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Debate on the oncologic potential of sex steroid preparations

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ABSTRACT

Background. Thanks to numerous worldwide studies, the significant contribution of the hormonal component to the oncological risks of the organs of the female reproductive system is beyond doubt. Of great interest is the analysis of world research on the oncological potential of hormonal drugs, namely COCs and MGT, since this issue continues to be one of the most complex and controversial.

Aim. This study aimed to contribution of hormonal factors to the development of cancer of the female reproductive system, namely breast, cervical, endometrial and ovarian cancers.

Materials and Methods. The study was conducted on the basis of the Center of Gynecology and Reproductive Technologies of the FSAU "National Medical Research Center "Treatment and Rehabilitation Center" of the Ministry of Health of the Russian Federation, the Department of Oncogynecology of the University Clinical Hospital No. 4 of the I.M. Sechenov First Moscow State Medical University. The analysis of medical documentation for the period from January 2015 to December 2021 was carried out. The study included 1842 patients with verified oncological disease of the female reproductive system, who had a history of taking hormonal drugs of the following pharmacological groups: hormonal contraceptives, menopausal hormone therapy drugs. The age of all patients ranged from 26 to 83 years (mean age 51.98±10.3 years). The control group consisted of 611 patients without oncological diseases, who have a history of indications for taking hormonal drugs of these pharmacological groups.

Results. When assessing the effect of the duration of MGT intake on the risk of developing breast cancer, it was found that MGT intake for a total of more than 6 years was associated with a higher risk of developing breast cancer (HR 1.18; CI 1.02–1.36; p <0.001). Using the Wald method, we found that the probability of developing breast cancer is associated with a BMI of more than 25 kg/m^2 and long-term intake of combined MGT for a total of more than 6 years. When assessing the effect of the duration of MGT intake on the risk of developing RTM, it was found that MGT intake for a total of more than 6 years was associated with a higher risk of developing RTM (HR 1,432; CI 1,172–1,750; p <0.001). Using the Wald method, we found that the probability of developing RTM is associated with the presence of a BMI of more than 25 kg/m^2, prolonged MGT intake for a total of more than 6 years and the presence of endometrial hyperplastic processes, adenomyosis, hypertension in the anamnesis. When assessing the effect of the duration of COC intake on the risk of developing breast cancer, it was found that taking COC for a total of more than 7 years was associated with a higher risk of developing breast cancer (HR 1.68; CI 1.1–2.5; p=0.010). According to the Wald method, it was revealed that the probability of developing breast cancer is associated with the presence of HPV type 16, a BMI of more than 25 kg/m^2 and prolonged intake of COCs for a total of more than 7 years. When assessing the effect of the duration of MGT intake on the risk of developing PC, it was found that MGT intake for a total of more than 9 years was associated with a higher risk of developing PC (HR 1.65; CI 1.2–2.3; p=0.010). Using the Wald method, we found that the probability of developing RYA is associated with the presence of a BMI of more than 25 kg/m^2, MGT intake and the presence of endometrial hyperplastic processes in the anamnesis.

Conclusions. With prolonged use of sex steroids, there is a tendency to increase the risk of developing cancer of the female reproductive system. Careful follow-up and limitation of the duration of taking sex steroids in risk groups will reduce carcinogenic risks.

Keywords: hormonal contraceptives; menopausal hormone therapy drugs; endometrial cancer; breast cancer; cervical cancer; ovarian cancer.

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Дискуссионные вопросы онкологического потенциала препаратов половых стероидов

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АННОТАЦИЯ

Введение. Благодаря многочисленным общемировым исследованиям весомый вклад гормональной составляющей в онкологические риски органов женской репродуктивной системы не вызывает сомнений. Большой интерес представляет анализ мировых исследований по онкологическому потенциалу гормональных препаратов — комбинированных оральных контрацептивов (КОК) и менопаузальной гормональной терапии (МГТ), так как данный вопрос по-прежнему остаётся одним из самых сложных и противоречивых.

Цель работы — изучить частоту и особенности рака органов женской репродуктивной системы, а именно: молочной железы, шейки матки, эндометрия и яичников, у женщин, принимавших препараты половых стероидов.

Материалы и методы. Исследование проводилось на базе центра гинекологии и репродуктивных технологий «Национальный медицинский исследовательский центр «Лечебно-реабилитационный центр» Минздрава РФ, отделения онкогинекологии Университетской клинической больницы № 4 Первого Московского государственного медицинского университета им. И.М. Сеченова. Авторы проводили анализ медицинской документации за период с января 2015 года по декабрь 2021 года. В исследование вошли 1842 больные с верифицированным онкологическим заболеванием органов женской репродуктивной системы, у которых в анамнезе отмечен приём гормональных препаратов следующих фармакологических групп: гормональные контрацептивы, препараты МГТ. Возраст всех пациенток составил от 26 до 83 лет (средний возраст 51,98±10,3 года). Группу контроля составили 611 пациенток без онкологических заболеваний, у которых в анамнезе есть указания на приём гормональных препаратов указанных фармакологических групп.

Результаты. При оценке влияния длительности приёма МГТ на риск развития рака молочной железы (РМЖ) обнаружено, что приём МГТ суммарно более 6 лет ассоциирован с более высоким риском развития РМЖ (ОР 1,18; ДИ 1,02–1,36; p <0,001). По методу Вальда мы выявили, что вероятность развития РМЖ ассоциирована с индексом массы тела (ИМТ) более 25 кг/м^2 и длительным приёмом комбинированной МГТ суммарно более 6 лет. При оценке влияния длительности приёма МГТ на риск развития рака тела матки (РТМ) обнаружено, что приём МГТ суммарно более 6 лет ассоциирован с более высоким риском развития РТМ (ОР 1,432; ДИ 1,172–1,750; p <0,001). По методу Вальда мы выявили, что вероятность развития РТМ ассоциирована с наличием ИМТ более 25 кг/м^2, длительным приёмом МГТ суммарно более 6 лет и наличием гиперпластических процессов эндометрия, аденомиоза и гипертонической болезни в анамнезе. При оценке влияния длительности приёма КОК на риск развития рака шейки матки (РШМ) обнаружено, что приём КОК суммарно более 7 лет ассоциирован с более высоким риском развития РШМ (ОР 1,68; ДИ 1,1–2,5; p=0,010). По методу Вальда выявлено, что вероятность развития РШМ ассоциирована с наличием ВПЧ 16-го типа, ИМТ более 25 кг/м^2 и длительным приёмом КОК суммарно более 7 лет. При оценке влияния длительности приёма МГТ на риск развития рака яичников (РЯ) установлено, что приём МГТ суммарно более 9 лет ассоциирован с более высоким риском развития РЯ (ОР 1,65; ДИ 1,2–2,3; p=0,010). По методу Вальда мы выявили, что вероятность развития РЯ ассоциирована с наличием ИМТ более 25 кг/м^2, приёмом МГТ и наличием гиперпластических процессов эндометрия в анамнезе.

Заключение. При длительном приёме препаратов половых стероидов прослеживается тенденция к повышению рисков развития рака органов женской репродуктивной системы. Тщательное диспансерное наблюдение и ограничение длительности приёма препаратов половых стероидов в группах риска позволит снизить канцерогенные риски.

Ключевые слова: гормональные контрацептивы; препараты менопаузальной гормональной терапии (МГТ); рак эндометрия; рак молочной железы (РМЖ); рак шейки матки (РШМ); рак яичников (РЯ).

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BACKGROUND

Given the globally high prevalence of cancer in the female reproductive system among women of all age groups, a comprehensive study of risk factors, their development, and treatment to stratify the risks of neoplasia is needed. Risk factors for the development of cancer of the female reproductive system are heterogeneous, and possible risk factors include age, hereditary predisposition, infectious and immunological factors, and hormonal factors, including the use of sex steroids.

The theory of hormonal carcinogenesis enables the differentiation of the organs of the female reproductive system with direct and indirect hormonal dependence, where the mammary gland, ovaries, and endometrium have direct hormonal dependence, whereas indirect hormonal dependence is more typical for the cervix.

According to statistical data in the Russian Federation, approximately 13% of women of reproductive age use highly effective hormonal contraceptives to prevent pregnancy, and in 14% of women, the therapeutic effect of these drugs is a priority [1]. Since the creation of the first tablet of combined oral contraceptives (COCs) in 1960 by an American scientist, many years have passed, during which the improvement of hormonal contraceptives was only gaining momentum. Thus, numerous studies have enabled us to minimize the dose of the estrogen component, synthesize a new-generation progestogen component, and optimize regimens and routes of administration of hormonal drugs. As is known, the contraceptive effect of hormonal drugs is achieved mainly by the action of progestogens, which also determines the therapeutic effects of these drugs. The estrogenic component is necessary to neutralize the negative effect of progestogens on ovulation, control the menstrual cycle, and prevent intermenstrual bleeding from the genital tract [2]. Over time, lowering the dosage of the estrogen component minimized the development of adverse estrogen-dependent effects.

According to global statistics, the life expectancy of the population is currently increasing, which translates to an increase in the number of women of menopausal age. The aging process of the female reproductive system is inextricably linked with a deficiency of sex hormones, which is accompanied in 85% of women by the development of vasomotor symptoms and psycho-emotional and urogenital disorders. Menopausal hormone therapy (MHT) drugs are actively used in clinical practice to correct the manifestations of estrogen deficiency. Thus, if patients of both fertile and menopausal age need prescribed hormonal drugs for a long period, the increase in possible risks, particularly oncological ones, is a concern.

MATERIALS AND METHODS

The study was conducted at the Center for Gynecology and Reproductive Technologies "National Medical Research Center" "Treatment and Rehabilitation Center" of the Russian Ministry of Health and the Department of Oncogynecology of the University Clinical Hospital No. 4 of I.M. Sechenov, First Moscow State Medical University. The authors analyzed medical records from January 2015 to December 2021. The study included 1842 patients with verified cancer of the female reproductive system who had a history of taking hormonal contraceptives and MHT drugs. The patients were between 26 and 83 years old (mean age, 51.98 ± 10.3 years). The control group consisted of 611 patients without cancer who had a history of taking hormonal drugs from the indicated pharmacological groups. We retrospectively analyzed patient records from the beginning of hospitalization to hospital discharge.

The inclusion criteria were age ⩾18 years, verified diagnosis of cancer of the female reproductive system (stages I–IV according to FIGO), endometrioid adenocarcinoma of the uterine body, and a history of taking hormonal medications for 1 year. The exclusion criteria were age <18 years, pregnancy and/or breastfeeding, verified multiple primary cancer, verified cancer of other localizations, uterine corpus cancer with morphological characteristics of nonendometrioid (mesenchymal and mixed epithelial) adenocarcinoma, a history of taking hormonal medications for 1 year, and endometrial cancer (EC) with a history of taking tamoxifen.

All patients in the COC group used low-dose drugs that contained no more than 30–35 μg of estradiol per day. All patients received MHT drugs in the form of combination therapy in a cyclic mode and in monophasic combination therapy in a continuous mode.

Statistical data processing

Mathematical statistical analysis of the study data was performed using SPSS Statistics version 23.0. To determine the significance of the normal distribution of indicators, the Kolmogorov–Smirnov test was used. Digital results were described using the arithmetic mean (M) and its root-mean-square deviation (±σ). The mean and standard error of the mean were determined in parameters with normal distribution. Otherwise, the quartile range (25^{th}, 50^{th}, and 75^{th} percentiles) was determined. To assess correlations, the Spearman and Pearson methods were used. 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 statistical studies were considered significant if the probability of error was p <0.05, which corresponds to the criteria accepted in biomedical research.

Multivariate logistic regression analysis was used to determine the effect of taking hormonal drugs on cancer development. ROC analysis was performed to assess the sensitivity and specificity of the markers. Risk factors that statistically significantly increased the risk of developing cancer of the female reproductive system were selected using the Wald method.

RESULTS

The clinical characteristics of patients with verified cancer of the female reproductive system are presented in Tables 1–4 depending on the tumor location, namely, breast cancer (BC), uterine corpus cancer (UCC), cervical cancer (CC), and ovarian cancer (OC).

DISCUSSION

Oncological risks of COCs

Does the risk of OC and BC increase when patients with *BRCA1*/2 mutations take COCs? A similar question always arises in the case of a need to prescribe COCs to patients with a family history of OC and BC.

Table 1. Clinical and morphological characteristics of a group of patients with verified breast cancer

Clinical and morphological characteristics	Main group with verified BC, *n*=753 (100%)	Control group, *n*=190 (100%)	*p*
Age, years	50.24±8.5	48.91±11.12	0.136
T1a	148 (19.7%)	–	–
T1b	279 (37.1%)	–	–
T2a	100 (13.3%)	–	–
T2b	222 (29.5%)	–	–
Unspecified invasive ductal carcinoma	323 (42.9%)	–	–
Unspecified invasive lobular carcinoma	283 (37.6%)	–	–
Intraductal papillary adenocarcinoma with invasion	147 (19.5%)	–	–
G1	124 (19%)	–	–
G2	521 (69%)	–	–
G3	108 (12%)	–	–
Luminal A	242 (32.1%)	–	–
Luminal B HER2-negative	281 (37.3%)	–	–
BRCA1 mutations	7 (0.9%)	–	–
BRCA2 mutations	5 (0.7%)	–	–
CHECK mutations	15 (2%)	–	–
Fibrocystic mastopathy with proliferation	53 (7%)	7 (3.7%)	0.091
Fibrocystic mastopathy without proliferation	37 (4.9%)	11 (5.8%)	0.624
BMI: Me [Q25; Q75], kg/m^2	26.54 [21.3; 29.4]	23.77 [20.2; 26.1]	0.001*
Degree III obesity	77 (10.2%)	0 (0%)	< 0.001*
Uterine fibroids	92 (12.2%)	13 (6.8%)	0.035*
Regular menstrual cycle	733 (97.3%)	179 (94.2%)	0.031*
COC intake	64 (8.5%)	23 (12.1%)	0.289
MHT intake	94 (12.5%)	10 (5.3%)	0.005*
Duration of MHT use (years)	7.68±2.92	4.8±2.04	0.002*

*The relationship of the predictor with the probability of breast cancer development is statistically significant (p <0.05); BC, breast cancer; T1a, T1b, T2a, and T2b, stages of breast cancer; G1, G2, and G3, degrees of breast cancer differentiation; *BRCA1* and *BRCA2*, genes protecting against spontaneous DNA damage; CHECK, tumor-suppressor gene; BMI, body mass index; Me (from English mean), average value; Q25 and Q75, 25th and 75th quartiles, respectively; COC, combined oral contraceptives; MHT, menopausal hormone therapy.

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Table 2. Clinical and morphological characteristics of a group of patients with verified uterine cancer

Clinical and morphological characteristics	Main group with verified UBC, *n*=474 (100%)	Control group, *n*=170 (100%)	*p*
Age, years	58.86±10.14	51.77±10.86	<0.001
T1a	345 (72.8%)	–	–
T1b	79 (16.6%)	–	–
G1	278 (58.6%)	–	–
G2	175 (36.9%)	–	–
G3	20 (4.2%)	–	–
Menopause, age, years	52.51±2.51	51.94±3.11	0.037*
Duration of menopause, years	10.37±6.25	6.72±4.81	<0.001*
BMI: Me [Q25; Q75], kg/m^2	33.34 [26.4; 35.5]	22.95 [19.0; 24.6]	<0.001*
Excess body weight	106 (22.4%)	19 (11.2%)	0.002*
Degree I obesity	85 (18%)	11 (6.5%)	<0.001*
Degree II obesity	40 (8.4%)	3 (1.8%)	0.003*
Degree III obesity	138 (29.1%)	3 (1.8%)	<0.001*
Chronic salpingoophoritis	111 (23.4%)	10 (5.9%)	<0.001*
Adenomyosis	224 (47.3%)	17 (10%)	<0.001*
Uterine fibroids	248 (52.3%)	27 (15.9%)	<0.001*
Hyperplastic processes in the endometrium	129 (27.2%)	24 (14.1%)	<0.001*
Dyslipidemia	82 (17.3%)	5 (3%)	<0.001*
Diabetes mellitus	53 (11.2%)	5 (3%)	0.004*
Hypertensive disease	216 (45.6%)	17 (10%)	<0.001*
COC intake	18 (3.8%)	9 (5.3%)	0.404
MHT intake	164 (34.6%)	33 (19.4%)	<0.001*
Duration of MHT use, years	3.63±4.41	1.91±3.03	<0.001*

*The relationship of the predictor with the probability of uterine body cancer development is statistically significant (p <0.05); UBC, uterine body cancer; T1a and T1b, stages of

BRCA1/BRCA2 mutations are an important risk factor for BC and OC development. According to V. Beral et al., COC intake led to a significant (by 20%) reduction in the risk of OC development with a tendency to further decrease every 5 years of taking the drugs, and the effect persists for many years after cessation [3]. Many major studies obtained similar results for the protective effect of COCs on OC [4]. In a large meta-analysis, S. Iodice et al. confirmed a significant reduction in the risk of OC associated with COC intake in carriers of *BRCA1* (standardized cancer incidence rate, 0.51; 95% confidence interval, [CI], 0.40–0.65) and *BRCA2* (standardized cancer incidence rate, 0.50; 95% CI, 0.29–0.89) mutations.

In addition, an increase in the duration of oral contraceptive use is associated with a linear decrease in the risk of OC by 36% for each additional 10 years of use (95% CI, 22%–47%; p <0.01) [5]. J.R. McLaughlin et al. obtained similar results, which revealed a decrease in the risk of OC for carriers of *BRCA1* (odds ratio [OR], 0.56; 95% CI, 0.45–0.71; p <0.0001) and *BRCA2* (OR, 0.39; 95% CI, 0.23–0.66; p=0.0004) mutations associated with COC intake. The study also reported a significant trend toward a decreased risk of OC associated with an increase in the duration of COC intake (p <0.0001) [6].

In our study, COC intake was noted in 3.4% of women with verified OC, and the duration of COC intake was 9.0 ± 2.4 years. The results of the multivariate regression analysis revealed that COC intake did not affect the risk of OC development, which is also consistent with the results of previously published studies.

Most global studies have indicated the protective effect of COCs against EC. In a meta-analysis, J.M. Gierisch et al.

Table 3. Clinical and morphological characteristics of a group of patients with verified cervical cancer

Clinical and morphological characteristics	Main group with verified CC, *n*=291 (100%)	Control group, *n*=120 (100%)	*p*
Age, years	48.55±9.94	47.09±9.17	0.334
PCR, HPV type 16	61 (21%)	7 (5.8%)	<0.001
PCR, HPV type 18	24 (8.2%)	5 (2.9%)	0.142
Tis	57 (19.6%)	–	–
T1a	33 (11.3%)	–	–
T1a1	37 (12.7%)	–	–
Squamous cell carcinoma	287 (98.6%)	–	–
Adenocarcinoma	4 (1.4%)	–	–
G1	254 (87.3%)	–	–
G2	31 (10.7%)	–	–
G3	4 (1.4%)	–	–
Childbirth: Me [Q25; Q75]	1.26 [1; 2]	1.45 [1; 2]	0.036*
BMI: Me [Q25; Q75], kg/m^2	23.98 [20.4; 26.1]	22.44 [19.65; 24.3]	0.001*
Excess body weight	52 (17.9%)	8 (6.6%)	0.003*
Degree II obesity	11 (3.8%)	0 (0%)	0.031*
Moderate to severe cervical dysplasia	16 (5.5%)	1 (0.8%)	0.031*
COC intake	54 (18.5%)	11 (9.1%)	0.018*
Duration of COC use, years	3.04±5.09	1.24±2.99	0.011*
MHT intake	27 (9.3%)	7 (5.8%)	0.250

*The relationship of the predictor with the probability of cervical cancer development is statistically significant (p <0.05); CC, cervical cancer; PCR, polymerase chain reaction; HPV, human papillomavirus; Tis, T1a, and T1a1, stages of cervical cancer; G1, G2, and G3, degrees of differentiation of cervical cancer; Me (from English mean) average value; Q25 and Q75, 25th and 75th quartiles, respectively; BMI, body mass index; COC, combined oral contraceptives; MHT, menopausal hormone therapy.

revealed a significant reduction in the EC risk of women who take COCs (relative risk [RR], 0.57; 95% CI, 0.43–0.77) [7]. The results of a meta-analysis assessing cancer risks in 27,276 women with verified EC also indicated a protective effect of COCs, and its use for 10–15 years reduces the risk of EC by 50% and persists for another 30 years after its cessation [8].

In our study, COC intake was registered in 3.8% of patients with verified EC, and the duration of intake was 1.52 ± 2.96 years. The results of the multivariate regression analysis revealed that COC intake did not affect the risk of EC development, which is consistent with the results of previously published studies.

Scientific studies assessing the effect of COC intake on the risk of BC development presented contradictory results. According to Huber et al., COC intake is associated with an increased risk of BC development in the general population (RR, 1.20; 95% CI, 1.14–1.2) [9]. Moreover, this risk varies depending on the type of progestogen and duration of COC intake.

A cohort study by R.M. Brohet et al. included 1181 female carriers of *BRCA1* mutation and 412 female carriers of *BRCA2* mutation, among whom BC was verified in 597 *BRCA1* mutation carriers and 249 *BRCA2* mutation carriers [10]. An increased risk of COC-associated OC was revealed in both *BRCA1* (RR, 1.47; 95% CI, 1.13–1.91) and BRCA2 (RR, 1.49; 95% CI, 0.82–2.70) mutation carriers. On the contrary, L.H. Schrijver et al. reported that COC intake was not associated with increased risks of BC in the presence of *BRCA1* (RR, 1.08; 95% CI, 0.75–1.5) and *BRCA2* (RR, 1.75; 95% CI, 1.03–2.9) mutations [11].

J. Kotsopoulos et al. analyzed BC risk adjusted for the age of BC verification and the age of starting of COC intake and revealed an increase in the risk of BC development in *BRCA1* mutation carriers who started taking COCs before the age of 20 years (OR, 1.45; 95% CI, 1.20–1.75; p=0.0001) and a slight increase in carriers who started taking COCs between the ages of 20 and 25 years (OR, 1.19; 95% CI, 0.99–1.42; p=0.06) [12]. The researchers also noted an increased risk

Table 4. Clinical and morphological characteristics of a group of patients with verified ovarian cancer

Clinical and morphological characteristics	Main group with verified OC, *n*=324 (100%)	Control group, *n*=131 (100%)	*p*
Age, years	53.18±9.03	51.02±10.95	0.133
T2a	66 (20.4%)	–	–
T2b	115 (35.5%)	–	–
Serous carcinoma	279 (86.1%)	–	–
Clear cell adenocarcinoma	22 (6.8%)	–	–
Granulosa cell tumor	3 (1%)	–	–
Mucinous adenocarcinoma	4 (1.2%)	–	–
Brenner tumor	2 (0.6%)	–	–
Endometrioid carcinoma	14 (4.3%)	–	–
Low-grade	84 (26%)	–	–
High-grade	240 (74%)	–	–
BMI: Me [Q25; Q75], kg/m^2	29.67 [22.7; 33.5]	24.1 [20.2; 26.9]	<0.001*
Excess body weight	62 (19.1%)	42 (32%)	0.003*
Degree I obesity	41 (12.6%)	8 (6.1%)	0.042*
Degree II obesity	25 (7.7%)	2 (1.5%)	0.011*
Degree III obesity	61 (18.8%)	0 (0%)	<0.001*
Surgeries for benign ovarian tumors	36 (11.1%)	29 (22.1%)	0.002*
Endometrioid cysts	13 (4%)	13 (10%)	0.014*
COC intake	11 (3.4%)	4 (3%)	0.854
MHT intake	49 (15.1%)	10 (7.6%)	0.035*
Duration of MHT use, years	9.35±2.86	9.09±2.3	0.708

*The relationship of the predictor with the probability of ovarian cancer development is statistically significant (p <0.05); OC, ovarian cancer; T2a and T2b, stages of ovarian cancer; low-grade, low degree of malignancy; high-grade, high degree of malignancy; BMI, body mass index; Me (from English mean), average value; Q25 and Q75, 25th and 75th quartiles, respectively; COC, combined oral contraceptives; MHT, menopausal hormone therapy.

of BC associated with COC use in carriers aged 40 years (RR, 1.40; 95% CI, 1.14–1.70; p=0.001). In cases of BC diagnosed at the age of 40 years or later, no increase in BC risk was registered (OR, 0.97; 95% CI, 0.79–1.20; p=0.81).

In this study, 8.1% of women from the BC group were taking COCs for 7.38 ± 2.65 years. Then, we examined the effect of COC intake on the risk of BC development, and the results of multivariate regression analysis did not reveal a significant increase in risk.

Oncological risks of MHT

The problem of cancer alertness when taking MHT drugs is also interesting. Assessing the risk of developing cancer associated with taking MHT drugs is quite difficult primarily because the duration of menopause, dosage and duration of drug intake, route of administration, and type of progestogen component must be considered. Most studies that have examined the effect of MHT drugs on the risk of cancer development in women have focused on BC.

According to A. Fournier et al., the risk of BC was slightly higher when taking MHT preparations containing a progestogen with androgenic and antiandrogenic activities than when taking MHT preparations containing dydrogesterone and micronized progesterone.

Ya. Vinogradova et al. analyzed 33,703 women diagnosed with BC and 134,39 control women. They studied the possible association of the risk of BC with MHT in the form of estrogen monotherapy and combination therapy with estrogens and progestogens [13]. When MHT drugs were taken for >5 years, an increased risk of BC was detected in groups with estrogen monotherapy (RR, 1.15; 95%, CI 1.09–1.21) and combination therapy (RR, 1.79; 95% CI, 1.73–1.85). The researchers also

noted that the risk of BC was highest for norethisterone (RR, 1.88; 95% CI, 1.79–1.99) and the lowest for dydrogesterone (RR, 1.24; 95% CI, 1.03–1.48). Eventually, the authors concluded that 3–8 additional cases of BC could be expected per 10,000 women on monoestrogen therapy and 2–8 additional cases of BC per 10,000 women on combination MHT.

Vurrently, MHT use is more associated with the risk of developing lobular carcinoma than ductal carcinoma [14]. A. Fournier et al. conducted a major study involving 80,391 postmenopausal women and examined the risks of BC of various molecular subtypes associated with combination MHT [15]. The result revealed that intake of combination MHT containing estrogen with dydrogesterone is associated with a significant increase in the risk of lobular carcinoma (RR, 1.7; 95% CI, 1.1–2.6) and that of estrogen with other progestogens is associated with an increased risk of ductal carcinoma (RR, 1.6; 95% CI, 1.3–1.8) and lobular carcinoma (RR, 2.0; 95% CI, 1.5–2.7). A study of the association of MHT intake with the receptor status of BC revealed a correlation of MHT intake containing estrogen plus other progestogens with the risk of receptor-positive BC, namely, the presence of estrogen receptors (ER) +/progesterone receptors (PR) + (RR, 1.8; 95% CI, 1.5–2.1) and presence of ER +/absence of PR (RR, 2.6; 95% CI, 1.9–3.5).

A rather complex group consists of patients with identified *BRCA1/2* gene mutations. Most available data do not confirm an increase in the risk of BC when carriers of *BRCA1/2* mutations take MHT, and according to the results of some studies, the risk of BC development decreased from 48% to 43% [16]. J. Kotsopoulos et al. analyzed whether the use of MHT in 432 women with an inherited *BRCA1* mutation is safe with respect to the risk of BC [17]. The researchers revealed that the risk of BC was not associated with MHT (RR, 0.80; 95% CI, 0.55–1.16; p=0.24).

Although the results of some studies have revealed an increase in the risk of BC associated with MHT, its value is insignificant and amounts to 0.1% annually, and the prevalence is <1.0 cases per 1000 women and is comparable to the risk in the presence of factors such as early menarche (before age 11 years), late menopause, absence of childbirth, obesity and diabetes mellitus, and low physical activity [18].

In this study, 12.5% of patients with verified BC were taking a combination of MHT drugs, which was statistically significant when compared with the control group (p=0.005). Most often, BC was verified at stage T1b (37.1%). According to the morphological characteristics, BC was more often represented by unspecified invasive ductal carcinoma (42.9%) and moderate differentiation (69%). When determining the molecular biological subtype of BC, luminal B HER2-negative was more often detected (37.3%), as was luminal A (32.1%).

In this study, we assessed the effect of MHT on the risk of BC development. Multivariate regression analysis revealed that combination MHT is associated with a slight increase in the risk of BC (RR, 1.22; 95% CI, 1.120–1.338; p=0.004). A trend toward an increase in the risk of BC is associated with an increase in the duration of MHT (years). We established that MHT for >6 years is associated with a higher risk of cancer development (RR, 1.18; 95% CI, 1.02–1.36; $p < 0.001$). We used the Wald method and revealed that the probability of BC development is associated with a BMI of >25 kg/m^2 and intake of combined MHT drugs for more than 6 years.

In a large study, B. Trabert et al. assessed the risk of OC development in 92,601 postmenopausal women on MHT, considering the type of drug, dosage of the progestogen component, duration of use, and histological subtype of OC [19]. The control group comprised women who had never taken MHT drugs. In women who underwent hysterectomy, MHT in the form of estrogen monotherapy was associated with an increased risk of OC (RR, 1.69; 95% CI, 1.05–2.71). The risk of OC was significantly higher in women on MHT for >10 years (RR, 2.151; 95% CI, 1.30–3.57). Combination MHT was also associated with an increased risk of OC (RR, 1.43; 95% CI, 1.09–1.86), and a significant increase in risk was noted in those taking these drugs for >10 years (RR, 1.68; 95% CI, 1.13–2.49). When adjusted for progestogen dosages of 5 and 10 mg, the risk of OC, although increased, did not reach statistical significance (at 5 mg, RR, 1.60; 95% CI, 0.95–2.68; at 10 mg, RR, 1.58; 95% CI, 0.90–2.79).

In those following a combined MHT regimen, both cyclic and continuous regimens were associated with an increased risk of OC (RR, 1.60; 95% CI, 1.10–2.33; RR, 1.43; 95% CI, 1.03–2.01, respectively). In the analysis of the histological types of OC, mono-MHT and combination MHT were associated with an increased risk of serous OC (OR, 2.82; 95% CI, 1.31–6.04; RR, 1.83; 95% CI, 1.28–2.61, respectively).

In a cohort study, J.V. Lacey et al. revealed that mono-MHT is statistically significantly associated with an increased risk of OC (RR, 1.6; 95% C,I 1.2–2.0); for the combination MHT, this risk tended to increase (RR, 1.1; 95% CI, 0.64–1.7) [20]. An increased risk of MHT-associated OC was also noted according to a meta-analysis of 36 studies (RR, 1.29; 95% CI, 1.19–1.40) [21]. When studying the histological subtype of OC, an increased risk was revealed for serous OC (RR, 1.50; 95% CI, 1.35–1.68) and endometrioid OC (RR, 1.48; 95% CI, 1.13–1.94).

The results of our study demonstrated an increased risk of OC associated with the combination MHT (OR, 1.21; 95% CI, 1.062–1.422; p=0.004). According to the morphological structure, OC was more often represented by serous carcinoma (86.1%) and high-grade carcinoma (73.8%). When assessing the effect of the duration of MHT on the risk of OC development, MHT duration for >9 years was associated with a higher risk of cancer (OR, 1.65; 95% CI, 1.2–2.3; p=0.010). We used the Wald method and found that the probability of OC occurrence is associated with a BMI of >25 kg/m^2, MHT intake and a history of endometrial hyperplastic processes.

Progestogens have an antiproliferative effect on the endometrium, and many randomized controlled studies have shown a reduction in the risk of endometrial hyperplasia with combination MHT, in contrast to monotherapy. Thus,

endogenous progesterone may inhibit most (but not all) estrogen-associated endometrial proliferation.

However, recent studies have increasingly mentioned that with combination MHT, the risk of EC tended to increase. Based on the results of a prospective study, N. Allen et al. revealed an increased risk of EC with both mono-MHT (RR, 2.52; 95% CI, 1.77–3.57) and combination MHT (RR, 1.41; 95% CI, 1.08–1.83) [22]. Similarly, J.V. Lacey Jr et al. reported that combination MHT was associated with an increased risk of EC (RR, 2.6; 95% CI, 1.9–3.5), both for the cyclic (RR, 3.0; 95% CI, 2.0–4.6) and continuous (RR, 2.3; 95% CI, 1.3–4.0) regimens [23]. The researchers noted that the risk of EC increased with increasing duration of drug intake; in year 1 of combination MHT, the RR increased by 0.38 (95% CI, 0.20–0.64). In addition to the tendency to increase the risk of EC with MHT, in women with metabolic disorders taking these drugs, moderate- and low-grade EC is often verified at a stage with greater invasion of the myometrial wall, which in turn requires an integrated treatment approach [25].

In this study, multivariate analysis revealed the effect of MHT on the risk of EC development (OR, 1.29; 95% CI, 1.029–1.239; p <0.001). Our results are consistent with those of C. Bergeron et al., where EC was verified at stage T1a in 72.8% of cases, and its morphological structure corresponded to high-grade endometriotic adenocarcinoma (58.6%). When assessing the effect of MHT duration on the risk of UCC development, MHT for >6 years was associated with an increased risk of cancer (RR, 1.432; 95% CI, 1.172–1.750; p < 0.001). We used the Wald method and revealed that the probability of EC is associated with a BMI of >25 kg/m^2, MHT for a total of >6 years, and the presence of endometrial hyperplastic processes, adenomyosis, and a history of hypertension.

Hormonal components of CC

CC refers to cancer of visual localizations. Under the influence of exogenous and endogenous estrogens, the count of cells increases in which DNA mutation has already occurred as a result of exposure to an oncogene or viruses, as is the case with human papillomavirus (HPV).

Numerous studies have confirmed that the pathological processes of the exocervix and endocervix are polyetiological, although HPV is of key significance in the etiology and pathogenesis of cervical pathology. According to L.A. Torre et al., approximately 95% of women with verified CC are infected with one or more subtypes of HPV, with the detection rate of HPV type 16 reaching 50%–61% and HPV type 18 reaching 10–15% [25]. In this study, an association between the squamous cell form of CC and HPV was registered in 43% of cases, with HPV type 16 (21%) and type 18 (8.2%) being the most common types.

The HPV integrates its DNA into the basal cells of the cervical transformation zone, which leads to the production of oncoproteins E6 and E7, which further cause cervical carcinogenesis because of their ability to enhance cell proliferation, allowing the accumulation of chromosomal abnormalities [26]. This is how HPV converts from the episomal form to the integrated form. In nearly 90% of cases, HPV infection is eliminated within 2 years from the time of infection and persists only in approximately 10% of women [26]. However, only a tenth of all infections become persistent, and precancerous lesions and CC may occur in these women.

M.Kh. Ibragimova et al. analyzed 735 women aged 17–83 years, and in its course, they identified and genotyped HPV DNA by assessing the viral load and determined oncoproteins E1/E2 and E6 when identifying HPV type 16 [27]. Researchers established a connection between a high clinically significant viral load (>3 lg HPV DNA/10^5 cells) and the risk of CIN I–III of 69.3% (p=3.5×10^{-16}) and CC of 82.8% (p=7×10^{-29}). Researchers have suggested that high viral load can be used as a prognostic risk factor for the development of high-grade squamous intraepithelial lesion and CC; however, its prognostic value is currently only promising for HPV type 16 [27–28]. Similarly, M. Moberg et al. suggested that the initially large number of copies of the HPV genome increases the probability of viral DNA integration into the cellular genome and therefore the risk of carcinogenesis [29].

HPV infection of cervical epithelial cells is not a sufficient condition for cervical carcinogenesis, and the outcome of such infection is largely determined by associated risk factors. Considering that the cervical epithelium is an estrogen-sensitive tissue, among the possible risk factors for CC in HPV-positive women, hormonal factors, including the intake of sex steroids, are of the greatest interest.

I.I. Frolova studied immunohistochemical biopsy samples of the cervix without pathology and discovered the presence of ERs in the unchanged epithelium. ERs in the cervix are localized in the nuclei of the basal and parabasal cell layers, and mitotic activity increases as the blood level of estrogen increases [30].

When studying tissue changes in the exocervix and endocervix under conditions of HPV persistence, the localization of specific changes was precisely discovered in the estrogen-sensitive areas of the cervix. Normally, cervical epithelial cells cannot provide the conditions for the formation of the estrogen metabolite 16α-OH; however, under conditions of active expression of oncoproteins E6 and E7, a high level of 16α-OH was recorded, comparable to that in BC cells. This was confirmed by O.N. Churuksaeva et al., who recorded a high level of 16α-hydroxyestrone (16α-ONE1) under conditions of active expression of the E7 protein [31].

Thus, the integration of HPV into cervical cells with the production of oncoproteins contributes to the formation of aggressive estrogen metabolites and the development of CC. According to O.N. Churuksaeva et al., in the future, this can be taken into account when prescribing etiopathogenetic drugs that block key mechanisms of carcinogenesis in the combined treatment of CC [31].

Along with estrogen metabolites, oncoproteins E6 and E7 can serve as promising biomarkers in determining the risk of CC. However, the possible introduction of laboratory

diagnostics of oncoproteins into widespread clinical practice remains a problem because of the high cost of the technique.

T.E. Belokrinitskaya et al. studied 104 samples of healthy cervical tissue and revealed receptors for sex steroids in 54% of cases, including PRs in 27% of cases and ERs in 18% [32]. A negative relationship was noted between age and the number of receptors for sex steroids; in the menopausal period, the degree of receptor expression was often negative.

The hormonal dependence of the cervix has been proven by studying changes in hormonal saturation during pregnancy and the timing of cervix epithelization; thus, with the predominance of progesterone, the border of the epithelial junction shifts toward the vaginal segment of the cervix, and under conditions of predominance of estrogens, it shifts toward the cervical canal [33]. According to A.F. Kupert, the cervical transformation zone is labile and susceptible to the influence of both progesterone and estrogens, and this localization is critical for HPV persistence and CC development [33].

In our study, 5.5% of patients with CC had a history of severe cervical dysplasia associated with HPV infection, and 4.5% of patients had mild cervical dysplasia associated with HPV infection.

HPV invades actively proliferating cells of the parabasal layer of the cervix. According to Castellsague et al., the state of hyperestrogenism led to increased proliferative activity of the parabasal epithelial layer of the cervix and therefore becomes one of the important factors inducing cervical carcinogenesis [34].

The important role of HPV in cervical oncogenesis has been proven and is beyond doubt; however, in recent years, studies have increasingly been conducted worldwide on the association of the intake of hormonal drugs with an increased risk of CC associated with HPV infection. Thus, several large studies have noted an increased risk of CC with a positive HPV infection status and COC intake [35–36]. The results of a multivariate analysis revealed a trend toward an increased risk of CC development in HPV-positive women taking COCs (RR, 1.230; 95% CI, 1.064–1.423, p=0.018), as well as to CC progression with the development of invasive forms (T1b1; p=0.009) [37]. The assessment of the prognostic significance of this marker by ROC analysis revealed that COC intake has a high prognostic significance for determining the risk of CC occurrence (AUC=0.742), with a sensitivity of 74.07% and specificity of 72.73% [37].

V. Moreno et al. combined data from eight case-control studies involving patients with verified CC associated with HPV and concluded that continuous use of COCs is associated with a statistically insignificant increase in the development of invasive CC (OR, 1.29; 95% CI, 0.88–1.91) and CC in situ (OR, 2.54; 95% CI, 0.95–6.78) [38]. However, when adjusting for the duration of use, intake of COCs for 5–9 years in the presence of HPV infection significantly increased the risk of CC (RR, 2.82; 95% CI, 1.46–5.42; for 10 years, OR, 4.03; 95% CI, 2.09–8.020). According to the results of a cohort study conducted in Denmark by L. Iversen et al. (2021), with the participation of 3643 female patients with verified CC, the risk of CC increases with increasing duration of taking hormonal contraceptives. The researchers concluded that more frequent screening for CC is necessary in women who take COCs.

In our study, COC use was noted in 18.6% of patients with verified CC compared with the control group, where only 6.5% of patients took COCs, and the difference was statistically significant (p=0.018). Morphologically, CC was of the squamous cell type in 287 (98.6%) patients. When studying the incidence of CC in HPV-positive women who were taking COCs, CC was found to be verified in 52.5% of cases, CC was not diagnosed in 12 (33.3%) HPV-positive patients, and the difference was statistically significant (p=0.049).

Major publications discussing the problem of a possible increase in the risk of CC in women taking MHT drugs did not reveal an increased risk of CC occurrence. However, conducting these studies is complicated by the fact that to completely understand the effect of MHT on the risk of CC, not only aspects of MHT but also the status of HPV infection must be considered. In a study by S. Jaakkola et al. involving 243,857 women aged >50 years on combination MHT for 5 years, a reduced risk of developing squamous cell CC (RR, 0.41; 95% CI, 0.28–0.58) and an increased risk of cervical adenocarcinoma (RR, 1.31; 95% CI, 1.01–1.67) were noted [39]. Similarly, J.V. Lacey et al. reported that combination MHT is associated with a reduced risk of squamous cell carcinoma (RR, 0.85; 95% CI, 0.34–2.1) and an increased risk of cervical adenocarcinoma (RR, 2.1; 95% CI, 0.95–4.6) [40].

In this study, MHT was registered in 9.3% of patients with verified CC compared with the control group with 4.1%, and the difference was not statistically significant (p=0.250). According to the morphological type of CC, 98.6% of cases were of the squamous cell type and 1.4% were adenocarcinoma.

We also assessed the effect of COC intake on the risk of CC development. According to multivariate analysis, COC intake increased the risk of CC (OR, 1.230; 95% CI, 1.064–1.423; p=0.018). A multivariate regression analysis revealed that the risk of CC development increased with extended COC use in years. COC intake for >7 years is associated with a higher risk of cervical neoplasia (RR, 1.68; 95% CI, 1.1–2.5; p=0.010). Using the Wald method, the results revealed that the probability of CC development is associated with the presence of HPV type 16, BMI of >25 kg/m^2, and COC intake for a total of >7 years.

CONCLUSION

Thus, the problem of cancer alertness when taking COCs and MHT drugs is currently being actively studied worldwide. However, several contradictory results from studies in this field do not enable the complete exclusion of the absence of a triggering effect of taking sex steroids on the risks of the development of cancer in female reproductive organs, which confirms the relevance of further study of this problem.

ADDITIONAL INFO

Authors' 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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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 publication of their medical data.

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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.

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