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Literature reviews

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CONTRACEPTIVE HISTORY AND RISK OF CANCER OF THE FEMALE REPRODUCTIVE ORGANS: THE REALITIES OF TODAY (LITERATURE REVIEW)

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In modern conditions, an increasing number of women resort to the use of hormonal contraception drugs, and their number is constantly increasing, but systematic studies on the possible role of hormonal contraceptives as independent triggers or cofactors of the development of oncological diseases of the reproductive system are currently few, which does not allow us to draw objective conclusions. In this paper, we analyzed global data on the risks and frequency of detected oncopathology of the reproductive organs, taking into account the contraceptive history of women.

K e y w o r d s : combined oral contraceptives (COC); breast cancer; cervical cancer; endometrial cancer; ovarian cancer.

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КОНТРАЦЕПТИВНЫЙ АНАМНЕЗ И РИСКИ ОНКОПАТОЛОГИИ ЖЕНСКИХ РЕПРОДУКТИВНЫХ ОРГАНОВ: РЕАЛИИ СЕГОДНЯШНЕГО ДНЯ (ОБЗОР ЛИТЕРАТУРЫ)

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В современных условиях всё больше женщин прибегают к помощи препаратов гормональной контрацепции, и их число постоянно увеличивается, однако системных исследований о возможной роли гормональных контрацептивов как самостоятельных триггеров или кофакторов развития онкологических заболеваний органов системы репродукции в настоящее время очень мало, что не позволяет сделать объективные выводы. В данной работе проведён анализ мировых данных о рисках и частоте выявляемой онкопатологии репродуктивных органов с учётом контрацептивного анамнеза женщин.

К л ю ч е в ы е с л о в а : комбинированные оральные контрацептивы (КОК); рак молочной железы; рак шейки матки; рак эндометрия; рак яичников.

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The problem of malignant neoplasms (MN) of the female reproductive system is still a focus of attention worldwide. It is associated with an annual increase in the prevalence of oncological diseases, as well as high mortality resulting from them. According to the global cancer epidemiology resource GLOBOCAN of the International Agency for Research on Cancer, in 2018, 2,088,849 new cases of breast cancer (BC), 569,847 new cases of cervical cancer (CC), 382,069 new cases of uterine corpus cancer, and 295,414 new cases of ovarian cancer (OC) were registered worldwide.

Concurrently, hundreds of millions of women in the modern world use hormonal drugs, and their number is steadily increasing; however, the issue of the relationship

between the use of sex steroids and the incidence of MN of the female reproductive system remains debatable today. There are only few studies on this problem, and the opinions of scientists about the possible influence of hormonal drugs on the frequency of oncopathology of the reproductive organs are totally opposite. In this regard, the analysis of global data on the incidence of detected oncopathology of the reproductive organs, taking into account the contraceptive history of women, is of great interest. Therefore, in the present study, we summarized current data on the risk factors and incidence of cancers of the reproductive organs in women taking hormonal contraceptives, since high oncological alertness is one of the most important reasons for refusing to take them or limiting their use.

Hormonal contraceptives and breast cancer

BC is still the major oncological pathology in the female population in Russia, accounting for approximately 20.9% of all MN in women [1]. In 1975, E. Fasal et al. suggested that an increase in the risk of BC may be associated with hormonal contraceptives (HC) use, and the results of the authors' study confirmed the assumption that the relative risk (RR) of BC among women taking hormonal contraceptives can be 1.1 and can also reach 1.9 and 2.5, and depends on the duration of the drug intake [2]. Recent data from various parts of the world are quite contradictory. An increase in the incidence of BC was recorded simultaneously with an increase in the number of women using contraceptives, explained by the fact that women who started taking combined oral contraceptives (COCs) were closely followed up by specialists, which led to the more frequent detection of BC in the early stages [3]. According to the results of a prospective cohort study conducted in Denmark, the RR of BC when HC were used was 1.20 (95% CI (confidence interval) 1.14–1.26) [4]. This risk increased from 1.09 (95% CI 0.96–1.23) when using HC for less than 1 year to 1.38 (95% CI 1.26–1.51) when using them for more than 10 years ($p = 0.002$). In comparing the RR of BC when taking triphasic or monophasic preparations containing levonorgestrel (LNG), the researchers obtained similar rates of 1.21 (95% CI 1.04–1.41) and 1.45 (95% CI 1.26–1.67), respectively [4]. Thus, according to this study, the RR for developing BC increases by 20% with the use of any type of HC, and increases to 38% with long-term use (10 years or longer). After cessation of the HC use, the risk of BC remains high for another 5 years.

The use of an intrauterine system (IUS) with LNG can also lead to an increased risk of BC [5], according to the results of a prospective cohort study by L.S. Morch et al. (2017); in this group of women, the RR of BC was 1.45; 95% CI 1.26–1.67 [4]. According to S.K. Bardaweel et al., the risk of BC increases with HC use regardless of their composition, whether they are COCs or pure progestogens [6].

No less important is the study of risk factors for BC in women taking COCs. One of the main risk factors for BC is known to be the carriage of a mutation in the *BRCA1* or *BRCA2* gene. Analysis of the risk of BC among *BRCA* carriers does not show unequivocal results nowadays. According to a large cohort study by R.M. Brohet et al., which included 1593 *BRCA* carriers, the risk of BC was 1.47 and increased with the long-term use of COCs (more than 5 years), namely 1.51 for *BRCA1* and 2.27 for *BRCA2* [7]. According to the results of 23 studies, among women who have ever taken COCs, there is a slight increase in the risk of BC (RR 1.08; 95% CI 1.00–1.17), especially in carriers of the *BRCA* mutation (RR 1.21; CI 0.93–1.58) [8]. R.L. Milne et al. showed that the risk of BC was slightly higher with long-term use of COCs among *BRCA2* carriers (1.34), in contrast to *BRCA1* carriers (odds ratio (OR) 0.22) [9].

During the study, R.W. Haile et al. obtained the following results. For *BRCA1* carriers, no association was noted with the development of BC (for women with a history of using HC, the risk index was 0.77, and 0.63 for those using COCs at the time of the study); for *BRCA2* carriers, the risk of BC increased (for women with a history of using HC, the indicator was 1.62) [10]. Evaluation of the long-term use of COCs (more than 5 years) revealed an aggravation of the risk of BC for *BRCA2* carriers (2.06) compared to *BRCA1* carriers (0.80) [10]. However, there is evidence in the literature that associations between previous use of COC and BC in women who carry *BRCA1* or *BRCA2* mutations are similar to those in the general population of women taking COCs [11].

Thus, based on the data analyzed, we can conclude the following:

- the risk of BC increases with the use of COCs;
- there is no correlation between BC risk and the type, dose, and duration of the drug intake;
- there is no increase in risk with the use of pure gestagens;
- the risk of BC still remains high for 5 years after the cessation of COCs;
- data on BC risk in the presence of mutations in the *BRCA1/2* gene when using COCs are ambiguous.

Hormonal contraceptives and cervical carcinogenesis

According to the 2018 statistics of the Russian Federation, among the range of oncological diseases in women, the percentage of MNs of the reproductive organs was 17.4% and more than 17,700 cases (5.3%) of MNs of the cervix were registered [1]. It is noteworthy that in the age category of women under 40, the percentage of CC was 23% [1]. The role of CC as a cause of death in women under 30 years of age (7.1%) is also significant [1]. The fact that the incidence of CC remains high and the unfavorable tendency toward its "rejuvenation" indicates the relevance of the search, development, and implementation of new approaches toward the examination and management of women who take HC for a long time, with the aim of promoting the early diagnosis of preinvasive damage to the epithelium (cervical intraepithelial neoplasia or squamous intraepithelial lesions) and CC.

A special place in the pathogenesis of CC is given to the human papillomavirus (HPV) as the main etiological factor in cervical carcinogenesis, whose DNA is found in 98.7% of all cases of CC [12]. Constant persistence of highly oncogenic HPV types 16 and 18 leads to the development of up to 70% of invasive CC and precancerous lesions, where HPV type 16, having the highest carcinogenic potential, is detected in 60% of all cases of CC [13, 14].

Considering the leading role of HPV infection in the genesis of CC, it is important to study the effect of HC on both the risk of HPV infection and the aspects of oncogenic transformation of already infected cells. A possible mechanism for the association between COCs use and CC is that steroid hormones, both estrogens and progestogens, bind to the corresponding cervical receptors and change the course of HPV infection [15]. Under the action of sex steroids, the expression of HPV 16 oncogenes E6 and E7 is increased, which inactivate suppressor proteins p53 and retinoblastoma protein (pRb), thereby increasing the ability of viral DNA to transform cells and inducing the process of oncogenic transformation of infected cells [15, 16].

Y.A. Yoo et al. studied the mechanism of the effect of progesterone on cervical carcinogenesis in transgenic mice models expressing HPV 16 E6 and/or E7 oncogenes and revealed that progesterone inhibits cervical carcinogenesis *in vivo* [17]. According to R. Samir et al., the mechanism of cervical carcinogenesis when using COCs can be triggered by the overproduction of cyclooxygenase-2 (COX-2) and an increase in the level of interleukin-10 (IL-10) [18]. In addition, when analyzing the use of contraceptives containing only the progestogen component, low production of cytokeratin-10 and IL-10 was revealed [18]. Overexpression of COX-2 is a poor prognostic marker in CC, associated with an increased risk of tumor recurrence and metastasis [19].

Contemporary studies in the field of risk assessment for the development of CC have assessed the association between HC use and the presence of HPV infection. A study by P. Appleby et al. (2007) revealed that COCs use for 5 years or more leads to an increase in the RR of invasive CC and *Ca in situ colli uteri* (carcinoma *in situ* of the cervix) by almost 2 times (RR 1.90; 95% CI 1.69–2.13) compared with women who never used COCs [20]. In the study by J.S. Smith et al., the COCs use for 5 years or more led to a pronounced increase in the risk of *Ca in situ colli uteri* in contrast to invasive CC (2.1 and 1.4, respectively) [21]. According to researchers, when COCs are used for 10 years by women aged 20–30 years, the cumulative incidence of invasive CC increases by the age of 50 years from 7.3 to 8.3 per 1000 persons in less developed countries and from 3.8 to 4.5 per 1000 persons in more developed countries [20]. According to the results of a retrospective cohort study by D.L. Loopik et al., which included 702,037 women, the risk of CC and CIN3 was higher with OCs than with IUSs [22]. According to a meta-analysis of 28 studies (Smith J.S. et al., 2003), the risk of CC increased significantly with an increase in the duration of COC use and decreased significantly with an increase in the time after discontinuation of HC [21]. A similar reduction in the risk of CC after cessation of HC was noted in a study by P. Appleby et al. [20]. In the presence of HPV infection, the risk of CC increased after 5 years of COCs use from 0.9 to 1.3, and after 10 years of COCs use, it was already 2.5; in the group of HPV-negative women, this risk increased only after 10 years of taking COCs from 0.9 to 1.3 [21].

Morphological characteristics of CC in women using COCs also differed, and the risk of glandular CC was 2.8 after 10 years of COCs use and higher than for the squamous type (2.0 after 10 years of COCs intake) [21]. In turn, a joint WHO study on neoplasia and steroid contraceptives showed that the RR of adenocarcinoma of the cervix was 1.5 for women who have ever used COCs [23]. Concurrently, according to the results of a meta-analysis of 16 case–control studies, on the contrary, no relationship was found between the use of COCs and the risk of CC; in addition, there was no increase in the risk of CC in women with HPV infections who took HC [24].

Analysis of published studies showed the following:

- the risk of CC increases with the use of COCs;
- the presence of HPV infection leads to a higher risk of CC when taking COCs compared to HPV-negative women;
- the intake of COCs leads to a pronounced increase in the risk of *Ca in situ colli uteri*;
- the risk of glandular CC while taking COCs is higher than that of squamous cell type cancer;
- the risk of CC decreases with an increase in the time after cessation of COCs use.

Hormonal contraceptives and endometrial cancer (EC)

Although most modern studies demonstrate a decrease in the risk of EC in patients taking HC, discussions about the influence of various groups of contraceptive drugs on the development of EC are actively continuing today. Currently, there is no convincing evidence that sex steroids can be independent triggers for the emergence of cancer cells [25]. It is assumed that estrogens act to trigger proliferation on already existing cancer cells, whereas progestogens have an antiproliferative effect on them [25]. Since HC consist of a progestogen component, a reduction in the risk of EC becomes possible if the progestogen is effective enough to counteract estrogen-induced proliferation [26].

Various pharmacological classes of HC are now considered from the viewpoint of oncoprotective action against EC, along with high parity, physical activity, and smoking [27]. A large case–control study conducted in China in 2006, which included 1204 new cases of endometrial cancer and 1212 healthy controls, showed that the risk of EC was reduced with COC use (RR 0.75; 95% CI 0.60–0.93), and the protective effect increased with the duration of use (5 years or more, RR 0.50; 95% CI 0.30–0.85) [28].

Similar results were obtained by L.S. Cook et al. (2014) and J.M. Gierisch et al. (2013) [27, 29]. In most studies, the oncoprotective effect of COCs persisted for more than 10–25 years after discontinuation of the drugs [28, 30, 31]. Similar results were obtained in a German population-based case–control study, which showed a reduction in the risk of EC in all COC users, and this effect was manifested within 5 years of using the contraceptive drug (RR 0.63; CI 0.47–0.86), progressed as the duration of use increased, reaching 75% after 10 years of using the contraceptive drug [30]. There was no change in the oncoprotective effect depending on the composition of COCs [31]. However, tumor morphology analysis showed that OC intake was associated with a greater risk reduction for developing carcinomas (RR 0.69; 95% CI 0.66–0.71) than sarcomas (0.83; 0.67–1.04; $p = 0.02$) [32].

Evaluation of the efficiency of gestagen-containing drugs in relation to protection against EC is one of the most essential problems of the oncoprotective effect of hormonal drugs. Progestogens provide cell cycle arrest, induce cell apoptosis, and regulate the expression of numerous signaling pathways involved in oncogenesis; however, it has not yet been determined how exactly these effects are associated with a long-term reduction in the risk of EC [33, 34]. Several authors have reported a reduction in the risk of EC when using gestogen-containing drugs, including LNG-IUSs, but since this has been recorded only in a small number of studies, unambiguous conclusions cannot be made, and therefore, further large studies are required [27, 28, 31].

Analysis of the available research results enables led to the following conclusions:

- a decrease in the risk of EC by approximately 50% with COCs use was noted;
- a pronounced reduction in the risk of EC with long-term COCs use;
- the reduction in the risk of EC persists for 10–25 years after cessation of COCs use;
- COCs have a dose-independent oncoprotective effect in relation to the risk of EC;
- the efficiency of contraceptives in the group of women at high risk of EC has not been studied enough;
- evaluation of the efficiency of progestogen drugs is also insufficient.

Hormonal contraceptives and ovarian neoplasia

OC is considered as one of the most complicated problems in modern oncogynecology. OC accounts for approximately 4% of the incidence of cancers worldwide and has the highest mortality rate among gynecological cancers. One of the main reasons for the poor efficiency of the treatment for OC is its late detection due to the lack of screening programs for early diagnosis, as well as a long asymptomatic course.

In 2008, V. Beral et al. analyzed the results of 45 epidemiological studies from 21 countries, which included 23,257 patients with OC and 87,303 healthy control women [35]. Overall, 7,308 (31%) female patients in the main group and 32,717 (37%) women in the control group used COCs for an average of 4.4 and 5.0 years, respectively. A significant reduction in the risk of OC was recorded with the use of COCs, whereas an increase in the duration of COC use led to a greater reduction in the risk of OC ($p < 0.0001$) [35]. The use of HC provided sufficiently long-term protection of the ovaries, which persisted for 30 years or more after discontinuation of the drugs [35]. A large prospective study (K.K. Tsilidis et al., 2011) confirmed a significant reduction in the risk of OC in women taking COCs, and a progressive decrease in this risk was noted with an increase in the duration of oral contraceptive use, as COCs use for 10 years or more decreased the risk of OC by 45% (RR 0.55; 95% CI 0.41–0.75) [36].

The dose of the estrogen component contained in the hormonal contraceptive did not significantly affect the risks of OC [35, 36].

In terms of morphology, the incidence of mucinous tumors (12% of the total) seems to be practically independent of HC use; however, the proportional risk reduction does not differ significantly between different histological tumor variants [35].

The issue of the risk of OC in women taking COCs, depending on risk factors, modifiable and non-modifiable, is also important. In 2018, researchers from the National Institute of Health (Maryland, USA) published the results of a prospective study that included data on 100,000 women who had ever taken HC, considering modifiable risk factors (smoking, alcohol consumption, body mass index, and physical activity) [37]. There were 1241 cases of OC, 2337 cases of EC, and 11,114 cases of BC. It was found that long-term intake of COCs leads to a 40% reduction in the risk of OC (RR 0.60; 95% CI 0.47–0.76; $p < 001$), regardless of modifiable risk factors [37].

Particular attention should be paid to female patients with a *BRCA1* or *BRCA2* mutation, as this factor leads to an increase in the risk of OC by 56% and 27%, respectively [38]. However, the research that has been conducted so far is insufficient to draw definitive conclusions. An analysis of a series of publications on the relationship between the HC use and OC risk among carriers of the *BRCA1*/2 gene mutation indicates a potential reduction in the risk of OC in this group of women, and for every additional 10 years of COCs use, OC risk decreased by 36% [39, 40]. Currently, adnexectomy is considered the only effective strategy to reduce the risk of OC in carriers of *BRCA1*/2 mutations [39]. According to a meta-analysis by D. Cibula et al., the researchers suggested that COCs can be considered as an alternative strategy for OC chemoprophylaxis in carriers of the *BRCA1* gene mutation, if the woman does not consider surgical treatment (adnexectomy) after 30 years as an acceptable prevention of OC [39]. However, it is still necessary to carefully evaluate all the risks of developing BC in patients with *BRCA1*/2 gene muta-

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tions and OC who are taking COCs, since some studies reveal an increased risk of BC in these patients (RR 1.48; 95% CI 1.14–1.92) [39].

The data analyzed enable us to make the following conclusions:

- the risk of OC in patients taking COCs is reduced;
- a pronounced reduction in the risk of OC was established with the long-term use of COCs;
- the reduction in the risk of OC persists 30 years after the cessation of COC intake;
- COCs have a dose-independent oncoprotective effect in relation to the risk of OC;
- there was a decrease in the risk of borderline ovarian tumors when taking COCs;
- the risk of OC in the presence of mutations in the *BRCA1/2* genes with COCs use is ambiguous.

Thus, the few available data indicate the presence of a carcinogenic effect of HC in relation to BC and CC, but an oncoprotective effect in relation to OC and EC. A further study on different aspects of the carcinogenic potential of HC will allow a more detailed approach to the management of patients using HC for a long time, which will ensure risk reduction and the timely diagnosis of cancers of the female reproductive organs.

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