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# Cervical Intraepithelial Lesions: Socio-economic and Behavioural Risk-factors in Western Georgia

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**Abstract**

**Introduction.** Cervical Cancer is dangerous gynecological disease, especially in low and middle income countries. HPV is the main risk-factor of cervical carcinogenesis. Unfortunately, there is very few information about the frequency of meal intake, breakfast skipping, protein lack diet, sleep disorders, and their relation with cervical cancer. Therefore, the purpose of our study was the assessment of socio-economic and behavioural factors of cervical intraepithelial lesions (CIL) in Western Georgia.

**Methods.** 893 women (age – 25-60 years; mean age – 40.56±8.97 years) have been studied by gynecological examination, PAP-test and colposcopically. The special structured questionnaire consisted of the lifestyle, socio-demographic and other characteristics of participants. CIL risk-factors have been assessed by case-control study.

**Study Results.** The analysis of demographic and socio-economic characteristics shows that age, family status, urban/rural habitants and educational characteristics did not significantly differed between groups. Low family income is significantly higher in CIL group compared to non-CIL participants ($p<0.05$). BMI values were significantly differed in groups ($31.32\pm4.92$ kg/m$^2$ vs. $29.46\pm5.23$ kg/m$^2$, $p=0.0005$). Protein-lack diet (OR=2.2041), breakfast skipping (OR=1.7669), discrete sleep (OR=1.7121), insomnia (OR=2.8335), and frequent induced abortions (OR=2.1979) are significant risk-factors of CIL. The analysis of cervical background diseases indicated that high percentage of erosions found in CIL cases compared to controls (OR=2.4783).

Multiple regression analysis revealed significant risk-factors: family income, protein-poor food, breakfast skipping, deliveries and abortions in early youth, impaired menstrual cycle, cervical erosions.

Vol. 5, No. 02; 2021

ISSN: 2581-3366

**Conclusion.** Study results indicated the possible impact of energy imbalance on the development of CIL. Breakfast skipping, protein-lack diet, sleep disorders should be considered as risk-factors of energy imbalance, which is cause of altered metabolic characteristics, inflammation, obesity and insulin resistance. Furthermore, energy imbalance should be the reason of decreased levels of estrogens. Our data of multiple regression analysis revealed the significant risk-factors of CD development: family income, protein-poor food, breakfast skipping, deliveries and abortions in early youth, impaired hormonal status, clinical sign – pain/discomfort/heaviness in lower abdomen. The energetic imbalance and impaired hormonal homeostasis are principal issues in the strategy of the CC prevention. However, the evidence of our results has to be confirmed by further valid randomized control trials.

**Keywords:** Cervical Intraepithelial Neoplasia, Diet habits, Nutrition, Sleep disorders

## Introduction

Cervical Cancer (**CC**) is dangerous gynecological disease, especially in low and middle income countries [1]. Recent data predict the elevation of **CC**incidence and mortality rates [2]. According statistical data of Global Cancer 569,847 new **CC**cases have been diagnosed in 2018. It is 6.9% of all cancer cases [3]. According the data of National Center of Disease Control **CC** took 4$^{th}$ place among diagnosed women cancers in 2016 [4]. The rate of CC of I and II stages is 55.3%. These values was explained by low coverage of screening program: 18% of women population – in Tbilisi (Capital of Georgia), and 11.5% - in regions. The prevention of malignancy is possible and effective when the diagnosis of precancerous damages is set on earlier stages [1, 5]. Human Papilloma Virus (HPV) is the main risk-factor of cervical carcinogenesis [5, 6]. Diet and dietary habits, smoking, weak immune system, obesity and overweight, application of contraception, and family history were often mentioned among other CC risk-factors [7-9].

Recent data revealed that food intake is associated with the cancer, and also inflammation [10]. Antioxidants, minerals and vitamins set the desirable antioxidative balance by the inhibition of oxidation and inflammative processes [11]. Inflammative markers: C-reactive protein,Tumor necrosis factor and interleukine 6 were associated with chronic diseases and modulated by food [12]. Plant products with antioxidative properties reduced the risk of cancer development [13]. Food with high risk of inflammation were associated with high risk of malignant processes [14,15]. The intake of such products was associated with both inflammation and high risk of CC [16]. Unfortunately, there is very few information about diet habits (the frequency of meal intake, breakfast skipping, sweets and snacks) and sleep, and their relation with CC. However, disorders in nutrition, meal intake and sleep were significantly correlated with energy imbalance and metabolic syndrome [17,18]. Latter state is also possibly the inducer of cancer by the development of inflammation processes [19]. Some studies were confirmed the association between obesity, physical activity, calorie intake and gynecological cancers, but the data about association with CC were limited [20].

Vol. 5, No. 02; 2021

ISSN: 2581-3366

The objectives of our study were the assessment of well-known socio-economic and establishment of behavioural (diet and its habits, meal intake, its frequency, sleep disorders) of cervical intraepithelial lesions (CIL) in Western Georgia.

**Methods**

893 women (age – 25-60 years; mean age – 40.56±8.97 years) of Western Georgia have been studied by gynecological examination, PAP-test and colposcopically. Cytomorphological study has been carried out in case of necessity.

Study participants were sexually active or planning pregnancy, weren't pregnant, had intact cervix, did not refer because of hysterectomy, had not anti-CIN therapy during last 18 years. Exclusion criteria were gynecological cancer (ovarian or endometrial) in anamnesis; insufficiency of questionnaire data; chronic somatic diseases, drug dependency or mental problems. All participants signed the consent agreement prior to enrollment in the study according to the protocol approved by Institutional Review Board.

Cytological study was based on Bethesda Classification System [21] for smear PAP-test. All patients with the diagnosis of atypical squamous cells of undetermined significance (ASCUS) or cytological diagnosis of atypical squamous cells which can not exclude high-grade lesions (ASC-H), Low grade squamous intraepithelial lesions (LSIL), and High-grade squamous intraepithelial lesions (HSIL) were diagnosed histopathological study. Specimens have been obtained by colposcopy-assisted biopsy. Histological grade has been carried out by WHO criteria.

The special structured questionnaire consisted of the lifestyle, socio-demographic and other characteristics of participants. Among of them were:

- Dietary habits and nutrition (the frequency of meal intake; breakfast skipping; protein-lack, fat- and carbohydrate-rich diet; sweets and sneaks);
- Sleep regime (sleep duration, discrete sleep, late bedtime, late waking, chronic insomnia, hypersomnia);
- Sexual behavior (age at first sexual act, the abortions and deliveries at earlier age, quantity of sex partners, quantity of spontaneous and induced abortions);
- Clinical signs (disparenuria, blood discharge during sexual intercourse, pain/discomfort in lower abdominal area, itch/burning of vagina/vulva, excessive discharge during menstrual cycle);
- Cervical background diseases (erosion, leukoplakia, polyps, condylomas);
- Coexisted genital diseases (cervicitis, vaginitis, salpingo-oophoritis, endometritis, cervical myoma, ovarian cyst, endometriosis, endometrial polyp);
- Harmful habits (smoking, alcohol overconsumption);
- Education level (middle-school, high-school, college, university);
- Socio-economic characteristics (family status, employment, family income, private income);
- Use of contraceptives and sex-hormone preparations + ovulation stimulated anti-androgens in details of duration and types;

Vol. 5, No. 02; 2021

ISSN: 2581-3366

- Family history of genital and other type cancers.

Body mass index (**BMI**) was calculated by the division of body mass (in kilograms) by body height (in meters) in square [22], followed by categorization of obesity definition by WHO (normal mass – 20-24.99 kg/m$^2$; overweight – 25-29.99 kg/m$^2$; obesity – ≥30 kg/m$^2$).

CIL risk-factors have been assessed by case-control study, and determination of odds ratios (OR) and 95% confidence intervals (95%CI). Control cases were randomly selected from non-CIL participants of same age and BMI. Case-control ration was 1:3.

Statistical treatment has been carried out by software SPSS 22.0. Quantitative results in the groups were assessed by 2-tail t-test. Qualitative variables in groups were statistically assessed by $\chi^2$-test taking into account Yate's correction. The criterion of the rejection of null hypothesis was $p<0.05$. Pearson coefficient has been used for correlation analysis. Multiple regression analysis was carried out for determination of CD risk-factors.

**Study Results**

**CIL** were diagnosed in 108 cases; the distribution of patients by type of lesion is presented in Table #1.

**Table #1. Distribution of patients by type of cervical intraepithelial lesion.**

| # | Type of CIL | n= | % |
|---|---|---|---|
| 1 | LSIL | 37 | 34,26% |
| 2 | HSIL | 32 | 29,63% |
| 3 | CIN1 | 29 | 26,85% |
| 4 | CIN2 | 7 | 6,48% |
| 5 | CIN3 | 3 | 2,78% |

Demographic and Socio-economic characteristics are given in Table #2. Table shows that age, family status, urban/rural habitants and educational characteristics did not significantly differed between groups. Only one characteristic is low family income which is significantly higher in CIL group compared to non-CIL participants ($p=0.0323$).

Vol. 5, No. 02; 2021

ISSN: 2581-3366

**Table #2. Demographic and socio-economic characteristics in groups.**

| # | Characteristic | Group 1 - CIL n= | % | Group 2 –non-CIL n= | % | $\chi^2$ (p) |
|---|---|---|---|---|---|---|
| **1** | **Age** | | | | | |
| | ≤ 30 years | 10 | 9.26% | 95 | 12.10% | 1.9904 (p=0.5744, NS) |
| | 31-40 years | 34 | 31.48% | 277 | 35.29% | |
| | 41-50 years | 44 | 40.74% | 274 | 34.90% | |
| | > 50 years | 20 | 18.52% | 139 | 17.71% | |
| **2** | **Family Status** | | | | | |
| | Married | **99** | 91.67% | **682** | 86.88% | 3.2681 (p=0.1951, NS) |
| | Unmarried | **8** | 7.41% | **69** | 8.79% | |
| | Divorsed or widow | **1** | 0.93% | **34** | 4.33% | |
| **3** | **Urban/Rural** | | | | | 1.203 (p=0.2727, NS) |
| | Urban | **44** | 40.74% | **368** | 46.88% | |
| | Rural | **64** | 59.26% | **417** | 53.12% | |
| **4** | **Family Income** | | | | | |
| | Low | **23** | 21.30% | **103** | 13.12% | **4.583 (p=0.0323)** |
| | Middle | **85** | 78.70% | **682** | 86.88% | |
| **5** | **Education Level** | | | | | |
| | Middle or High School | **68** | 62.96% | **470** | 59.87% | 0.2605 (p=0.6097, NS) |
| | College or University | **40** | 37.04% | **315** | 40.13% | |

Distribution of habits (smoking, alcohol overconsumption) in groups is presented in Table #3. The difference between groups was not significant.

**Table #3. Distribution of habits (smoking, alcohol overconsumption) in groups.**

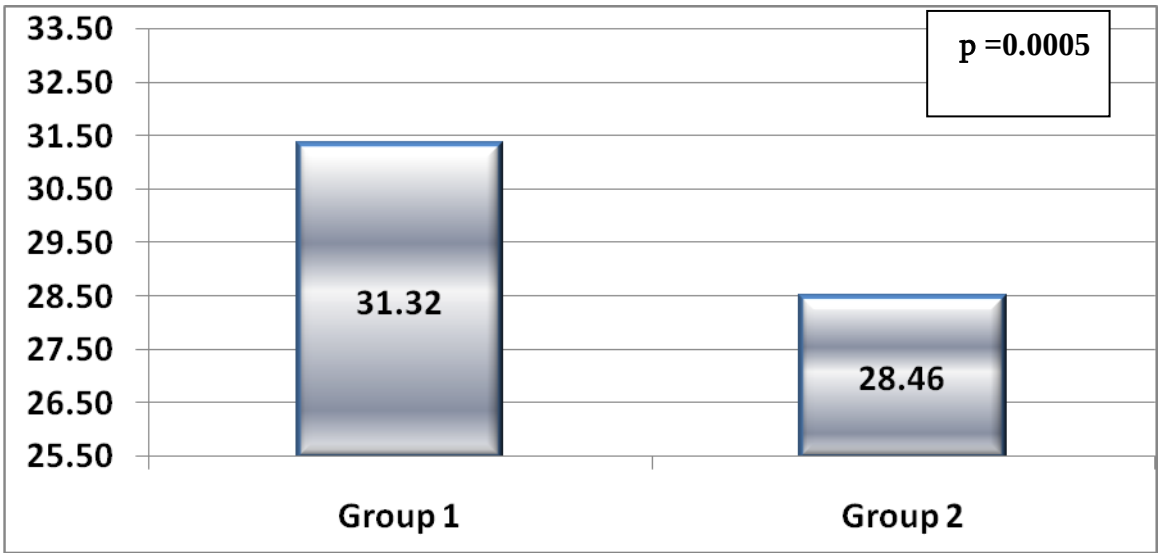
| # | Characteristic | Group 1 - CIL n= | % | Group 2 – non-CIL n= | % | $\chi^2$ (p) |
|---|---|---|---|---|---|---|
| **1** | **Smoking** | 3 | 2.54% | 52 | 6.62% | 1.8103 (p=0.1784) |
| **2** | **Alcohol overconsumption** | 3 | 2.54% | 55 | 7.01% | 2.1423 (p=0.1433) |

Diagram#1shows the significant difference of BMI values in groups (31.32±4.92 kg/m$^2$ vs. 29.46±5.23 kg/m$^2$, p=0.0005).

Vol. 5, No. 02; 2021

ISSN: 2581-3366

**Diagram #1. BMI mean values in groups.**




The distribution of study participants by diet, dietary habits and sleep disorders is presented in Table #4. As it is shown from Table #4, protein-lack diet (OR=2.2041), breakfast skipping (OR=1.7669), discrete sleep (OR=1.7121) and insomnia (OR=2.8335) are significant risk-factors of CIL.

**Table #4.The distribution of study participants by diet, dietary habits and sleep disorders.**

| # | Characteristic | Group 1 - CIL | | Group 2 – Non-CIL | | OR (95%CI, p) |
|---|---|---|---|---|---|---|
| | | n= | % | n= | % | |
| 1 | Frequency of meal intake <3 | 48 | 44.44% | 364 | 46.37% | 0.9253 (0.6174-1.3868, p=0.7068) |
| 2 | **Protein-lack meals** | **54** | **50.00%** | **245** | **31.21%** | **2.2041(1.4682-3.3089, p=0.0001)** |
| 3 | Fat-rich meals | 6 | 5.56% | 49 | 6.24 % | 0.8836(0.3692-2.1146, p=0.7810) |
| 4 | Carbohydrate-rich meals | 5 | 4.63% | 49 | 6.24% | 0.7291(0.2840-1.8722, p=0.5115) |
| **5** | **Breakfast skipping** | **49** | **45.37%** | **251** | **31.97%** | **1.7669(1.1756-2.6556, p=0.0062)** |
| **6** | **Discrete sleep** | **21** | **19.44%** | **97** | **12.36%** | **1.7121(1.0160-2.8849, p=0.0434)** |
| **7** | **Insomnia** | **19** | **17.59%** | **55** | **7.01%** | **2.8335 (1.6087-4.9909, p=0.0003)** |

Vol. 5, No. 02; 2021

ISSN: 2581-3366

The results of case-control study of risk-factors from gynecologic history are given in Table #5. Table #5 shows that significant risk-factor is only frequent induced abortions (OR=2.1979).

**Table #5. Characteristics of gynecologic history of participants in groups.**

| # | Characteristic | Group 1 - CIL | | Group 2 – Non-CIL | | OR (95%CI, p) |
|---|---|---|---|---|---|---|
| | | n= | % | n= | | |
| 1 | Abortions and deliveries at early ages | 48 | 44.44% | 297 | 37.83% | 1.3145(0.8758-1.9728, p=0.1869) |
| 2 | Frequent abortions and deliveries | 46 | 42.59% | 371 | 47.26% | 0.8279(0.5515-1.2430, p=0.3624) |
| 3 | Spontaneous abortions | 23 | 21.30% | 149 | 18.98% | 1.1550(0.7047-1.8929, p=0.5675) |
| **4** | **Induced abortions** | **72** | **66.67%** | **374** | **47.64%** | **2.1979(1.4385-3.3581, p=0.0003)** |
| 5 | Infections | 3 | 2.54% | 45 | 5.73% | 0.4698(0.1434-1.5389, p=0.2121) |
| 6 | Oral Contraception | 3 | 2.54% | 28 | 3.57% | 0.7724(0.2308-2.5854, p=0.6753) |
| **7** | Intracervical contraception | 7 | 6.48% | 43 | 5.48% | 1.1959(0.5239-2.7302, p=0.6709) |
| 8 | Cervical Trauma | 2 | 1.85% | 31 | 3.95% | 0.4589 (0.1083-1.9453, p=0.2905) |

The analysis of cervical background diseases indicated that high percentage of erosions found in CIL cases compared to controls (28.70% vs. 14.52%; OR=2.4783, 95%CI – 1.5672-3.9191; p=0.0001).
The correlation of the development of CD and above mentioned all risk-factors established set of significant risk-factors. They are presented in Table #6.

These significant risk-factors were included in multiple logarithmic regression analysis as variables and CD – as outcome (marked as Y). First non-significant variable (risk-factor) was excluded from the model on the first stage. Finally, the β-coefficients of significant variables are presented in Table #7.

**Table #6. The results of correlation of the development of CD and significant risk-factors.**

| Risk-factor | marked as | Pearson coefficient r | p |
|---|---|---|---|
| Family income | X1 | - 0.090 | 0.007 |
| Protein-poor food | X2 | 0.095 | 0.004 |
| Frequency of food intake | X3 | - 0.080 | 0.016 |
| Breakfast skipping | X4 | - 0.090 | 0.007 |
| deliveries and abortions at the early youth | X5 | 0.090 | 0.007 |
| Frequent deliveries and abortions | X6 | 0.086 | 0.010 |
| Spontaneous abortions | X7 | 0.071 | 0.033 |

Vol. 5, No. 02; 2021

ISSN: 2581-3366

| | | | |
|---|---|---|---|
| Impaired Menstrual Cycle | X8 | - 0.085 | 0.010 |
| Cervical erosions | X9 | 0.102 | 0.002 |

**Table #7. β-Coefficients of significant variables included in multiple regression analysis.**

| | Coefficient | SE | t-test | P |
|---|---|---|---|---|
| β | 0,2300 | 0,0548 | 4,1940 | < 0.0001 |
| β1 | -0,0839 | 0,0314 | -2,6756 | 0.0076 |
| β2 | -0,2018 | 0,0727 | -2,7743 | 0.0057 |
| β4 | 0,0668 | 0,0233 | 2,8639 | 0.0043 |
| β5 | 0,0574 | 0,0226 | 2,5430 | 0.0112 |
| β8 | -0,1029 | 0,0384 | -2,6772 | 0.0076 |
| β9 | 0,1014 | 0,0297 | 3,4144 | 0.0007 |

Multiple regression analysis revealed significant risk-factors:

1. Family income;
2. Protein-poor food;
3. Breakfast skipping;
4. Deliveries and abortions in early youth;
5. Impaired menstrual cycle;
6. Cervical erosions;

Non-significant variables excluded from analysis were – the frequency of food intake, frequent abortions and deliveries, spontaneous abortions in anamnesis. Final view of functional relationship between outcome and variables is following:

$$\ln(Y)=0.230-0.084\cdot\ln(X1)-0.202\cdot\ln(X2)+0.067\cdot\ln(X4)+0.057\cdot\ln(X5)-0.103\cdot\ln(X8)+$$

$$+ 0.101\cdot\ln(X9)$$

$$Y=1.2586\cdot X_1^{-0.0839}\cdot X_2^{-0.2018}\cdot X_4^{0.0668}\cdot X_5^{0.0574}\cdot X_8^{-0.1029}\cdot X_9^{0.1014}$$

**Pearson correlation coefficient r= 0.2393 (p<0.0001).**

**Discussion**

The prevalence of CC is 10 times higher in low-income and middle-income countries (LMIC) compared to developed ones [23]. WHO advocates the approach “reveal and treat” in LMIC using visual examination of cervix by acetic acid and/or iodine dyeing followed by cryotherapy, and this approach would be implemented in many high-risk countries [24]. However, the efficacy of this primary screening method in the diagnosis of cervical precancerous conditions

Vol. 5, No. 02; 2021

ISSN: 2581-3366

and CC is significantly lower compared to HPV-testing. But we don't discuss the efficacy of screening methods. Our approach is pointed to reveal those risk-factors which can assist to reveal high-risk patients for these conditions.

Firstly, we would like to pay attention the energy imbalance. The responsibility for this condition has to take the metabolic characteristics and physical activity, also diet and dietary habits, nutrition, circadian rhythms and sleep. 11 year follow-up Me-Can cohort study results showed that the increase of BMI by 1 standard deviation increased the CC risk by 12%, hypertension – by 25%, and dyslipidemia – by 39% [25]. Our data showed that CIL patients were differed by significantly higher BMI compared to non-CIL participants.

Desynchronization between the central and peripheral clocks by altered timing of food intake can lead to uncoupling of peripheral clocks from the central pacemaker and is related to the development of metabolic disorders, including obesity and Type 2 diabetes [26,27]. It should be noted our results showed the significance of breakfast skipping in the development of CIL. However, the frequency of meal intake was not significantly altered between groups. Alterations in meal frequency and meal timing have the potential to influence energy and macronutrient intake. A regular meal pattern including breakfast consumption, consuming a higher proportion of energy early in the day, and regular fasting periods may provide physiological benefits such as reduced inflammation, improved circadian rhythmicity, increased autophagy and stress resistance, and modulation of the gut microbiota [28].

It is also interesting the comparison of macronutrient contents in groups. The percentage of participants with fat- and carbohydrate-rich diet was not altered in groups. However, lack of proteins in the diet of CIL patients was not significant factor. It should be also noted that the frequency of erosions was also higher in study group. This fact should be considered as the marker of estrogen deficiency. Sleep disorders were also significant risk-factor of CIL.

The developed energy imbalance causes the redistribution of remain resources towards providing the vital functions of organism [29]. So called secondary functions – ovulation, thyroid function - were sequestered; the concentrations of catabolic agents (estrogens, thyroid hormones and etc.) were decreased; cortisol levels and androgen/estrogen ratio were increased. The achievement of energy balance by proper diet and circadian rhythm has to normalize main basic criteria of many conditions – metabolites and weight excess [30,31].

**Conclusion**

Study results indicated the possible impact of energy imbalance on the development of CIL. Breakfast skipping, protein-lack diet, sleep disorders should be considered as risk-factors of energy imbalance, which is cause of altered metabolic characteristics, inflammation, obesity and insulin resistance. The unity of these conditions builds the basis for the development of CIL. Furthermore, energy imbalance should be the reason of decreased levels of estrogens.

Our data of multiple regression analysis revealed the significant risk-factors of CD development: family income, protein-poor food, breakfast skipping, deliveries and abortions in early youth,

Vol. 5, No. 02; 2021

ISSN: 2581-3366

impaired hormonal status, clinical sign – pain/discomfort/heaviness in lower abdomen. The energetic imbalance and impaired hormonal homeostasis are principal issues in the strategy of the CC prevention. However, the evidence of our results has to be confirmed by further valid randomized control trials.

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