension	2.15	(1.604, 2.875)	0.327
Diabetes status			
Normal	1.00	Reference	
Impaired Fasting glucose	1.48	(1.093, 2.003)	<0.001
Diabetes	2.71	(1.903, 3.871)	0.001
Dyslipidemia status			
Normal	1.00	Reference	
Dyslipidemia	4.32	(2.959, 6.293)	<0.001

Note: BMI, body mass index; CI, confidence interval; OC, oral contraceptive; COR, crude odds ratio; Q, quarter.

TABLE 3. Multivariate logistic regression analysis of cervical cancer risk by chronic disease status.

	Risk for cervical cancer compared to non-cervical cancer		
	AOR*	95% CI	*p*-value
Hypertension status			
Normal	1.00	Reference	
Prehypertension	1.14	(0.832, 1.547)	0.112
Hypertension	0.74	(0.440, 1.254)	0.156
Diabetes status			
Normal	1.00	Reference	
Impaired Fasting glucose	0.96	(0.661, 1.395)	0.662
Diabetes	1.11	(0.617, 1.979)	0.674
Dyslipidemia status			
Normal	1.00	Reference	
Dyslipidemia	2.88	(1.785, 4.654)	<0.001

Note: AOR, adjusted odds ratio; CI, confidence interval.
**Results of multivariate logistic regression analysis adjusted with age, education, waist circumference, BMI, and number of pregnancies.*

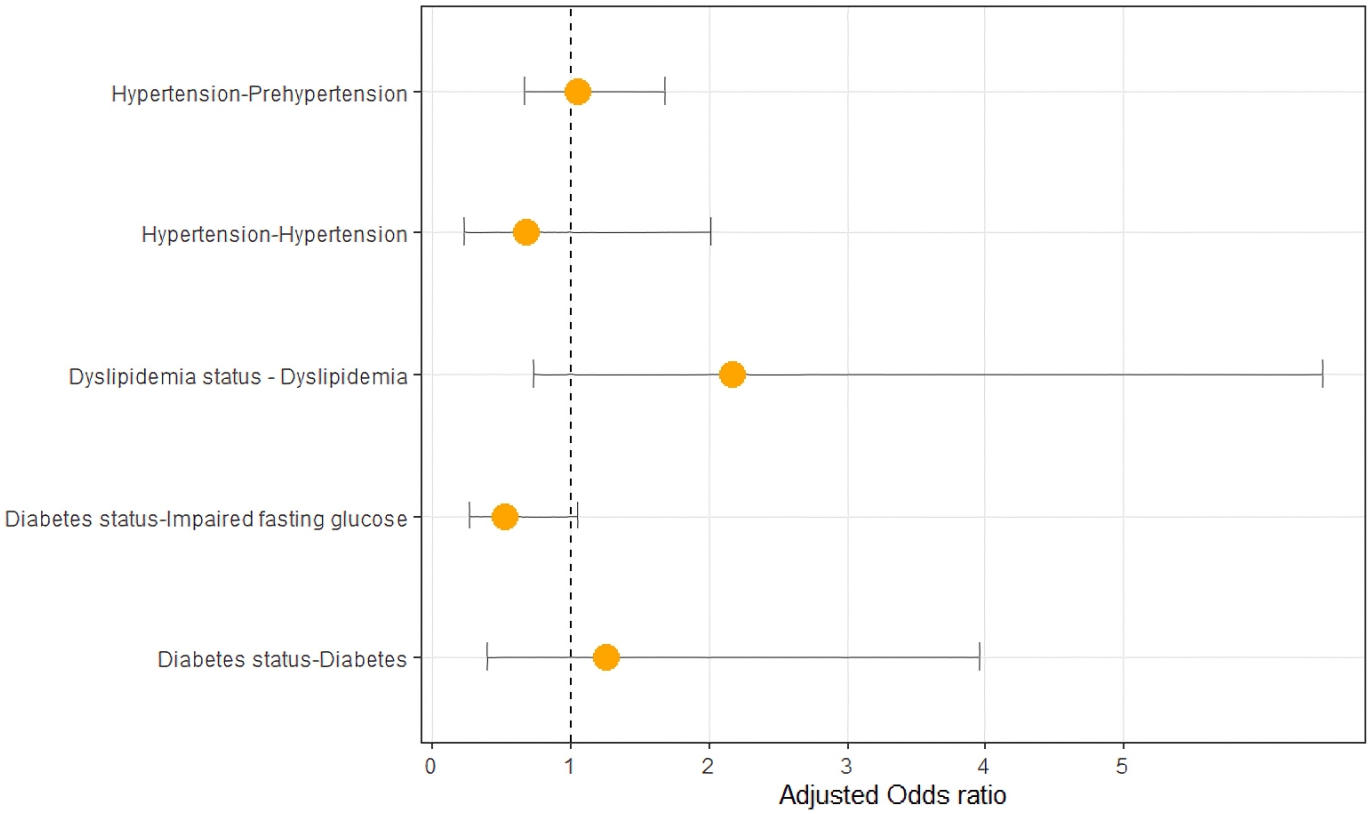

FIGURE 2. Forest plot graphy of multivariate logistic regression analysis of cervical cancer risk by chronic disease status.

the association between cervical cancer and OC use. Thus, the possibility that these differences in variables setting caused the bias of statistical results cannot be ruled out.

Smoking is a well-known risk factor for cervical cancer. Although the mechanism of increased cervical cancer risk has not been accurately identified, several possibilities may explain

it. Smoking interferes with immune system activation against HPV, making the body vulnerable to HPV infection. Further, smoking accelerates DNA damage when HPV-infected cells are exposed to tobacco smoke [20], inducing carcinogenesis. HPV oncoproteins inhibit apoptosis and cell cycle arrests, resulting in tumor growth [20]. Nevertheless, the effects of the relationship between smoking and cervical cancer have been inconsistent. One study suggests increased cervical cancer risk in HPV-positive female Korean smokers [18]. However, other studies have reported no relationship between smoking and cervical cancer or CIN [14, 19]. As such, although some study findings are similar to that of our study, we evaluated the reason behind smoking not being associated with cervical cancer in this study. We classified the participants into non-smokers, those who have smoked less than 100 cigarettes, and those who have smoked more than 100 cigarettes. Since both current and former smokers were included in the smoker categories, the effect of smoking on cervical cancer risk may have been reduced. KCDC analyzed the proportion of male and female smokers who had smoked 100 or more cigarettes from 2009 to 2020. The proportion of female smokers was 7.4% in 2008 and 6.6% in 2020, which is lower than that of male smokers at 47.8% in 2008 and 34.0% in 2020 [21]. On the other hand, the US CDC analyzed the percentages of male and female smokers, which were 11.0% and 14.1% in 2020, respectively [22]. The percentage of female smokers in Korea is approximately twice as low as that of female smokers in the US. Therefore, examining the relationship between cervical cancer and smoking in Korea may be limited, as opposed to that of the US, which has a relatively high smoking rate.

Earlier published papers suggested that the association between hypertension and cancer incidence may depend on the location and type of cancer. Further, the relationship between hypertension and cancer may be explained by carcinogenic factors induced by a hypoxic environment [23] and chronic inflammation [24]. Hypoxia-inducible factors are activated in a hypoxic environment created by hypertension, increasing the expression of tumorigenesis genes, such as vascular endothelial growth factors (VEGFs) and platelet-derived growth factors [23]. Additionally, chronic inflammation persists in a hypertensive environment because of the lack of smooth contraction and relaxation of vascular endothelial cells, which act as tumor-producing factors [24]. However, this epidemiology may not apply to all cancers. Several studies have reported a positive correlation between hypertension and renal cell carcinoma, esophageal squamous cell carcinoma (SCC), colorectal cancer, breast cancer, and endometrial cancer [24–27]. A European prospective study by Christakoudi *et al*. [28] showed a negative relationship between cervical SCC and hypertension. Additionally, no association is observed between cervical adenocarcinoma and hypertension. According to the 2012 Metabolic Syndrome and Cancer project by Stocks *et al*. [27], hypertension is positively correlated with cervical cancer and cancer mortality. Further, in the Metabolic Syndrome and Cancer Project by Ulmer *et al*. [13], hypertension is positively correlated with cervical SCC (Hazard Ratio (HR): 1.28; 95% CI, 1.05, 1.57), but not cervical adenocarcinoma (HR: 1.07; 95% CI, 0.65, 1.83).Since the KNHANES data only indicate the presence of cervical cancer, we did not classify and analyze certain cancer types, such as SCC and adenocarcinoma. In this regard, our study found no association between cervical cancer and hypertension. Future studies are required to examine the same relationshipby cancer type.

No relationship was found between diabetes and cervical cancer. Likewise, Ulmer *et al*. [13] found no association between diabetes and cervical SCC (HR 0.87; 95% CI, 0.58, 1.32) and cervical adenocarcinoma (HR 0.84; 95% CI, 0.31, 2.33). However, other studies have reported a positive association between diabetes and cervical cancers [29–32]. In a multivariate analysis by Jee *et al*. [31], diabetes is associated with cervical cancer incidence (HR: 2.20; 95% CI, 1.90, 2.54); however, the reverse is true when fasting serum glucose levels are classified into <90 mg/dL (reference), 90–109 mg/dL (HR 1.03; 95% CI, 0.94, 1.13), 110–125 mg/dL (HR: 0.87; 95% CI, 0.71, 1.08), 126–139 mg/dL (HR 0.97; 95% CI, 0.66, 1.43), and ≥140 mg/dL (HR 1.24; 95% CI, 0.98, 1.58). Insulin resistance causes diabetes, resulting in hyperinsulinemia. This increases IGF-1 and decreases IGF-binding protein, ultimately increasing free IGF-1 [9].Cell proliferation and the phosphatidylinositol 3-kinase (PI3K)/protein kinase B pathway guarantee cell survival, increasing the binding of IGF-1 to its receptor, which activates the p21 ras/mitogen-activated protein kinase pathway [9]. Since IGF-1 decreases apoptosis and increases the angiogenesis factor VEGF, diabetes makes tumor cell proliferation easier [9]. The aforementioned mechanism is generally established in colon, breast, liver, and prostate cancers but not in cervical cancer.

The result of our study that dyslipidemia contribute to increasing incidence of cervical cancer is consistent with other previously published papers [29, 33]. A cohort study on Icelanders reported that dyslipidemia increases the incidence of not only cervical cancer in females, but also colorectal and thyroid cancers in males [29]. Additionally, a large cohort study in Austria reported that dyslipidemia with an elevated serum triglyceride level tends to increase the incidence of gynecological cancers, such as cervical, ovarian, and endometrial cancers [33]. Since 1901, many studies have attempted to prove that cholesterol contributes to cancer growth. Based on these studies, a high-cholesterol environment increases ROS in the mitochondria; aldehydes and carcinogens are produced from the reaction of ROS and lipids; and increased COX-2 creates a favorable environment for cancer growth [9, 10]. Studies have investigated the effects of unregulated lipid metabolism on gynecological cancers [34–38]. Unregulated lipid metabolism increases fatty acid synthase-mediated phospholipids interacting with receptor tyrosine kinases. This overactivatesthe PI3K/mammalian target of rapamycin (mTOR) pathway, promoting cancer cell proliferation [34–36]. As a result, it was reported that gynecological cancer cell proliferation and viability were increased, as well as resistance to chemotherapy of cisplatin [37, 38]. Several papers reported the results of comparing cancer treatment effects after treating various cancer cells with dyslipidemia treatments [39–41]. In an experiment, colon cancer cells were treated with the hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor lovastatin, reducing colon cancer metastasis [39]. Similarly, the coadministration of the HMG-CoA reductase inhibitor atorvastatin and the antioxidant phloretin arrests the cell

cycle of colon cancer cells and activates apoptosis [40]. According to an *in vivo* experiment on prostate cancer, ezetimibe, a cholesterol uptake inhibitor, also suppresses the angiogenesis of cancer cells [41].

This study had some limitations. First, owing to the cross-sectional design of this study, we were unable to perform a longitudinal follow-up to establish the causal relationship between chronic diseases and cervical cancer. Second, an unanswered questionnaire was treated as a missing value and excluded, resulting in potentially biased estimates. Third, since the survey responses depend on each individual's memory, potential recall bias cannot be ruled out. Fourth, depending on the cell type, cervical cancer can be largely classified into SCC and adenocarcinoma. These types also differ in proliferation and metastasis. However, the KNHANES data used in this study did not suggest cervical cancer by cell type, we could not evaluate cervical cancer by classifying it as SCC and adenocarcinoma. Fifth, the KNHANES data did not provide information on HPV infection history, and we could not evaluate the association between HPV and cervical cancer, one of the risk factors for cervical cancer. Nevertheless, the strength of our paper was that 11 years of large national representative sample data were used, analyzed to find out the association between cervical cancer and various factors, and statistical analysis was also performed by adjusting the confounding variables. Consequently, we confirmed the association between dyslipidemia and cervical cancer. In the future, a longitudinal follow-up study is needed to evaluate how correcting dyslipidemia contributes to lowering the risk of cervical cancer.

5. Conclusions

In our study, dyslipidemia was a higher risk of cervical cancer than women with normal plasma lipid levels in Korea. Therefore, encouraging proper treatment of dyslipidemia in gynecological patients with dyslipidemia might contribute to lowering the potential risk of cerivical cancer in the future.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding authors.

AUTHOR CONTRIBUTIONS

SML, SHL and TK—Conceptualization; SML, HWC and KJM—data curation; SML, SHL, JYS and TK—data analysis and interpretation; SML and SHL—writing-original draft preparation; SHL, TK and JYS—writing-review and editing; SML, JHH, JKL and NWL—visualization; SHL and TK—supervision. All authors have read and agree to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All of the participatns in the KNHANES were informed that they had been randomly chosen to participate in the survey with the right to participate in further analyses and signed an informed consent form. As this was a cross-sectional study that used and analyzed only non-identifying data from KNHANES (https://knhanes.kdca.go.kr/knhanes/sub03/sub03_02_05.do), ethical approval was not required.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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