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Cervical carcinogenesis associated with the use of combined oral contraceptives: is there a relationship?

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ABSTRACT

BACKGROUND: Cervical cancer is one of the leading cancers in women of reproductive age. The etiological role of the human papillomavirus (HPV) in cancer development is long known and undisputed. However, owing to the widespread use of combined oral contraceptives (COCs), scientists actively investigate possible mechanisms of interrelation between sex steroids and HPV in terms of cervical cancer risk.

AIM: This study aimed to assess the risk of cervical cancer in women of reproductive age, depending on the use of COCs for different durations.

MATERIALS AND METHODS: The study included 411 patients of reproductive age who were treated at the Center for Gynecology and Reproductive Technologies of the Russian Ministry of Health and the Department of Oncogynecology at the University Clinical Hospital No. 4 of the I.M. Sechenov First Moscow State Medical University between January 2015 and December 2021. All patients were divided into two groups. The study group included 291 patients with verified cervical cancer, and the control group included 120 patients without cancer.

RESULTS: The study group was significantly more likely to take COCs (56, or 19.2%) than the control group (11, or 6.5%; p=0.018). In addition, the study group had significantly longer treatment durations (p=0.011). Overweight (n=52, or 17.9%) and grade II obesity (n=11, or 3.8%, vs. 0; p=0.03) were significantly more common in the study group than in the control group (n=8, or 4.7%; p=0.003). The result of the multivariate analysis showed that taking COCs negatively affect cervical cancer development (p=0.018; odds ratio (OR) 1.230; CI 1.064–1.423). The receiver operating characteristic analysis revealed that the use of COCs has a high predictive value for determining the risk of cervical cancer (area under the curve, AUC=0.742); the sensitivity and specificity of this predictor were 74.07% and 72.73%, respectively. In the assessment on the effect of duration of COC use on the risk of cervical cancer, the results showed that total use of COCs for over 7 years was associated with a higher risk of cervical cancer development (p=0.010; OR 1.68; CI 1.1–2.5).

CONCLUSIONS: Prescribing COCs in patients with HPV infection requires a personalized approach to consider etiologic factors of cervical cancer and reduce possible carcinogenic risks.

Keywords: cervical cancer; human papillomavirus; combined oral contraceptives; endogenous estradiol.

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Цервикальный канцерогенез, ассоциированный с приёмом комбинированных оральных контрацептивов: есть ли взаимосвязь?

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АННОТАЦИЯ

Введение. Рак шейки матки — одна из ведущих локализаций рака у женщин репродуктивного возраста. Этиологическая роль вируса папилломы человека в развитии онкологических заболеваний известна давно и не вызывает сомнений. Однако ввиду широко распространённого применения комбинированных оральных контрацептивов (КОК) учёные активно изучают возможные механизмы взаимосвязи половых стероидов и вируса папилломы человека (ВПЧ) с точки зрения риска развития рака шейки матки (РШМ).

Цель работы — оценить риск развития рака шейки матки у женщин репродуктивного возраста с учётом приёма КОК различной длительности.

Материалы и методы. В исследование включили 411 пациенток репродуктивного возраста, проходивших лечение в Центре гинекологии и репродуктивных технологий НМИЦ «Лечебно-реабилитационный центр» Минздрава России и в отделении онкогинекологии Университетской клинической больницы № 4 Первого МГМУ им. И.М. Сеченова, госпитализированных в период с января 2015 по декабрь 2021 года. Всех пациенток разделили на две группы: в основную группу включили 291 пациентку с верифицированным РШМ, в группу контроля вошли 120 пациенток без онкологической патологии.

Результаты. Пациентки с РШМ достоверно чаще принимали КОК (56, или 19,2%), чем пациентки в группе контроля (11, или 6,5%; p=0,018), у пациенток с РШМ также отмечен достоверно более длительный приём препаратов (p=0,011).

В группе пациенток с РШМ достоверно чаще выявлена избыточная масса тела (52 пациентки, или 17,9%), чем в контрольной группе (8, или 4,7%; p=0,003), и ожирение II степени (11, или 3,8% против 0; p=0,03), соответственно. Результат многофакторного анализа показал, что приём КОК оказывает отрицательное влияние на риск развития РШМ (p=0,018; odds ratio (OP) 1,230; ДИ 1,064–1,423). По результатам ROC-анализа установлено, что приём КОК обладает высокой прогностической значимостью для определения риска развития РШМ (AUC=0,742); чувствительность этого предиктора составляет 74,07%, специфичность 72,73%. Оценка влияния длительности приёма КОК на риск развития РШМ показала, что приём КОК суммарно более 7 лет ассоциирован с более высоким риском развития онкологии шейки матки (p=0,010; ОР 1,68; ДИ 1,1–2,5).

Заключение. Назначение КОК у ВПЧ-положительных пациенток требует персонифицированного подхода с целью учёта этиологических факторов рака шейки матки и снижения возможных канцерогенных рисков.

Ключевые слова: рак шейки матки; вирус папилломы человека; комбинированные оральные контрацептивы (КОК); эндогенный эстрадиол.

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BACKGROUND

Despite improvements in screening and prevention methods, cervical cancer (CC) remains a global problem. According to the International Agency for Research on Cancer (IARC), 604,127 new cases of CC were registered worldwide in 2020. This cancer type is the leading one in women of reproductive age. Although the main etiological role of human papillomavirus (HPV) in CC development has been proven, cofactors such as immunosuppression (particularly human immunodeficiency virus, HIV), smoking, sexually transmitted infections, and use of combined oral contraceptives (COCs) have also been identified. The IARC classifies 12 HPV strains as group1 carcinogens in CC development, along with COCs, whose use is associated not only with the risk of preinvasive and invasive forms of CC but also with liver cancer and breast cancer [1–2].

Indirect evidence of a possible relationship between taking COCs and the risk of developing CC has been obtained from epidemiological studies that have shown that taking COCs increases the risk of CC in HPV-positive women [3]. Currently, various COCs are available; however, they all contain progestogens and estrogens. Estrogens and progestogens can regulate cell growth and proliferation, and this proliferative influence may promote carcinogenesis in susceptible cervical tissues.

After a detailed analysis of the results of recent studies, we conducted this study to assess the risk of CC in women of reproductive age, considering the use of COCs of various durations.

MATERIALS AND METHODS

The study included 411 patients of reproductive age who were treated at the Center for Gynecology and Reproductive Technologies of the National Medical Research Center "Treatment and Rehabilitation Center" of the Ministry of Health of Russia and at the Department of Oncogynecology of the University Clinical Hospital No. 4 of the I.M. Sechenov First Moscow State Medical University, hospitalized from January 2015 to December 2021. All patients were divided into two groups: the main group included 291 patients with verified CC, and the control group included 120 patients without cancer pathology. All patients underwent HPV diagnostic examination using polymerase chain reaction (PCR). The study materials were scrapings of the epithelium of the cervical canal for cytological examination. Scrapings of the cervical canal epithelium for PCR were collected using Dacron brushes into 1.5-mL Eppendorf tubes with a transport medium. All postoperative preparations of the removed tissues were delivered to the anatomic pathology department and the immunohistochemical research laboratory of the National Medical Research Center "Treatment and Rehabilitation Center" of the Russian Ministry of Health for subsequent histological examination to verify the diagnosis and for immunohistochemical examination.

The CC stage was determined based on the International Federation of Gynecology and Obstetrics classification (2019) and the international classification of stages of malignant neoplasms (TNM, 8th edition, 2016) [4].

The main group included women of reproductive age diagnosed with histologically verified CC. The control group included women of reproductive age without CC in history and at the time of the study. Women who were <18 and >48 years old, were pregnant, had hormone-dependent diseases of the female genital organs, refused participation in the study, and had an indication of the use of Mirena intrauterine system were excluded.

This study was performed as part of L.A. Klyukina's thesis work, and its implementation was approved by the local ethics committee of I.M. Sechenov First Moscow State Medical University (extract from the LEC protocol dated 02/11/2021, No. 03-21). All study participants signed the necessary documents and provided voluntary informed consent to participate in the study and publish the data obtained.

Statistical data processing

IBM SPSS Statistics version 23.0 was used for the statistical analysis of the study data. The significance of the normal distribution of indicators was determined using the Kolmogorov–Smirnov test. If the distribution of the parameter was normal, the mean value and standard error of the mean were determined. Otherwise, the quartile range (25th, 50th, and 75th percentiles) was determined. Digital results were described using the arithmetic mean M and its root-mean-square deviation ±σ. Correlations were assessed using the Spearman and Pearson methods.

Statistical analysis was performed using the nonparametric Mann–Whitney U test. The statistical significance of differences between qualitative indicators was assessed using the χ^2 test. The results of the statistical studies were considered significant if the probability of error was p <0.05, which corresponds to the criteria accepted in biomedical research. To determine the effect of taking hormonal drugs on the development of events, multivariate regression logistic analysis was used. Receiver operating characteristics (ROC) analysis was performed to evaluate marker sensitivity and specificity.

RESULTS

The average age of the patients in the main and control groups was 41.55 ± 9.94 and 42.09 ± 9.17 years, respectively. In the study groups, the clinical and clinical morphological data of the patients were studied (Table 1).

According to the somatic analysis, differences in body mass index (BMI) were significant between the studied groups (p=0.001). An overweight status was significantly more common in the main group (n=52, or 17.9%) than in the control group (n=8, or 6.7%; p=0.003), as was degree II obesity (n=11, or 3.8%, versus n=0, or 0%, respectively; p=0.031).

Table 1. Clinical characteristics of patients in the study groups

Indicators	Main group, *n* (%)	Control group, *n* (%)	*p*
Number of patients	291 (100%)	120 (100%)	–
Age, years	41.55±9.94	42.09±9.17	0.334
HPV type 16 (PCR)	61 (21%)	7 (5.8%)	<0.001
HPV type 18 (PCR)	24 (8.2%)	5 (4.2%)	0.142
HPV type 31 (PCR)	17 (5.8%)	5 (4.2%)	0.493
HPV type 39 (PCR)	15 (5.2%)	5 (4.2%)	0.672
HPV type 52 (PCR)	10 (3.4%)	5 (4.2%)	0.720
Tis	57 (19.6%)	–	–
T1a	33 (11.3%)	–	–
T1a1	37 (12.7%)	–	–
T1a2	23 (7.9%)	–	–
T1b	15 (5.2%)	–	–
T1b1	27 (9.3%)	–	–
T1b2	23 (7.9%)	–	–
T2a	24 (8.2%)	–	–
T2a1	16 (5.5%)	–	–
T2a2	11 (3.8%)	–	–
T2b	17 (5.8%)	–	–
T3a	5 (1.7%)	–	–
T3b	4 (1.4%)	–	–
Squamous cell carcinoma	287 (98.6%)	–	–
Adenocarcinoma	4 (1.4%)	–	–
G1 (high grade)	254 (87.3%)	–	–
G2 (moderate grade)	31 (10.7%)	–	–
G3 (low grade)	4 (1.4%)	–	–
Negative family history	9 (3.1%)	3 (2.5%)	0.746
Timely age of menarche	290 (99.7%)	119 (99.2%)	0.517
Cycle regularity	285 (97.9%)	116 (96.7%)	0.447
Infertility	6 (2.1%)	2 (1.7%)	0.792
Pregnancy, Me [Q25–Q75]	2.56 [1; 4]	2.81 [2; 4]	0.106
Childbirth, Me [Q25–Q75]	1.26 [1; 2]	1.45 [1; 2]	0.036
Abortions, Me [Q25–Q75]	1.31 [0; 2]	1.35 [0; 2]	0.657
Body mass index (BMI), kg/m^2	23.98 [20.4; 26.1]	22.44 [19.65; 24.3]	0.001
Excess body weight, the number of patients	52 (17.9%)	8 (6.7%)	0.003
Degree I obesity	19 (6.5%)	4 (3.3%)	0.201
Degree II obesity	11 (3.8%)	0 (0%)	0.031
Degree III obesity	1 (0.3%)	0 (0%)	0.521
Cervical erosion	19 (6.5%)	10 (8.3%)	0.517

End of the Table 1

Indicators	Main group, *n* (%)	Control group, *n* (%)	*p*
Cervical leukoplakia	12 (4.1%)	5 (4.2%)	0.984
Hysterocervicorrhesis during childbirth	24 (8.2%)	8 (6.7%)	0.587
Mild cervical dysplasia	13 (4.5%)	3 (2.5%)	0.349
Moderate and severe cervical dysplasia	16 (5.5%)	1 (0.8%)	0.031
Herpes simplex virus types 1 and 2	10 (3.4%)	3 (2.5%)	0.622
Trichomonas vaginalis	3 (1%)	1 (0.8%)	0.853
Neisseria gonorrhoeae	2 (0.7%)	0 (0%)	0.363
Chlamydia trachomatis	12 (4.1%)	4 (3.3%)	0.707
Mycoplasma genitalium	4 (1.4%)	3 (2.5%)	0.423
Paroxysmal form of atrial fibrillation	4 (1.4%)	0 (0%)	0.197
Bronchial asthma	5 (1.7%)	2 (1.7%)	0.971
Dyslipidemia	5 (1.7%)	3 (2.5%)	0.602
Liver pathology	4 (1.4%)	2 (1.7%)	0.823
Kidney pathology	6 (2.1%)	4 (3.3%)	0.447
Cholelithiasis (CL)	7 (2.4%)	4 (3.3%)	0.597
Chronic gastritis	16 (5.5%)	4 (3.3%)	0.354
Duodenal ulcer	6 (2.1%)	2 (1.7%)	0.792
Gastric ulcer	4 (1.4%)	0 (0%)	0.197
Pathology of the thyroid gland	7 (2.4%)	5 (4.2%)	0.336
Diabetes mellitus	4 (1.4%)	1 (0.8%)	0.649
Hypertension	9 (3.1%)	5 (4.2%)	0.586

Note. ВПЧ — human papillomavirus; ПЦР — polymerase chain reaction; Me — average value; Q25, Q75 — 25th and 75th quartiles; Tis, T1a, T1a1, T1a2, T1b, T1b1, T1b2, T2a, T2a1, T2a2, T2b, T3a, T3b — stages of cervical cancer; G1, G2, G3 — indicators of the degree of differentiation of the tumor.

The studied patients had significant differences in reproductive history. Parity was significantly different between the study groups (p=0.036). Precancerous changes in the cervix according to medical history were significantly different between the groups. Moderate and severe cervical dysplasia was registered significantly more often in the main group (n=16, or 5.5%) than in the control group (n=1, or 0.8%) (p=0.031).

In the main group, 127 (43.6%) CC cases were associated with the persistence of highly oncogenic HPV types.

Depending on the HPV status, the main and control groups were divided into those who took COCs (n=41) and those who did not (n=36) (Fig. 1).

In the COC group, CC was verified in 29 (70.7%) patients but was not verified according to histological examination in 12 (29.2%) patients, and the difference was significant (p=0.049). In the non-COC group, CC was registered in 8 (22.2%) patients but was not detected in 28 (77.7%) patients according to histological examination.

In the main group (n=291), 56 (19.2%) patients took COCs, and in the control group, 11 (9.2%) patients took COCs (n=120) (p=0.018), indicating that COC intake was significantly

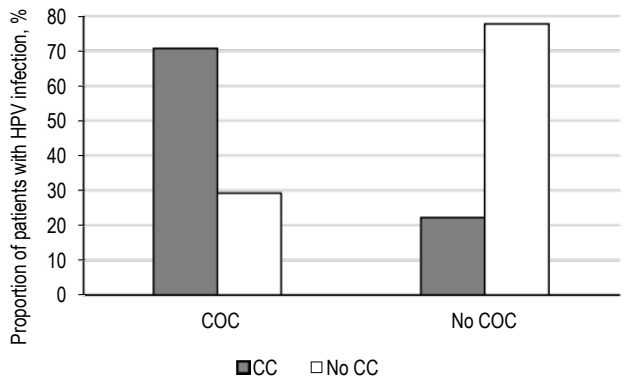

Fig. 1. Patients of the study groups with a positive HPV infection status who took and did not take combined oral contraceptives (COC).
CC — cervical cancer.

more often noted in the main group. In the COC group, all patients took low-dose drugs that contained no more than 30–35 μg of estradiol per day.

The main group also had a significantly longer intake of hormonal drugs (3.04 ± 0.42 versus 1.24 ± 0.25 years) than the control group (p=0.011).

Table 2 presents the clinical and morphological characteristics of patients with verified CC who were taking COCs.

To assess the effect of taking COCs on the risk of CC development, a multivariate analysis was performed, which revealed that COC intake had a negative effect, increasing the CC risk (p=0.018; risk ratio [RR] 1.230; confidence interval [CI] 1.064–1.423), and affected the development of stage T1b1 (p=0.009).

Table 2. Clinical and morphological features of patients with verified cervical cancer who took COC

Clinical and morphological aspects	Main group (n=291), n (%)	Including those who took COCs (n=56), n (%)
Age, years	41.55±9.94	–
HPV type 16 (PCR)	61 (21%)	20 (36%)
HPV type 18 (PCR)	24 (8.2%)	5 (9%)
HPV type 31 (PCR)	17 (5.8%)	6 (10.7%)
HPV type 39 (PCR)	15 (5.2%)	2 (3.6%)
HPV type 52 (PCR)	10 (3.4%)	2 (3.6%)
Tis	57 (19.6%)	7 (12.5%)
T1a	33 (11.3%)	10 (18%)
T1a1	37 (12.7%)	4 (7.1%)
T1a2	23 (7.9%)	6 (10.7%)
T1b	15 (5.2%)	4 (7.1%)
T1b1	27 (9.3%)	12 (21.4%)
T1b2	23 (7.9%)	5 (9%)
T2a	24 (8.2%)	3 (5.3%)
T2a1	16 (5.5%)	2 (3.6%)
T2a2	11 (3.8%)	2 (3.6%)
T2b	17 (5.8%)	1 (1.8%)
T3a	5 (1.7%)	1 (1.8%)
T3b	4 (1.4%)	1 (1.8%)
Squamous cell carcinoma	287 (98.6%)	56 (100%)
Adenocarcinoma	4 (1.4%)	–
G1	254 (87.3%)	47 (84%)
G2	31 (10.7%)	8 (14.3%)
G3	4 (1.4%)	1 (1.8%)

Note. ВПЧ — human papillomavirus; ПЦР — polymerase chain reaction; Tis, T1a, T1a1, T1a2, T1b, T1b1, T1b2, T2a, T2a1, T2a2, T2b, T3a, T3b — stages of cervical cancer; G1, G2, G3 — indicators of the degree of differentiation of the tumor.

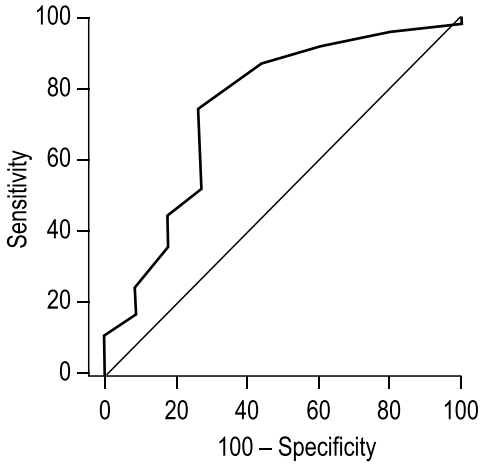

Fig. 2. ROC-risk curve for cervical cancer when taking combined oral contraceptives.

To assess marker sensitivity and specificity, ROC analysis was performed, and its results revealed that COC intake had a high prognostic value for determining the CC risk (area under the curve=0.742). The sensitivity and specificity of this predictor were 74.07% and 72.73%, respectively (Fig. 2).

An assessment of the effect of the duration of COC intake on the risk of CC development revealed that COC intake for a total of >7 years was associated with a higher risk of CC development (p=0.010; RR 1.68; CI 1.1–2.5).

DISCUSSION

HPV plays the main etiological role in CC development, particularly HPV types 16 and 18. The stable persistence of these HPV types is associated with the development of invasive CC in 70% of cases [5]. According to the literature, 90% of cases of the squamous cell type of CC are HPV-positive, whereas 86% of cases of cervical adenocarcinoma are HPV-positive [6]. In this study, 43.6% of CC cases are associated with persistent HPV, with type 16 registered in 48% and type 18 in 8.2% of cases.

Taking into account the leading role of HPV infection in CC development, the findings about the effect of COC intake on the risk of HPV infection and viral progression are interesting. Scientists have proposed several hypotheses about the possible mutual influence of these factors on CC risk. First, when taking COCs, the probability of HPV infection increases because of sexual behavior. Second, the cervical epithelium is sensitive to estrogens and progesterone, and COCs may contribute to the biological vulnerability of the cervix [7]. Thus, several studies have reported that COC intake for 1 year leads to an increase in the size of cervical ectopia, thereby facilitating infection of endocervical cells with latent strains of HPV infection deep in the crypts of the glands [8–9].

Third, COC components can change the metabolic and proliferative activities of infected cervical cells. Samir et al. noted that when using COCs, the mechanism of cervical carcinogenesis can be induced by the overproduction of cyclooxygenase-2 (COX-2) and an increase in the level of interleukin-10 (IL-10) [10]. In CC, COX-2 overexpression is a poor prognostic marker because it is associated with an increased risk of tumor relapse and metastasis [11], suppression of apoptosis, and increased tumor invasion into lymph nodes and parametrial tissue [12].

A study of the changes in the metabolic activity of the infected cervical epithelial cells under the influence of oral contraceptives showed that one of the main ways of malignancy of HPV-infected cervical cells is that the virus modifies cellular metabolism and the cell acquires the ability to ensure the conversion of estradiol into the "aggressive metabolite" 16a-hydroxysterone (16a-OH). This metabolite is a direct activator of the E7 oncogene expression, which is responsible for the malignant transformation of cervical cells [13].

One of the possible mechanisms for CC development may be a synergistic interaction between HPV infection and exogenous sex steroids, estrogens and progestogens, which, by interacting with the corresponding cervical receptors (mainly progesterone receptors), influence the course of HPV infection, namely, they enhance the expression of HPV-16 oncoproteins E6 and E7, stimulating the degradation of the tumor suppressor protein p53, increasing the ability of viral DNA to transform cells, and inducing the oncogenic transformation of infected cells [14–15].

In this study, CC was verified in 29 (70.7%) patients who had a positive HPV status and took COCs. In 12 (29.2%) patients, CC was not verified according to histological examination. These data were statistically significant (p=0.049) and are consistent with the results of other studies [3, 16].

S. Fischer et al. conducted the first prospective study of the effect of sex steroids on the persistence of highly oncogenic HPV strains [17]. They revealed that HPV-positive women had higher levels of morning (p=0.007; partial eta^2=0.221) and daily (p <0.001; partial eta^2=0.442) estradiol levels than HPV-negative women. A potential explanation is that estradiol may impair innate and adaptive immune responses, thereby contributing to the maintenance of high levels of highly oncogenic HPV strains. Indeed, an original study in healthy women demonstrated that in vitro stimulation of HPV type 16 virus-like particles in combination with the exogenous administration of estradiol and progesterone decreased the production of proinflammatory cytokines while increasing the levels of anti-inflammatory cytokines and transcriptional regulators of regulatory T cells [18].

Evidence supporting this hypothesis comes from in vivo experiments in mice transgenic for the E6 and E7 oncoproteins, in whom CC developed upon estrogen administration [19]. Thus, researchers have shown for the first time that endogenous estradiol and the persistence of highly oncogenic HPV strains can increase the risk of CC occurrence.

As regards endogenous estradiol, significant differences in BMI were found between the studied groups of patients (p=0.001). An overweight status was significantly more common in the main group (n=52, or 17.9%) than in the control group (n=8, or 6.7%) (p=0.003), and degree II obesity was registered in 11 (3.8%) patients versus 0 (p=0.031), respectively.

Scientists note that long-term intake of COCs by HPV-positive women is a particularly negative factor. A recent cohort study in Denmark included nearly two million women of reproductive age. An increased risk of CC was registered in women who were taking COCs (RR 1.40; 95% CI 1.28–1.53). The authors noted that the risk of CC in women who took and did not take COCs was comparable (the analysis was performed for adenocarcinoma and squamous cell CC). This risk was more pronounced with longer COC intake and decreased after its discontinuation [20].

Similar evidence of an increased CC risk was obtained from the results of a meta-analysis, which analyzed 24 studies that included nearly 17,000 female patients with cervical malignant neoplasms and approximately 36,000 patients in the control groups; the risk of invasive cervical malignant neoplasm was increased among regular users of COCs with long-term period of use the RR with ⩾5 years of COC use when compared with cases when COCs were never used was 1.90 (95% CI 1.69–2.13). An identical risk model was revealed for invasive and preinvasive forms of CC as well as high-risk HPV carriers [21].

The correlation between the duration of COC intake and an increased risk of CC in women with HPV infection was also confirmed in a large study by J.M. Gierisch et al. J.M. [22]. J.S. Smith et al. revealed that in the presence of HPV infection, the CC risk increased after 5 years of taking COCs from 0.9 to 1.3, and after 10 years of taking COCs, it reached 2.5, compared with the group of HPV-negative women, where this risk increased from 0.9 to 1.3 only after 10 years of taking COCs [23].

In this study, a correlation was found between the duration of COC use and the risk of CC development. According to our data, taking COCs for >7 years is associated with a higher risk of CC development (p=0.010; RR 1.68; CI 1.1–2.5).

CONCLUSION

According to the results of studies around the world, COC intake should be considered a risk factor for cervical carcinogenesis, particularly when high levels of endogenous estrogens and the persistence of highly oncogenic strains of HPV infection are detected. Further study of the mechanisms of CC formation in HPV-positive women who were taking COCs will enable the standardization of the algorithm for examining women before prescribing drugs in this group to reduce possible cancer risks.

ДОПОЛНИТЕЛЬНО

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Финансирование. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Этическое утверждение. Исследование выполнялось в рамках диссертационной работы Л.А. Клюкиной и его проведение согласовано с локальным этическим комитетом Первого Московского государственного медицинского университета им. И.М. Сеченова (выписка из протокола ЛЭК от 11.02.2021 г. № 03-21).

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ADDITIONAL INFO

Author's contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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Ethics approval. The study was carried out within the framework of L.A. Klyukina's dissertation work and its conduct was coordinated with the Local Ethics Committee of the I.M. Sechenov First Moscow State Medical University (extract from the LEC Protocol No. 03-21 dated February 11, 2021).

Consent for publication. All the patients who participated in the study signed the necessary documents on voluntary informed consent to participate in the study and the use of the received data.

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