

Associations of clinical and modifiable behavioral risk factors with the histological progression of squamous intraepithelial lesions

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Abstract. Cervical cancer is the third most common cancer in women worldwide. Human papillomavirus (HPV) has been established as a cause of invasive cervical cancer. However, HPV is predominantly transient and only a minority of cases persist and progress clinically. Certain epidemiological factors have been suggested to increase the risk of HPV persistence and progression. In the present study, 893 women were investigated, with an age range from 25 to 60 years old. PAP smears and colposcopy were used for assessment. Of these women, 108 were diagnosed with squamous intraepithelial lesions (SILs) and were further divided into high-grade SIL (HSIL) and low-grade SIL (LSIL). The dietary habits, sleep patterns and gynecological histories of these participants were studied, and it was found that the probability of having <3 meals a day [odds ratio (OR), 4.35; 95% confidence interval (CI), 1.73-10.95], having an unbalanced diet (OR, 3.90; 95% CI, 1.44-10.55), breakfast skipping (OR, 6.32; 95% CI, 2.40-16.61) and disrupted sleep (OR, 4.42; 95% CI, 1.79-10.93) was significantly higher in the HSIL group compared with the probability in the LSIL group. In addition, participants who had pregnancies prior to the age of 20 were 2.85 times more likely to have more advanced disease (OR, 2.85; 95% CI, 1.22-6.71). Cervical erosion was higher in the HSIL group compared with that in the LSIL group (OR, 3.31; 95% CI, 1.36-6.96). The present study highlights the protective effects of meal numbers, nutritious diet and sleep hygiene against HPV and the progression of SIL.

Introduction

Cervical cancer is the third most common cancer in women worldwide, with 604,000 new cases diagnosed in 2020; it remains the most common female cancer in certain regions of the world (primarily developing regions, such as Eastern Africa) (1). Human papillomavirus (HPV) has been established as a cause of invasive cervical cancer. Over 100 HPV types exist. However, types 16, 18, 31, 33 and 45 account for 83% of all cervical cancer cases (2). The prevalence of the disease has been gradually reduced in several developing countries due to primary screening and HPV vaccinations; for example, in South Korea, the incidence of cervical cancer has decreased from 16.3 per 10⁵ individuals in 1999 to 9.0 per 10⁵ individuals in 2014 (3).

The results derived from the majority of recent HPV natural history investigations have indicated that HPV is predominantly transient, and that only a minority of cases persist and progress clinically (4-6). The etiological causes that contribute to the progression of HPV infections, consequent squamous intraepithelial lesions (SILs) and cancer remain to be understood. However, epidemiological studies have demonstrated certain risk factors that are associated with the development of SILs and cervical cancer. These co-factors can be divided into the three following major categories: i) Exogenous or environmental cofactors, including the use of oral contraceptives, smoking, diet, sleep, sexual trauma or coinfection with other sexually transmitted organisms; ii) viral cofactors, such as viral load and variants; and iii) host cofactors, such as genetics and endogenous hormones (7).

Certain inconsistent and sparse studies have reported on the effect of a protective lifestyle and exogenous factors, such as the effect of the intake of certain vitamins and minerals on the progression of cervical cancer (8). In addition to diet, the immune system and cancer progression can be influenced by sleep and the circadian rhythm, smoking, alcohol consumption and certain gynecological factors (7,9,10).

The present study assessed the association between diet, meal skipping, sleep and previous gynecological history, and the risk of developing high-grade SIL (HSIL) compared with the risk of developing low-grade SIL (LSIL).

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Materials and methods

Study design and ethics. A cross-sectional study was conducted using a consecutive non-probability sample of 893 women (age range, 25-60 years; mean age, 40.56±8.97 years) in the Adjara region in Western Georgia (Batumi Iashvili Clinic, Mountain Adjara Regional Centers and Guria Regional Centers) in affiliation with David Tvildiani Medical University (Tbilisi, Georgia). Participants were tested from February 2016 to September 2017 under the free cervical cancer prevention program provided by the Ministry of Health and Social Affairs of Adjara, in partnership with the National Center for Disease Control and Public Health of Georgia. Among all the women tested by this program, those who consented to participate in this study were asked to complete a questionnaire. The cytological study results were collected from the medical records of the participants. All participants signed the consent agreement prior to inclusion in the study according to the protocol approved by the Ethics Committee of David Tvildiani Medical University (approval no. 2/30.09.2015).

Selection criteria. Study participants were sexually active; however, they were not pregnant, had an intact cervix and uterus, and had not received anti-cervical intraepithelial neoplasia (CIN) therapy during the last 10 years. The exclusion criteria were the presence of gynecological cancer (ovarian or endometrial), insufficient questionnaire data, the presence of chronic somatic diseases, drug dependency and the existence of current mental diseases.

Study methods. Cytological assessment with a PAP smear was performed for all patients, with the Bethesda Classification (11). In addition, all participants underwent colposcopic examination and colposcopy-assisted biopsy.

All participants were asked to complete a questionnaire that enquired about the following clinical, lifestyle and socioeconomic characteristics of the participants: i) Dietary habits and nutrition: The frequency of meal intake, breakfast skipping and self-rated balance of diet with inclusion of fruits and vegetables; ii) sleep regimen: Sleep duration, interrupted or uninterrupted sleep, late bedtimes, late waking and chronic insomnia; iii) sexual behavior: Previous pregnancies and number of sexual partners; iv) gynecological diseases: Erosion and chronic cervicitis/vulvovaginitis; v) harmful habits: Smoking and alcohol overconsumption; vi) educational level: High school and university; vii) socio-economic status: Family status, employment, family income and private income; and viii) use of contraceptives and type of contraception.

Statistical analysis. The risk factors were first assessed in the form of a univariate study by determining odds ratios (ORs) and 95% confidence intervals (CIs). OR analysis was performed using SPSS 22.0 software (IBM Corp.). A multivariate study (multiple logistic regression) was then performed with select variables that demonstrated statistical significance in the univariate study. The multiple logistic regression analysis was performed using GraphPad Prism 9.3.1 (Dotmatics). $P < 0.05$ was used to indicate a statistically significant difference.

Results

SIL was diagnosed in 108 out of 893 patients. Among them, 76 cases (70.4%) were designated as LSIL and 32 cases (29.6%) were designated as HSIL, based on cytological findings (the Bethesda Classification). The analysis of the demographic and socioeconomic characteristics indicated that family status, urban/rural habitats and educational characteristics did not significantly differ between these two groups. However, compared with that in the HSIL group, marital status was the only parameter that exhibited significantly higher levels in the LSIL group ($P = 0.03$) (Table I).

No significant difference was noted in terms of smoking or alcohol overconsumption between the HSIL and LSIL groups. The majority of the participants who were diagnosed with SIL were smokers and drank alcohol overtly (smoking in the HSIL and LSIL groups: 96.9 and 97.4%, respectively; alcohol overconsumption in the HSIL and LSIL groups: 96.9 and 97.4%, respectively) (Table II).

The distribution of study participants by dietary habits and sleep disorders indicated that compared with that in the LSIL group, the probability of having <3 meals a day (OR, 4.35; 95% CI, 1.73-10.95; $P < 0.001$), having an unbalanced diet (OR, 3.90; 95% CI, 1.44-10.55; $P < 0.001$), breakfast skipping (OR, 6.32; 95% CI, 2.40-16.61; $P < 0.001$) and disrupted sleep (OR, 4.42; 95% CI, 1.79-10.93; $P < 0.001$) was significantly higher in the HSIL group. However, the rate of insomnia was not significantly different between patients with HSIL and those with LSIL (OR, 2.58; 95% CI, 0.93-7.15; $P = 0.06$) (Table III).

The assessment of the characteristics of the gynecological history of the participants indicated that the frequency of having pregnancies prior to the age of 20 was significantly higher in the HSIL group compared with that in the LSIL group (OR, 2.85; 95% CI, 1.22-6.71; $P = 0.007$). In addition, a higher number of cervical erosion cases was noted in the HSIL group compared with that in the LSIL group (OR, 3.31; 95% CI, 1.36-6.96; $P = 0.004$). There was no association between the presence of chronic cervicitis/vulvovaginitis, oral contraception use and intrauterine contraception, and the progression of the disease (Table IV).

The variables with statistical significance were selected from the univariate analysis and assessed in a multiple logistic regression model (Table V). The study showed a significant intercept, meaning the log odds of the outcome significantly differed from 0 when all variables were at their reference levels. The analysis indicated that breakfast skipping, disrupted sleep, pregnancy prior to the age of 20 and visible cervical erosions were significant risk factors. The Tjur's R^2 value of this model was 0.4089.

Discussion

The cervix is lined by stratified squamous cells on the exocervix and mucous-producing columnar epithelium on the endocervix. The transition point between these two areas is called the squamocolumnar junction and exerts the greatest risk of viral neoplastic transformation. HPV DNA is found in ~95% of cervical cancer cases (12). The majority of HPV infections are cleared spontaneously from the body; however, if the infection persists it can lead to premalignant lesions,

Table I. Demographic and socio-economic characteristics in the two groups.

Factor	HSIL (n=32)	LSIL (n=76)	OR (95% CI)	P-value
Age, years ^a	43.3±10.6	40.6±8.5	NA	NA
Urban/rural, n (%)			1.71 (0.74-3.95)	0.20
Urban	16 (50.0)	28 (36.8)		
Rural	16 (50.0)	48 (63.2)		
Education, n (%)			0.67 (0.29-1.56)	0.34
High school	18 (56.3)	50 (65.8)		
University	14 (43.8)	26 (34.2)		
Family status, n (%)			0.3 (0.09-0.92)	0.03 ^b
Married	24 (75.0)	69 (90.8)		
Divorced/non-married	8 (25.0)	7 (9.2)		
Family income, n (%)			0.52 (0.18-1.53)	0.23
Low	5 (15.6)	20 (26.3)		
Medium	27 (84.4)	56 (73.7)		

^aMean ± SD. ^bP<0.05. HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; OR, odds ratio; CI, confidence interval; NA, not applicable.

Table II. Distribution of the smoking and alcohol overconsumption cases in the two groups.

Factor	HSIL (n=32)	LSIL (n=76)	OR (95% CI)	P-value
Smoking, n (%)			1.19 (0.10-13.65)	0.88
No	1 (3.1)	2 (2.6)		
Yes	31 (96.9)	74 (97.4)		
Alcohol overconsumption, n (%)			1.19 (0.10-13.65)	0.88
No	1 (3.1)	2 (2.6)		
Yes	31 (96.9)	74 (97.4)		

HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; OR, odds ratio; CI, confidence interval.

which can transition into invasive carcinoma over a period of months to decades (13). Various cofactors have been suggested to increase the risk of progression of the disease, such as cigarette smoking, long-term oral contraceptive use, high parity, coinfection with herpes simplex virus and human immunodeficiency virus, and diet (8,12).

In the present study, the role of certain lifestyle factors, such as diet, sleep and gynecological history, was investigated in the progression of SIL. Multiple studies have suggested that certain macro- and micro-nutrients can prevent the progression of HPV infection to invasive cervical cancer. González *et al* (8) investigated the dietary information of the participants in the European Prospective Investigation into Cancer study. It was concluded that there was an inverse correlation between fruit and vegetable consumption and invasive squamous cervical cancer (8). In particular, the consumption of fruits and vegetables, vitamins A, E and C, folates and carotenoids exhibits an inverse correlation with CIN, cervical cancer and its progression (14-22). Plausible biological mechanisms can explain these results. For example, vitamins A and E regulate

cell differentiation and proliferation, while vitamins C and E, and carotenoids act as scavengers of free radicals (22). When free radicals and oxidants are not neutralized, inflammatory processes can damage DNA. Moreover, animal experiments have demonstrated that supplementing vitamins and minerals can prevent the development of paraneoplastic lesions in rats (23). By contrast, nutrients with antioxidant properties modulate the immune response and can decrease viral replication. Folate and vitamins B6 and B12 are involved in DNA synthesis, repair and methylation, which may be important in viral integration and genome stability (24). It is important to note that skipping meals, notably breakfast, on a regular basis has been associated with a poor quality of diet and lower intake of vitamins, minerals and energy (25). In the present study, the association between SIL and frequency of meal intake <3, breakfast skipping and an unbalanced diet that did not include sufficient fruits and vegetables, was investigated. It was found that breakfast skipping, having <3 meals a day and an unbalanced diet were more prevalent in patients with more advanced SIL.

Table III. Distribution of study participants by dietary pattern and sleep disorders.

Characteristic	HSIL (n=32)	LSIL (n=76)	OR (95% CI)	P-value
Frequency of meal intake <3, n (%)			4.35 (1.73-10.95)	<0.001 ^a
Yes	24 (75.0)	31 (40.8)		
No	8 (25.0)	45 (59.2)		
Unbalanced diet, n (%)			3.90 (1.44-10.55)	<0.001 ^a
Yes	26 (81.3)	40 (52.6)		
No	6 (18.8)	36 (47.4)		
Breakfast skipping, n (%)			6.32 (2.40-16.61)	<0.001 ^a
Yes	25 (78.1)	26 (34.2)		
No	7 (21.9)	50 (65.8)		
Disrupted sleep, n (%)			4.42 (1.79-10.93)	<0.001 ^a
Yes	16 (50.0)	14 (18.4)		
No	16 (50.0)	62 (81.6)		
Insomnia, n (%)			2.58 (0.93-7.15)	0.06
Yes	9 (28.1)	10 (13.2)		
No	23 (71.9)	66 (86.8)		

^aP<0.05. HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; OR, odds ratio; CI, confidence interval.

Table IV. Characteristics of gynecological history of participants in the two groups.

Characteristic	HSIL (n=32)	LSIL (n=76)	OR (95% CI)	P-value
Pregnancy before the age of 20, n (%)			2.85 (1.22-6.71)	0.007 ^a
Yes	20 (62.5)	28 (36.8)		
No	12 (37.5)	48 (63.2)		
Chronic cervicitis/vulvovaginitis, n (%)			1.19 (0.10-3.65)	0.88
Yes	1 (3.1)	2 (2.6)		
No	31 (96.9)	74 (97.4)		
Oral contraception, n (%)			1.19 (0.10-3.65)	0.88
Yes	1 (3.1)	2 (2.6)		
No	31 (96.9)	74 (97.4)		
Intrauterine contraception, n (%)			1.19 (0.10-3.65)	0.88
Yes	1 (3.1)	2 (2.6)		
No	31 (96.9)	74 (97.4)		
Visible cervical erosion, n (%)			3.31 (1.36-6.96)	0.004 ^a
Yes	15 (46.9)	16 (21.1)		
No	17 (53.1)	60 (78.9)		

^aP<0.05. HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; OR, odds ratio; CI, confidence interval.

An additional factor studied was the effect of insomnia and disrupted sleep on the progression of SIL. In an experimental rat model, melatonin was shown to suppress the initial phases of tumorigenesis (26); it can do so by acting as a free radical scavenger and suppressing the accumulation of DNA adducts (the complexes formed when chemicals bind to DNA) (9). Surgical removal of the pineal gland or

exposure to constant light stimulates mammary tumorigenesis in rodents (27). In addition, an epidemiological study showed that women working night shifts have a significantly elevated risk of breast cancer (28). A reciprocal relationship has been noted between sleep and the immune system. Sleep deprivation can lead to the suppression of immune function and a change in the balance of cytokine production, with

Table V. Multiple logistic regression model of selected variables.

Variables	Estimate	Standard error	OR	95% CI	P-value
Intercept	-4.780	0.9496	0.0083	0.00-0.04	<0.0001 ^a
Married family status	1.247	0.8207	3.47	0.71-19.00	0.1288
Unbalanced Diet	0.872	0.8408	2.39	0.44-12.81	0.2997
Frequency of meal intake <3	0.428	0.7652	1.53	0.34-7.31	0.5762
Breakfast skipping	1.796	0.6398	6.02	1.81-23.14	0.0050 ^a
Disrupted sleep	1.467	0.6460	4.33	1.26-16.46	0.0232 ^a
Pregnancy before the age of 20	1.566	0.6036	4.78	1.55-17.04	0.0095 ^a
Visible cervical erosion	1.701	0.6221	5.48	1.69-20.14	0.0062 ^a

^aP<0.05. OR, odds ratio; CI, confidence interval.

higher production of cancer-stimulatory cytokines such as IL-10 (9). In the present study, patients with HSIL were four times more likely to have disrupted sleep than patients with LSIL.

Factors, such as long-term oral contraceptive use, high parity, previous abortions and long menstrual lifespan, have been studied in association with cervical cancer and they have been shown to increase cervical cancer risk. In contrast to these observations, intrauterine contraception with the use of intrauterine devices has been shown to decrease the risk of HSIL and invasive cervical cancer (29). Parazzini *et al* (30) demonstrated that the risk of cervical cancer increased markedly in women with higher parity. The study also demonstrated a significant effect of earlier first birth on the risk of cervical cancer. The gynecological history of the participants of the present study was investigated and a history of pregnancy prior to the age of 20 was found to be 2.85 times higher in patients with HSIL. However, no significant association was noted with the oral or intrauterine contraception use, probably due to the low number of patients using contraceptives, which was attributed to a lack of access and awareness in the region. The demographic and socioeconomic status of the patients was assessed, and no significant difference was noted between the education level, income level and the place of residence of the patients in the LSIL or HSIL groups; however, a higher number of patients in the LSIL group were married compared with that in the HSIL group.

The present study contains certain limitations, such as the population size. In the present study, 893 women received free cervical cancer screening in the underserved region of Adjara, but only 108 of them were diagnosed with SIL and were ultimately investigated. Larger numbers of patients with SIL should be tested in future.

In conclusion, the present study showed an inverse association between a balanced diet and uninterrupted sleep, and more advanced forms of SIL. Moreover, the protective effect of consuming fruits and vegetables with good sleep was highlighted to act against the progression of HPV and cervical cancer in women. Based on the results of the present study, healthcare professionals should consider educating women on the use of vitamins and proper nutrition, sleep and safe sex practices. Food consumption and nutritional value can vary

worldwide; therefore, it is important to consider different diets and practices worldwide in future studies. The majority of the research studies conducted to date are epidemiological; however, experimental research studies with measures of variables at different points in time can aid the identification of the effects of nutrition and sleep on cancer progression.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LB and BT conceptualized the study. LB, RT, SA, DT, UIU and BT were involved in the methodology, data collection, analysis of data and writing of the manuscript draft. All authors contributed to manuscript revisions and have read and approved the final version of the manuscript. LB and RT confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of David Tvildiani Medical University (Tbilisi, Georgia; approval no. 2/30.09.2015). All participants signed the consent agreement prior to inclusion in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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