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Effects of lifestyle on the occurrence of precancerous conditions and cervical cancer

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Summary

Cervical cancer is an important social problem. It is the fourth most widespread neoplasm in women, preceded by breast cancer, colon cancer, and lung cancer. The etiology of cervical cancer is certainly associated with a highly oncogenic type of human papillomavirus (HPV) and its long progression. The aim of this study was to assess the effect of lifestyle on the occurrence of precancerous conditions and cancer of the cervix. *Materials and Methods:* The study group comprised of 100 patients diagnosed with cervical intraepithelial neoplasia (CIN) grade III and diagnosed with cancer of the cervix. The control group consisted of 100 healthy women. In further analyses logistic regression and the χ^2 test were used. The χ^2 test is used to verify whether two variables are related to one another. Apart from verifying whether there is any relationship, attention is also paid to its strength. As the Pearson's χ^2 value cannot be used as the only measure of strength, Kendall's τ (tau) b and c coefficients were also employed. Each model had to be verified in terms of accuracy, thus the Hosmer-Lemeshow test was employed. This is a goodness-of-fit test that shows whether a given model is suitable for the data and the area under the curve (AUC). *Results:* The analysis demonstrated that women suffering from cervical cancer more frequently had previous gynaecological surgery (r = -0.19; p = 0.00003), had a history of cervical erosion (r = -0.21; p = 0.0088), received treatment due to reproductive tract infections (r = -0.29; p = 0.00004), declared being smokers (r = -0.14; p = 0.045), had hazardous sex (r = -0.28; p = 0.000001), used contraception (r = -0.16; p = 0.0017), and declared a family history of this type of neoplasm (r = -0.17; p = 0.00028). *Conclusions:* The main risk factor in the development of cervical cancer is having so-called hazardous sex; this behaviour is associated with a high, 21-fold increase in the risk of HPV infection, and thus the possible development of cervical cancer. The lifestyle-related risk factors analysed in the study, including: smoking cigarettes, using oral hormonal contraception, numerous reproductive tract infections and early sexual initiation, are all factors predisposing to the development of cancer. A history of cervical erosion has the most significant impact on the probability of cervical cancer incidence. This variable results in increasing the probability of this disease by a factor of 175.

Key words: Cervical cancer; Lifestyle; Genetic factors.

Introduction

Cervical cancer is an important social problem. It is the fourth most widespread neoplasm in women, preceded by breast cancer, colon cancer, and lung cancer and 528,000 new cases are found each year, and 266,000 deaths due to this neoplasm are observed. Its presence is the most significant in the developing countries of Sub-Saharan Africa. The majority of cases, nearly 70% in total, are observed in poorly developed areas, such as in the developing countries, with over 20% of all new cases being diagnosed in India [1].

According to the Polish National Cancer Registry, 2,783 new cases of cervical cancer and 1,669 deaths due to the disease were registered in Poland in 2012. Despite a persistent downward trend in general incidence, a visible upward trend in the incidence in increasingly younger age groups is presently being observed. In 2012, the standardized incidence ratio was 8.90, the mortality ratio was 4.83, and the five-year survival rate in Poland was 53%. According to these data, Poland has one of the highest rates in Europe regarding the prevalence of cervical cancer [2].

The etiology of cervical cancer is certainly associated with a highly oncogenic type of human papillomavirus (HPV) and its long progression. Apart from HPV infection, numerous other factors that contribute to the development of the disease are known, and these may be divided into two groups. The main factors contributing to the development of the disease include: a highly oncogenic HPV-type infection, age, early sexual initiation, a high number of sexual partners, a high number of births, smoking cigarettes, low socio-economic status, and pathological changes to the cervix. Probable factors include the use of oral hormonal contraception for many years, low antioxidant diet, frequent vaginal inflammations, and immunosuppression. When a woman is infected with HPV in favourable conditions, i.e. in the presence of one of the above factors, the neoplastic process begins in the cervix [3, 4]. If infection takes place when a woman is not exposed to any of the above risk factors, it takes the form of vaginal inflammation, visible in a cytological examination [3, 4].

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Table 1. — *Descriptive parameters (logistic regression analyses).*

Group	Variables	Median	Min.	Max.	SD	V	Skew	Kurtosis
Study group	Age (years)	47.8	23	76	13.61	0.69	-0.13	-1.14
	Body weight (kg)	68.12	44.00	103.00	14.39	21.12	0.90	0.01
	Height (m)	1.64	1.50	1.78	0.06	3.78	0.11	-0.46
	BMI	25.17	17.19	40.35	5.03	19.98	0.99	0.35
	Mother's age at the moment of birth	26.68	15.00	44.00	6.62	24.83	0.67	-0.34
	Father's age at the moment of birth	29.79	18.00	60.00	7.53	25.29	0.76	1.54
Control group	Age (years)	47.4	23	76	12.86	0.65	-0.06	-0.51
	Body weight (kg)	68.24	46.00	96.00	11.21	16.43	0.41	-0.08
	Height (m)	1.67	1.50	1.82	0.07	4.02	0.03	-0.51
	BMI	24.37	17.11	37.50	3.86	15.84	0.92	1.93
	Mother's age at the moment of birth	25.92	17.00	43.00	5.86	22.62	0.74	0.00
	Father's age at the moment of birth	29.61	19.00	45.00	6.01	20.30	0.57	-0.19

SD: standard deviation, Min.: minimum, Max.: maximum, V: coefficient of variation, Skew: skewness.

Table 2. — *Modelled probability of cervical cancer incidence according to risk factor.*

	Assessment	SD	Wald statistic	UCL 95.0%	LCL 95.0%	*p*	Odds ratio	OR confidence -95%	OR confidence +95%
Previous gynaecological surgeries	2.567	0.755	11.550	1.087	4.047	0.0007	13.025	2.964	57.242
Number of abrasion procedures	1.172	0.269	19.020	0.645	1.699	0.0000	3.229	1.907	5.468
Reproductive tract infections	1.211	0.298	16.493	0.627	1.796	0.0000	3.358	1.871	6.025
Smoking cigarettes	0.579	0.290	3.993	0.011	1.147	0.0457	1.784	1.011	3.149
Age of sexual initiation	-0.164	0.058	8.000	-0.278	-0.050	0.0047	0.849	0.758	0.951
Having hazardous sex	3.045	0.747	16.617	1.581	4.508	0.0000	21.000	4.858	90.776
Number of exposures of the pelvis to X-rays	0.607	0.204	8.820	0.206	1.007	0.0030	1.834	1.229	2.737
Use of contraception	0.713	0.303	5.550	0.120	1.306	0.0185	2.040	1.127	3.691
Family history of cervical cancer	1.853	0.566	10.708	0.743	2.963	0.0011	6.380	2.103	19.357

χ^2: *Pearson's test.*

Table 3. — *Modelled probability of cervical cancer incidence according to type of reproductive tract infection.*

	Level result	Assessment	SD	Wald statistic	UCL 95.0%	LCL 95.0%	*p*	Odds ratio	OR confidence -95%	OR confidence +95%
Type of infection	Fungal	1.585	0.435	13.261	0.732	2.438	0.0003	4.878	2.079	11.447
Type of infection	Bacterial	1.330	0.388	11.727	0.569	2.092	0.0006	3.782	1.766	8.099
Type of infection	Chlamydia	18.766	8968	0.000	-17559	17596	0.9983	141242496	0.000	
Type of infection	Mixed	0.563	0.662	0.723	-0.734	1.861	0.3950	1.756	0.480	6.428

χ^2*: Pearson's test.*

According to statistics, in approximately 80% of women, acute HPV infection resolves spontaneously, and no cervical changes are observed. In the remaining 20% of women it evolves into a chronic condition, and within two to four years cervical intraepithelial neoplasia (CIN) lesions develop in the cervix. However, in 15% of cases regression of the CIN lesions is observed, and the HPV infection clears spontaneously, while in 3-5% of women who did not see a gynaecologist and was not treated for cervical dysplasia, a cervical neoplasm develops after seven to 15 years [5].

The aim of this study was to assess the effect of genetic factors and lifestyle on the occurrence of precancerous conditions and cancer of the cervix.

Table 4. — *Pearson's χ^2 independence test. Measures of strength for the relationship between Kendall's τ b and b coefficients.*

Statistics	Statistics: group × previous gynaecological surgeries		
	χ^2	df	*p*
Pearson's χ^2	17.73520	1	0.00003
Kendall's tau b and c	b= -0.297785	c= -0.190000	

Materials and Methods

Surveys were conducted between April and July 2015 at the Laboratory of Cervical Pathophysiology of the Karol Marcinkowski Gynaecological and Obstetrical Clinical Hospital in Poznań and at the Greater Poland Centre of Oncology. The study group comprised of 100 patients diagnosed with CIN grade III and diagnosed with cancer of the cervix. The control group consisted of 100 healthy women who had regular follow-up visits in the outpatient clinic of the Gynaecological and Obstetrical Clinical Hospital in Poznań, i.e. once a year.

A fully anonymous survey questionnaire was used to obtain data for the statistical analysis. The survey comprised of 62 closed and open questions divided into four main parts. Questions in part one concerned basic demographic and social data, those in part two were related to obstetrical and gynaecological history, part three included questions regarding the genetic load, and part four was related to the patients' birth.

The statistical analyses were conducted using Statistica v. 12 software. In later analyses, logistic regression and the χ^2 test were used. The χ^2 test is used to verify whether two variables are related to one another. Apart from verifying whether there is any relationship, attention is also paid to its strength. As the Pearson's χ^2 value cannot be used as the only measure of strength, Kendall's τ (tau) b and c coefficients were also employed. A significance level of 0.05 was used for all analyses.

Each model had to be verified in terms of accuracy, thus the Hosmer-Lemeshow test was employed. This is a goodness-of-fit test that shows whether a given model is suitable for the data and the area under the curve (AUC). The goodness-of-fit assessment gave a Hosmer-Lemeshow test = 0.59, $p = 0.99$, and an AUC = 0.99, indicating that there were no grounds for considering the model ill-matched.

The research conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). All participants gave informed consent for the research, and that their anonymity was preserved.

Results

The basic characteristics of the study groups (Table 1) support the conclusion that the variable "age of the father at the moment of birth" was the most varied parameter at V=25.29% for the study group. Further analysis involved univariate logistic regression models, where the probability was modelled as belonging to the study group; that is women diagnosed with CIN III or cervical cancer.

The probability of developing cervical cancer was just over 13 times higher (OR= 13.025; 95% CI 2.964-57.242) in patients who had previous surgery in which the cervix was left intact (e.g. removal of uterine myomas or ovarian tumours). An increase in the number of curettage procedures by one unit resulted in a more than three-fold increase in the probability of cervical cancer (OR= 3.229; 95% CI 1.907-5.468). The probability of developing cervical cancer was almost 3.358 times higher (OR= 3.229; 95% CI 1.907-5.468) among women who had reproductive tract infections (bacterial, fungal or mixed infections) (Table 2).

A detailed analysis of the data regarding types of reproductive tract infections demonstrated that the risk of cervical cancer was greatly elevated by fungal infections, which caused about a five-fold increase in the probability of developing the disease, and by bacterial infection, due to which the incidence of cervical cancer was 3.8 times higher (Table 3).

Smoking cigarettes caused a nearly two-fold increase in the probability of developing a cervical neoplasm (OR = 1.78, 95% CI, 1.011-3.149). Regarding the age of sexual initiation, later initiation (by one age unit) the probability of developing cervical cancer was 1.17 times lower (OR = 0.849; 95% CI 0.758-0.951). Having hazardous sex (defined as sex without a condom, with random men) was a factor that significantly elevated the risk of developing cervical cancer. Hazardous sexual behaviour was associated with an incidence risk 21 times higher (OR = 21.000; 95% CI 4.858-90.776). Each additional exposure of the pelvis to X-ray radiation resulted in an approximately two-fold increase in the risk of developing the disease (OR = 1.83; 95% CI 1.229-2.737). Oral hormonal contraception was another factor associated with a statistically significant, over two-fold increase in the probability of cervical cancer (OR = 2.040; 95% CI 1.127-3.691). Cases of cervical cancer in the family (genetic background) was also a very important factor with the probability of developing the disease 6.38 times higher (OR = 6.380; 95% CI 2.103-19.357) (Table 2).

Further analyses were conducted on the basis of the χ^2 Pearson test of independence and strength of interdependence measures. The analysis demonstrated that women suffering from cervical cancer more frequently had previous gynaecological surgery ($r = -0.19$; $p = 0.00003$),

The analysis of the results presented in Table 4 allowed the rejection of the null hypothesis stating that the variables in question were independent, and for adopting an alternative hypothesis under which the variables were correlated ($p = 0.00003$). The analysis of the measures for strength of relationship revealed a weak negative correlation between the variables under analysis, with τ c = -0.19. Consequently, it was inferred that women suffering from cervical cancer had previous gynaecological surgeries significantly more frequently than women from the control group (11% *vs*. 1 %) and had a history of cervical erosion ($r = -0.21$; $p = 0.0088$),

The analysis of the measures for strength of relationship revealed a weak negative correlation between the variables in question. It was therefore inferred that women suffering from cervical cancer, including those in the study group, had a history of cervical erosion significantly more fre-

Table 5. — *LOGIT Probability modelling: GROUP = STUDY GROUP. Variable under analysis: "having hazardous sex".*

	Level result	Assessment	SD	Wald statistics	UCL 95.0%	LCL 95.0%	*p*	Odds ratio	Confidence OR -95%	Confidence OR +95%
Absolute term		-0.336	0.156	4.623	-0.643	-0.030	0.0315	0.714	0.526	0.971
Having hazardous sex	Yes	3.045	0.747	16.617	1.581	4.508	0.0000	21.000	4.858	90.776

Table 6. — *Multi-dimensional logistic regression model.*

Result	Level result	Column	Assessment	SD	Wald statistics	UCL 95.0%	LCL 95.0%	*p*	Odds ratio	Confidence OR -95%	Confidence OR +95%
Frequency of using public toilets	Often	3	10.479	3.762	7.757	3.105	17.83	0.005	35555	22.298	56697416
Frequency of using public toilets	Sometimes	4	2.444	1.597	2.342	-0.686	5.574	0.126	11.519	0.503	263.546
Number of abrasion procedures		5	6.232	2.182	8.161	1.957	10.58	0.004	509	7.075	36621
Diagnosed cervical erosion	No	6	-0.185	0.112	1.640	-0.393	0.123	0.299	0.673	0.311	1.138
Diagnosed cervical erosion	Yes	7	12.078	5.045	7.855	2.189	21.96	0.017	175876	8.922	34671507
Number of pelvic exposures to RTG		8	5.589	2.113	7.001	1.449	9.70	0.008	267.59	4.259	16814
Use of contraception	Yes	12	8.906	3.073	8.400	2.883	14.99	0.004	7378	17.872	3046244

quently (30%) than women from the control group (20%) , had received treatment due to reproductive tract infections (r = -0.29; p = 0.00004). Those women suffering from cervical cancer had a history of reproductive tract infections significantly more frequently than women from the control group (30% *vs*. 15%), declared being smokers (r = -0.14; p = 0.045), and had hazardous sex (r = -0.28; p = 0.000001),

The analysis of the measures for strength of relationship revealed a weak negative correlation between the variables under analysis, with τ = -0.28 (Table 5). The analysis led to the conclusion that women suffering from cervical cancer had declared having hazardous sex significantly more frequently (15%) than women from the control group (1%), used contraception (r = -0.16; p = 0.0017), and declared a family history of this type of neoplasm (r = -0.17; p = 0.00028),

The analysis of the results involving the parameter in question allowed the rejection of the null hypothesis stating that the variables analysed were independent, and for adopting an alternative hypothesis under which the variables were correlated (p = 0.00028). The analysis of the measures for strength of relationship revealed a weak negative correlation between the variables under analysis, with the ratio τ = -0.17. It was therefore inferred that women suffering from cervical cancer significantly more frequently declared a family history of this type of neoplasm (11%) as compared to the control group (2%). Further analyses enabled construction of a model using V-fold cross validation. The results are presented in Table 6.

Discussion

Demonstrating causal relationships in population studies regarding risk factors in cervical cancer poses a challenge for researchers, as there are numerous other possible explanations for the observed links between a risk factor and

cancer. Therefore, the development of statistical methods significantly facilitates data analysis and the identification of the causes.

Certainly, chronic HPV infection, diagnosed in 99.7% of patients, is an important risk factor in the development of cervical cancer [3]. The first person to observe a possible relationship between a HPV infection and cancer of the cervix was zur Hausen, a virologist [6]. This relationship is confirmed by the majority of epidemiological and clinical studies. Numerous studies demonstrated that virus types 16 and 18 are considerably more oncogenic than types 6 or 11 [7]. In this study only a small percentage of the survey subjects (34%) were aware of existing HPV infection. The risk of infection with the virus certainly increased if a woman had had hazardous sex, i.e. sexual intercourse with random men without using a condom. The analysis revealed that this factor was associated with a 21-fold increase in the risk of infection (Table 6). However, a condom does not provide protection against a HPV infection, due to possible transmission of the virus by contact with the labia, scrotum, or rectal area [8]. According to Shields *et al.* [9], cervical cancer is very rarely found in nuns and women living in celibacy, whereas it is significantly more often diagnosed in prostitutes. This fact indicates that sexual activity, age of the first sexual intercourse, and number of sexual partners considerably affect the risk of HPV infection and, as a result, the development of neoplastic disease [9, 10].

Use of oral hormonal contraception was another risk factor in cervical cancer, with a two-fold increase. In the study group the mean period of using hormonal contraception was 7.5 years. According to Professor Marek Sikorski, Vice-President of Polish Society of HPV Infection Prophylaxis [10], in women who used hormonal contraception, the risk of high grade neoplasia or invasive cervical cancer is higher. Moreover, the risk increases with the length of time of using hormonal contraceptives, and decreases proportionately to the time since discontinuing use of the same. However, studies on the frequency of HPV infections depending on the use of hormonal contraception did not confirm the effect of contraception on increasing the risk of infection [11]. Another study demonstrated a risk of CIN III and cervical cancer 2.8 to four times higher in women who already had HPV infection and who had used oral hormonal contraception for more than five to nine years [12]. The results of the statistical analysis in this study were similar to those obtained by other authors.

Another identified risk factor for cervical cancer was smoking cigarettes. Studies by Shields *et al.* [9] and Plummer *et al.* [11] confirmed a close relationship between habitual smoking, the increased risk of HPV infection, and the development of cervical cancer. They also found that smoking tobacco appears to be the most important environmental risk factor, which increases significantly along with the intensity and duration of the smoking habit.

Reproductive tract infections increase the risk of cervical cancer. Scientific reports mention the following infections as risk factors: *Chlamydiae trachomatis*, cytomegalovirus, *Neisseria gonorrhoeae*, *Trichomonas vaginalis,* and herpes simplex 2. In the present study, only one subject reported a *Chlamydiae trachomatis* infection. It has not yet been established whether the bacteria is merely a co-factor during an HPV infection, or the main factor promoting the development of the neoplasm. Due to the use of PCR to detect *Chlamydiae trachomatis* and HPV, Galijow *et al.* [13] demonstrated a relationship between this bacteria and the occurrence of LSIL and HSIL, but not of invasive cancer of the cervix. The study results suggest that *Chlamydiae trachomatis* may be considered a co-factor in HPV infection by creating an infection gate for the virus, i.e. a chronic inflammatory reaction process in the cervix.

Numerous authors emphasize the fact that early sexual initiation is a risk factor for the development of the neoplasm [14-16]. It is reported that the risk increases if the first sexual intercourse takes place before the age of 16 years [9]. The age of sexual initiation is emphasized as a risk factor because the highest risk of HPV infection correlates also with the highest metaplastic activity in the cervical epithelium, occurring at a young age, during the first pregnancy. The risk decreases after menopause, reducing the risk of infection [9].

Another risk factor studied was genetic predisposition. The statistical analysis demonstrated that this factor was associated with a 6.38-fold higher risk of the development of the neoplasm in women, although the available publications rarely mention this aspect as a risk factor. In her study, Evans [17] emphasized that there was no evidence of genes predisposing towards cervical cancer, and she stipulated that the increased incidence of this neoplasm among family members was more likely to be associated with environmental factors and higher exposure to HPV viruses. However, Evans also emphasized the importance of the fact that in those families a gene predisposing to higher sensitivity to HPV viruses may occur and may be inherited [17].

Investigations into the complex phenomenon of projecting the probability of cervical cancer incidence or the incidence of CIN grade III in one-dimensional terms served as the basis for constructing a multi-dimensional model. This model was based on logistic regression for binary dependent variables, where the actual occurrence, i.e. the modelled results for women with CIN III and cervical cancer diagnosis, served as the model class. In the course of model development, V-fold cross validation was employed. A history of cervical erosion was observed to have the largest impact on the probability of cervical cancer incidence. This variable results in increasing the probability of this disease by a factor of 175.

In summing up, only a current HPV infection can form a source for the development of cervical cancer. None of the above risk factors resulted in cervical cancer in patients without the presence of a HPV infection.

Conclusions

Cancer of the cervix is a neoplasm that develops on the basis of a chronic HPV virus infection. The main risk factor in the development of cervical cancer is having so-called hazardous sex; this behaviour is associated with a high, 21-fold increase in the risk of HPV infection, and thus the possible development of cervical cancer.

The lifestyle-related risk factors analysed in the study, including: smoking cigarettes, using oral hormonal contraception, numerous reproductive tract infections, and early sexual initiation, are all factors predisposing to the development of cancer.

A history of cervical erosion has the most significant impact on the probability of cervical cancer incidence. This variable results in increasing the probability of this disease by a factor of 175.

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All participants voluntarily agreed to participate in the study. Data confidentiality and survey procedures were reviewed with each participant before the questionnaire. Researchers assured participants that the contents of the questionnaire would be used solely for research purposes. The patients gave written obtained consent for this study. Ethics committees approved this consent procedure.

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