The Implications of Combined Hormonal Contraceptives in Cancer

https://doi.org/10.70921/medev.v31i3.1316

Florina Borozan[1], Alexandra-Denisa Semenescu[2,3], Larisa Tomescu[1], Ioan Sas[1]

[1]Faculty of Medicine, "Victor Babes" University of Medicine and Pharmacy Timisoara, 2nd Eftimie Murgu Square, 300041 Timisoara, Romania
[2]Faculty of Pharmacy, "Victor Babes" University of Medicine and Pharmacy Timisoara, 2nd Eftimie Murgu Square, 300041 Timisoara, Romania
[3]Research Centre for Pharmaco-Toxicological Evaluation, Faculty of Pharmacy, "Victor Babes" University of Medicine and Pharmacy, 2nd Eftimie Murgu Square, 300041 Timisoara, Romania

Correspondence to:
Name: Alexandra-Denisa Semenescu
E-mail address: alexandra.scurtu@umft.ro

Received: 09 August 2025; Accepted: 28 September 2025; Published: 30 September 2025

Abstract

1.Background/Objectives: Combined hormonal contraceptives (CHCs) are widely used by women during their fertile years. Often, these pills are taken without medical advice, which can lead to certain unwanted effects. This class of medication has been studied over the years for its impact on various types of cancer. Since cancer is becoming an increasingly common condition, understanding the factors that contribute to its development is important for prevention. *2. Methods*: This paper reviews recent literature from reputable sources such as PubMed, Google Scholar, ScienceDirect, and Scopus. *3. Results*: The review of the medical literature reported evidence about the risk of CHCs in developing breast and cervical cancer, and more, about the protective effect on ovarian, endometrial, and colorectal cancer. 4. Conclusion: This paper presents the risk/benefit balance of CHCs in terms of their impact on some cancerous pathologies. According to the analysis, we can state that CHCs are effective and even safe if administered appropriately and according to the recommendations of specialists, depending on the particularities of each patient.

Keywords: oral contraceptives, cancer, risk, benefit

INTRODUCTION

Nowadays, oral contraceptive pills (OCPs) are widely used, especially combined hormonal contraceptives (CHCs) [1].

Three types of oral contraceptive pills are known: progesterone-only, combined estrogen-progesterone, and extended-release pills. Estrogen is the hormone that stabilizes menstrual bleeding, while progesterone prevents pregnancy.

The mechanism of action of progesterone is to inhibit follicular development, which prevents ovulation [2]. Through negative feedback acts on the central nervous system, in the hypothalamus, leading to a decrease in the secretion of follicle-stimulating hormone and luteinizing hormone. Therefore, if the follicle does not develop, estradiol is not produced. In addition, progesterone can stop sperm from entering the upper genital tract.

Similarly, estrogen, through negative feedback on the pituitary gland, inhibits follicular development, with slowed secretion of follicle-stimulating hormone [3].

OCPs are prescribed to women to prevent pregnancy; however, they can also be indicated in menstrual disorders, polycystic ovary syndrome, endometriosis, and some cancers [4, 5]. The administration of OCPs should be done with caution, as there is evidence that these pills may induce a higher risk of cardiovascular disease among women who use them, especially those with other comorbidities [6-8].

Oral contraceptives are widely used by women between 15 and 44 years of age, but due to adverse reactions that occur especially in people at risk, other methods of contraception can also be used. These methods are chosen depending on the co-administered medications, comorbidities, and family history [3].

The first clinical trials of OCPs were conducted in South America in the 1950s when contraception was illegal. In 1957, the FDA introduced the first pill (mestranol 150 µg/norethynodrel 10 mg) for use in menstrual disorders, and a few years later, it was also used for contraceptive purposes [9, 10].

CHCs are classified by the WHO as class 1 carcinogens [11]. Thus, the possible relationship of combined contraceptives with the development of cancer has raised concerns among women and scientific researchers. Estrogens and progesterones can induce cell growth, which can also lead to the proliferation of cancer cells [12].

To date, there is no clear research showing the risk of oral contraceptives in the development of cancer. However, some studies show that continuous use of contraceptives may increase the risk of cancer, especially of the breast and cervix, compared to women who do not use oral contraceptives [13, 14]. However, on the other hand, CHCs may reduce the risk of malignancy in the endometrium and ovaries [15, 16].

Aim and objectives

Due to the intense use of combined oral contraceptives among women of childbearing age, this study aims to highlight the influence of oral contraceptives on different types of cancer to prevent certain risks for women.

MATERIALS AND METHODS

This research was conducted through a systematic review of the specialized literature on combined oral contraceptives, with a focus on their influence on cancer pathologies. Current clinical trials were extracted from scientific databases, including PubMed, Google Scholar, ScienceDirect, and Scopus. Articles were selected according to a series of keywords

such as: contraceptives, combined oral contraceptives, cancer and contraception, cervical cancer, breast carcinoma, endometrial and ovarian cancer, and colorectal carcinoma.

For methodological transparency and clarity in identifying and selecting relevant studies, the review process of this study followed the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The PRISMA framework was adapted to benefit from a structured search. The process of identifying and selecting studies is represented in a flow diagram (Figure 1).

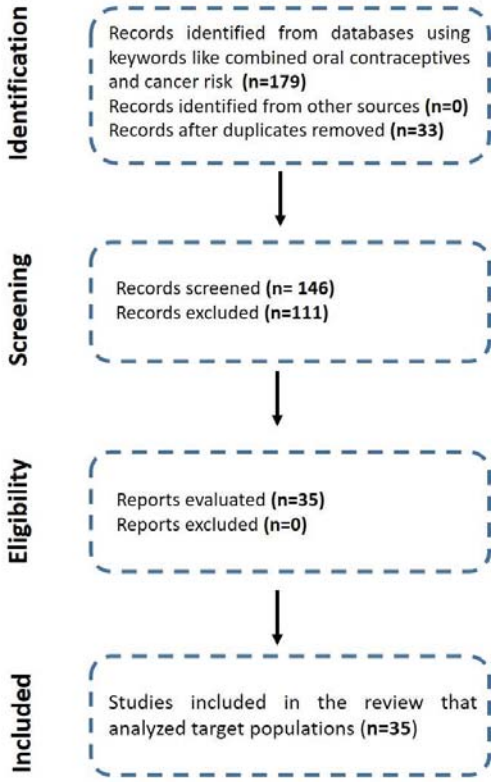

Figure 1. PRISMA 2020 flow diagram for the review

Inclusion criteria were based on prospective, retrospective, and meta-analyses studies that analyzed the influence of CHCs on the development of cancer in women of different ages. Reviews and case reports were excluded. Initially, 179 scientific articles were observed using the keywords, and of these, 35 studies met the criteria and were within the scope of this work.

RESULTS

The benefits and risks of CHCs vary depending on the region or area, with the balance influenced by disease incidence and maternal mortality rates. In underdeveloped nations with high maternal mortality, the use and effectiveness of contraceptives in preventing pregnancy are especially important. Furthermore, even within the same country, the benefits and risks differ for various groups of women. As a result, the balance shifts, with differences seen between smokers and non-smokers as well as between young and older women [17].

The evidence supporting the link between CHCs and cancer is derived from observational studies, including case-control studies and prospective cohort studies. However, these studies cannot show exactly whether oral contraceptive use increases or

reduces the risk of cancer, as there may be differences between the women in the study, which may also influence the development of cancer. This research provides ample evidence that women who use CHCs have a higher risk of developing breast or cervical cancer, while the risk is reduced for ovarian, endometrial, and colorectal cancer [18-20].

Risks of CHCs

Breast cancer

The main concern with CHCs is related to the development of breast cancer.

Breast cancer is the second most common cause of death, being one of the most diagnosed pathologies in women [21].

Sex hormones are factors that can increase the risk of breast cancer, especially in postmenopausal women who are undergoing hormone replacement therapy. Estrogen and progesterone promote the growth of breast tissue by stimulating the proliferation of stem cells [22]. Additionally, estradiol and estrone can damage genes, having a mutagenic potential [23].

Studies have indicated that women who have used CHC recently or are currently taking the pill have about a 24% higher risk of developing breast cancer compared to women who have never used it. The risk of developing cancer decreases after stopping contraceptives and returns to normal after 10 years [24].

An analysis that included 54 epidemiological studies (25 countries) with over 150.000 participants showed that women who used CHCs had a 7% risk of developing breast cancer compared to women who did not use CHCs [25].

Other studies that investigated over 110,000 nurses aged 24 to 43 also reported a risk of breast cancer among those who used contraceptives [26-28].

The same risk was also recorded in a 2017 Danish prospective study with newer contraceptives, reporting a 20% increase in cancer risk [29].

We can, however, state that the higher risk was given by a certain contraceptive, the "triphasic" oral pill, where the dose is released during the menstrual cycle in three stages [30].

More recently, in 2021, a prospective cohort study showed a higher risk for women using CHCs compared to those who do not; these risks were no longer present five years after quitting [31].

The risk of developing breast cancer ranged from 0% to 60% depending on the duration of administration and the contraceptive used.

Table 1 summarizes the studies that reported an increased risk of breast cancer with CHCS use.

Table 1. Relevant studies regarding the risk of breast cancer with CHCs use

Study design	Population	Results	Observations	References
Meta-analysis (54 studies, 25 countries)	53.000+ women	RR 1.24 (CI 95%: 1.15–1.33)	The risk ↓ after stopping: RR 1.16 (1–4 years), RR 1.07 (5–9 years), nil after 10 years. It does not matter the type or duration of CHCs. The tumors detected were less advanced.	[25]
Prospective cohort study	121.577 women	RR 1.26 (95% CI: 1.09–1.46) for use ≥5 years	Association with increased breast cancer mortality in long-term users	[28]
Prospective cohort study	1.8 million women, tracked for 11 years	RR 1.19 for current or late CHC users; RR 1.20 for any hormonal contraception.	Risk ↑ with duration of use. 1 additional case/7,690 women/year; <35 years: 1/50,000/year	[29]
Prospective cohort study	113.187 women	HR 1.31 (95% CI: 1.09–1.58) for current users	Former users: similar risk to non-users after 5 years of stopping	[31]

RR: Risk ratio; HR: Hazard ratio; CI: Confidence interval

Research results suggest that the breast cancer-inducing effect appears to be temporary or limited to recent or long-term use of CHCs.

However, in several prospective cohort studies, neither continuous use nor previous long-term use of CHCs indicated an increased risk of breast cancer [14, 32].

Furthermore, some data support that low concentrations of current preparations do not increase the risk of breast cancer in women with BRCA1 and BRCA2 genetic mutations [33].

Cervical cancer

Cervical cancer is one of the most diagnosed malignant pathologies in women and ranks 4th in the ranking of causes of death [12].

Women who have used combined oral contraceptives for ≥ 5 years have an increased risk of developing cervical cancer compared to women who have not used them. In one study, it was shown that the duration of use of CHCs influences the risk of cervical cancer. Therefore, a 10% increase in risk was reported when they were used < 5 years, while a 60% increase was recorded for use for 4-9 years, and use ≥ 10 years, the risk doubled [34].

In an EPIC cohort study, conducted over 9 years with over 300,000 women, the link between hormones and cervical cancer was investigated [35]. According to previous studies, it has been shown that the risk of cervical cancer increases with long-term use of CHCs.

A similar conclusion was reached in a Danish study of women of childbearing age (two million participants) who were not vaccinated against HPV. It was reported that the risk was the same for both squamous cell carcinoma and adenocarcinoma [36].

However, in all cases, this risk of developing cervical cancer decreases once the use of CHCs is stopped [15, 35, 37].

There is evidence to suggest that the use of CHCs may increase cervical vulnerability to HPV infection or alter the progression of malignant and premalignant lesions.

Thus, the hormones used in CHCs enhance the expression of HPV 16 E6 and E7 oncogenes, leading to damage to the p53 tumor suppressor gene and increasing the ability of viral DNA to promote neoplasticity [37-40].

Benefits of CHCs

Studies have shown several ways in which CHCs may reduce the risk of certain types of cancer, including: i) decreased ovulation, which reduces exposure to natural female hormones, in the case of ovarian cancer; ii) inhibition of endometrial cell proliferation, in the case of endometrial cancer; iii) decreased bile acids in the blood following the use of oral conjugated estrogens, in the case of colorectal cancer [20].

Ovarian cancer

Ovarian cancer is the 8th most diagnosed cancer and the 5th leading cause of death in women [41].

On the other hand, long-term use of CHCs reduces the risk of developing ovarian cancer. Numerous studies suggest their protective effect. Therefore, the longer CHCs were administered, the lower the impact of ovarian malignancy, with even a protective effect, and a decrease of up to 50% of the cancer risk [42-44].

A large analysis claims that contraceptives have prevented 200.000 ovarian cancer lesions and 100.000 deaths caused by this type of cancer [44].

The protective action intensifies with increasing duration of contraceptive use [45] and can continue for up to 30 years after women stop taking CHCs [46].

This effect has also been recorded among women who carry a mutation in the BRCA1 or BRCA2 gene [47-49].

Endometrial cancer

Endometrial cancer is also an important cause of morbidity and malignancy among women [50].

CHCs possess protection against endometrial malignancy. Women who have used and are using CHCs have a lower risk of endometrial cancer than those who have not used them, unlike previous cases, where they induce breast and cervical cancer [45].

Research has shown that the longer the use of CHCs, the lower the risk of endometrial cancer. Thus, after 10-15 years of administration, the risk of neoplasia decreases by approximately 50%. Moreover, after discontinuation of use, the protective effect persists for 30 years, suggesting that there are no individual characteristics that influence it [51].

Moreover, an NIH-AARP prospective study showed that women who used contraceptives, smoked, and were obese had a low risk of developing endometrial cancer [45].

Several studies support the protective action of the pill that persists for many years after stopping CHC treatment [15, 51, 52].

Colorectal cancer

Colorectal cancer is common among women, but it has a good survival rate. IARC has found that the use of oral contraceptives may have a positive impact on reducing the risk of colorectal cancer [12].

A meta-analysis of 29 studies found a relative risk of colorectal cancer for long-term use versus uncontrolled use of 0.8. A study in which the duration of CHC use was inversely associated with a decrease in risk, without influence of dose [53].

In another meta-analysis of 23 cohort and case-control studies, the relative score was similar at 0.8. This study did not examine whether there was a relationship between duration of use and risk, but showed that recent use was more beneficial [54].

Iversen et al. demonstrated that the protection against colorectal cancer by CHC use could be greater than 35 years [15].

Therefore, there is various research that states that the use of CHCs does not induce a high risk of colorectal cancer, and even presents a lower risk by up to 20% [15, 52, 53, 55-58].

In addition, in a cohort study of 1.3 million women, conducted over 13 years, it was shown that the use of CHCs is associated with an increased risk of anal cancer, where HPV may have an influence, similar to cervical cancer [59].

Figure 2 shows the benefit/risk balance regarding the influence of combined oral contraceptives on the most common cancers in women.

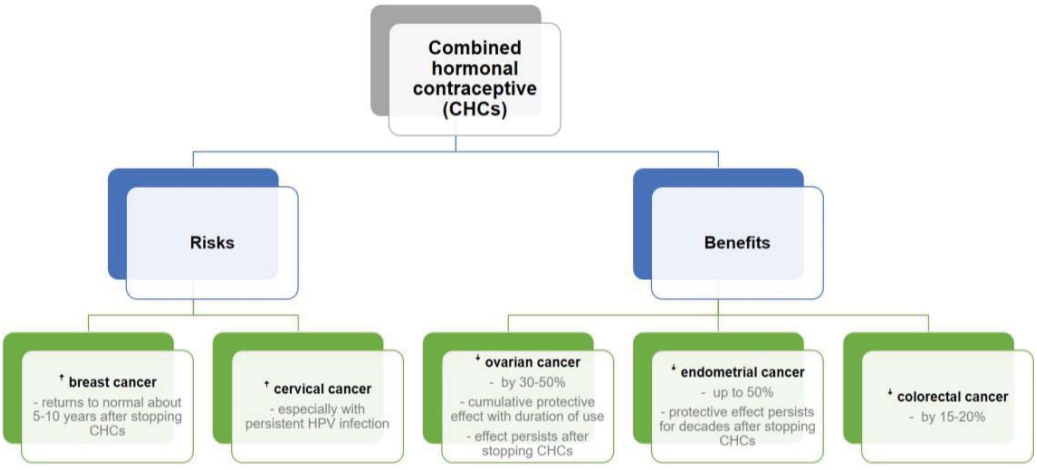

Figure 2. Risk/benefit balance of CHCs

DISCUSSIONS

The role of combined oral contraceptives in cancer development has been widely discussed in the medical literature since the 1970s [60, 61].

In 1979, the International Agency for Research on Cancer (IARC) reported that estrogen and progesterone might influence the differentiation, development, and growth of various tissues in both humans and animals. Additionally, laboratory animal studies have demonstrated that pregnancy, surgical removal of endocrine glands, or external steroid administration can alter the hormonal environment and may either increase or, in some cases, decrease the occurrence of cancerous lesions [62].

Because CHCs are synthetic versions of female hormones, they can increase the risk of carcinoma, especially types of cancer that express receptors for estrogen and progesterone, such as breast cancer [63].

In 2012, the same IARC reported that the use of CHCs may increase the risk of breast cancer in women of childbearing age who have recently used or are currently using the pill. CHCs may also raise the risk of developing cervical and liver cancer with longer treatment duration, and this risk may decrease after stopping therapy. The risk of developing cervical cancer may be due to changes in the susceptibility of cervical cells to infection with high-risk HPV.

Additionally, there has been discussion about a protective effect of combined contraceptives; this effect is attributed to the potency of progesterone and may be reduced by the strength of estrogen. CHCs may lower the risk of developing colorectal cancer and ovarian cancer, depending on how long they are used, and may also influence the risk of skin, pancreatic, lung, or thyroid cancer [64].

A meta-analysis examining the cancer risk in adult women (20-54 years) in the US who use CHCs highlighted these points. Therefore, over 8 years, for every 100,000 CHCs users, the estimated number of additional or reduced cases per 100,000 women was +125 (cervix), +151 (breast), -193 (ovarian), and -197 (endometrium) [65].

Given that numerous large-scale studies have consistently demonstrated a considerable increase in risk among current and recent users of CHCs, breast cancer has garnered the most attention in this context [25, 29]. After stopping, this increased risk steadily decreases and seems to revert to baseline in around ten years. Crucially, the absolute risk increase is minimal, especially for younger women, whose incidence of breast cancer is typically low.

Cervical cancer and CHCs have a more complicated relationship. Long-term usage, especially after five years, may raise the risk of invasive cervical cancer in women who have a history of oncogenic human papillomavirus infection [66, 67]. Although this risk seems to decrease after stopping, it is still a worry in areas with low HPV immunization and screening rates. The increasing use of immunization programs may lessen this association's significance for upcoming generations.

CHCs, on the other hand, have a remarkably protective impact against endometrial and ovarian malignancies. According to extensive collaborative assessments, using CHCs lowers the incidence of ovarian cancer by between 30 and 50 percent, and the protection lasts for decades after stopping [44]. According to Iversen et al. [15], there is a 50% reduction in the risk of endometrial cancer, with long-lasting advantages even for women who stop using it years early. Given the high mortality and usually delayed presence of ovarian cancer, as well as the increasing global incidence of endometrial cancer, these preventive benefits are especially pertinent.

Colorectal malignancies are less examined. Research points to a slight decrease in the risk of colon cancer in CHC users, which may be due to hormonal effects on inflammation and bile acid metabolism [67].

CHCs provide a heterogeneous cancer risk profile when combined. They significantly lower the burden of ovarian and endometrial cancers while moderately increasing the incidence of breast and cervical cancers. They may also provide extra protection against colorectal cancer. From the standpoint of public health, modeling studies indicate that the number of cancers averted frequently surpasses the number that are generated, particularly in populations with high rates of HPV vaccination and cervical cancer screening. However, a woman's lifestyle, family history, genetic predisposition, and access to preventative care can all affect how risks and benefits are balanced for her.

Two important risk factors are the age at which CHC use was initiated and the duration of administration. Current and recent users, particularly those under 35 years of age, are at the highest risk of breast cancer; however, this risk decreases after stopping use and returns to baseline within approximately ten years [15, 29, 44]. On the other hand, the preventive effect against ovarian and endometrial cancer increases with longer duration of use and lasts for decades after stopping use. These divergent durations highlight the importance of age-specific counselling and reproductive goals and demonstrate the dynamic nature of CHC-associated cancer risk.

The overall effect of CHCs is also influenced by socioeconomic and global conditions. The protective benefits could result in significant mortality reductions in high-income nations where screening for ovarian and endometrial cancer is common. The possible rise in cervical cancer risk, on the other hand, might be more significant in low- and middle-income nations, especially those with inadequate access to cervical screening and HPV vaccination [66, 67]. These differences highlight the necessity of context-specific recommendations and public health initiatives that strike a balance between cancer prevention and access to contraception.

The risk-benefit ratio is influenced by genetic predispositions. Although the possible effect on breast cancer risk should be carefully considered, women with BRCA1/2 mutations, who have an increased baseline risk of ovarian cancer, may benefit greatly from CHCs [68, 69]. Similarly, CHC-mediated endometrial protection may be disproportionately beneficial for women with Lynch syndrome or substantial family histories of endometrial or colorectal malignancies. Nevertheless, there is still a dearth of information on genetically predisposed groups.

As demonstrated by this comparative analysis, the effects of CHC use on cancer are neither consistently detrimental nor consistently protective. Rather, the total effect is the result of a balancing act between conflicting effects, mediated by patient-specific characteristics, pharmaceutical formulation, and length of administration. The long-term impacts of more recent contraceptive formulations, the mechanisms behind tissue-specific outcomes, and the integration of these discoveries into tailored contraceptive counseling will all require further research.

Globally, CHCs are some of the most widely used medications. In addition to their main therapeutic utility in preventing unwanted pregnancy, the use of CHCs can have both a positive and negative impact on the development of various types of cancer. However, with the evolution of the medical field, there are new alternatives that can influence this risk. Pharmaceuticals with very low doses of estrogen or alternative molecules (estetrol) or lower affinity for receptors may reduce systemic side effects, thereby reducing the carcinogenic potential [70]. Different receptor affinities between progestins impact cancer risk. New progestin molecules are improved in terms of tissue selectivity and efficacy [71]. Also, the class of selective progesterone receptor modulators (SPRMs) confers tissue-selective action. Therefore, these compounds may offer, in addition to endometrial and ovarian protection, a

reduction in the risk of breast cancer [72]. Research on alternative contraceptive methods, like compounds that block sperm function, is advancing. Non-hormonal options can remove the cancer risk associated with hormonal methods, but they lose the protective effects on the endometrium and ovaries [73]. Another category includes novelty, intrauterine devices that selectively eliminate SPRMs or vaginal rings with very low doses that reduce systemic exposure to hormones and maintain protective and local contraceptive action [74].

Oral contraceptives expose the dual side of hormonal therapy: they decrease the risks of some types of cancer while increasing others. Therefore, innovations such as selective receptor modulators, non-hormonal agents, and local administration may lead to a balance. In the future, personalized contraceptive options are needed that offer increased benefits and decreased risks, and monitoring of long-term safety remains a priority.

CHCs have been researched for more than 50 years, and their effect on cancer risk is still a major focus of studies on reproductive health. The database is still characterized by uncertainty, despite strong evidence showing protective effects against endometrial and ovarian malignancies as well as a moderate and typically temporary increase in the risk of breast cancer. To understand and improve patient care, several critical research gaps need to be addressed.

The long-term safety of contemporary contraceptive formulations, elucidation of progestin-specific effects, inclusion of genetically and ethnically diverse populations, a better understanding of mechanisms, integration with other preventive strategies, and a systematic evaluation of novel contraceptives are among the most urgent research gaps. By addressing these ambiguities, risk estimates will be improved, safer and more customized contraceptive options will be supported, and the body of evidence supporting reproductive health care will eventually be strengthened.

CHC'c understanding is further limited by the lack of diversity in the populations studied. Women of European descent constitute the majority of the current evidence, which comes mainly from high-income countries [15]. Data on non-European groups, as well as on women with genetic predispositions such as BRCA1/2, remain limited and sometimes contradictory [69]. To provide equitable and globally applicable contraceptive advice, research needs to be expanded to encompass a diverse range of populations.

Long-term oncological risks are given less consideration in current pharmacovigilance frameworks, which place more emphasis on acute adverse events like venous thromboembolism [75]. To assess oncological safety over time, it would be beneficial to link prescription registries with cancer outcomes and promote international partnerships.

The primary purpose of oral contraceptives is to prevent pregnancy. The specialist doctor should advise the woman on the best alternative, including the risks and benefits of the pills, as well as their other non-hormonal effects, especially if a woman has comorbidities that could increase her risk when using CHCs. Additionally, pharmacists should work with doctors to ensure patients receive the most effective and affordable treatment.

Pharmacists should also advise patients on adverse reactions, the correct dosage and use of CHCs, and most importantly, how to handle missed doses and other backup methods of contraception. Therefore, the team of professionals can achieve optimal results for women with maximum benefits of contraceptive therapy [3].

CONCLUSIONS

For decades, the carcinogenicity of oral contraceptives has been intensively analyzed. The research conducted reports the risk of breast and cervical cancer after long-term administration of CHCs. However, the long-term protective effect on ovarian, endometrial, and colorectal cancer has also been exposed. The carcinogenic effects of CHCs are reversible

and can be reduced by changing the lifestyle (physical exercise, smoking, breastfeeding, HPV vaccination).

Patients who use oral contraceptives should be warned about their possible carcinogenic action, in addition to their effective contraceptive effect. It is necessary to discuss the balance of benefits and risks and to choose the safest option for the woman. Updated and clear information can strengthen the patient-medical staff relationship, which will lead to the reduction of adverse effects and effective treatment.

Several factors, including age, length of usage, genetic background, tissue-specific mechanisms, and the global health context, influence how CHCs impact cancer. Although the balance is dynamic and unique to each individual, the protective effects against ovarian and endometrial cancers frequently outweigh the moderate rise in breast and cervical cancer risk. Future studies should combine mechanistic findings, incorporate genetically and ethnically diverse populations, prioritize long-term safety studies of newer contraceptive formulations, and assess results in light of changing preventive measures like cancer screening and HPV vaccination. Women around the world will be able to receive more accurate, fair, and knowledgeable contraceptive counseling because of such initiatives.

Following the existing studies, we can state that CHCs are effective and safe, but they must be administered according to the recommendations of specialists.

Conflicts of Interest

The authors declare no conflict of interest.

REFERENCES

[1] United Nations: Department of Economic and Social Affairs. Contraceptive Use by Method 2019: Data Booklet. United Nations; 2020.
[2] Baird DT, Glasier AF. Hormonal contraception. N Engl J Med. 1993;328(21):1543-1549.
[3] Cooper DB, Patel P. Oral Contraceptive Pills. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025.
[4] Schindler AE. Non-contraceptive benefits of oral hormonal contraceptives. Int J Endocrinol Metab. 2013;11(1):41–47.
[5] Cameron NA, Blyler CA, Bello NA. Oral Contraceptive Pills and Hypertension: A Review of Current Evidence and Recommendations. Hypertension. 2023;80(5):924-935.
[6] Tanis BC. Oral contraceptives and the risk of myocardial infarction. Eur Heart J. 2003;24(5):377–380.
[7] Oedingen C, Scholz S, Razum O. Systematic review and meta-analysis of the association of combined oral contraceptives on the risk of venous thromboembolism: The role of the progestogen type and estrogen dose. Thromb Res. 2018;165:68–78.
[8] US Medical Eligibility Criteria (US MEC) for Contraceptive Use, 2016. Published May 18, 2022. Available from: https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/summary.html (accessed on 17 July 2025)
[9] Roach RE, Helmerhorst FM, Lijfering WM, Stijnen T, Algra A, Dekkers OM. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. Cochrane Database Syst Rev. 2015;2015(8):CD011054.
[10] McCarthy KJ, Gollub EL, Ralph L, van de Wijgert J, Jones HE. Hormonal Contraceptives and the Acquisition of Sexually Transmitted Infections: An Updated Systematic Review. Sex Transm Dis. 2019;46(5):290-296.
[11] Cogliano V, Grosse Y, Baan R, Straif K, Secretan B, El Ghissassi F; WHO International Agency for Research on Cancer. Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment. Lancet Oncol. 2005;6(8):552-553.

[12] Kamani M, Akgor U, Gültekin M. Review of the literature on combined oral contraceptives and cancer. Ecancermedicalscience. 2022;16:1416.
[13] Beral V, Hermon C, Kay C, Hannaford P, Darby S, Reeves G. Mortality associated with oral contraceptive use: 25 year follow up of cohort of 46 000 women from Royal College of General Practitioners' oral contraception study. BMJ. 1999;318(7176):96-100.
[14] Vessey M, Yeates D. Oral contraceptive use and cancer: final report from the Oxford-Family Planning Association contraceptive study. Contraception. 2013;88(6):678–683.
[15] Iversen L, Sivasubramaniam S, Lee AJ, Fielding S, Hannaford PC. Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study. Am J Obstet Gynecol. 2017;216(6):580.e1-580.e9.
[16] Rosenblatt KA, Gao DL, Ray RM, Nelson ZC, Wernli KJ, Li W, Thomas DB. Oral contraceptives and the risk of all cancers combined and site-specific cancers in Shanghai. Cancer Causes Control. 2009;20(1):27-34.
[17] Institute of Medicine (US) Committee on the Relationship Between Oral Contraceptives and Breast Cancer. Oral Contraceptives & Breast Cancer. Washington (DC): National Academies Press (US); 1991. E, Risks and Benefits of Oral Contraceptives: Will Breast Cancer Tip the Balance? Available from: https://www.ncbi.nlm.nih.gov/books/NBK234345/
[18] Bassuk SS, Manson JE. Oral contraceptives and menopausal hormone therapy: Relative and attributable risks of cardiovascular disease, cancer, and other health outcomes. Ann Epidemiol. 2015;25(3):193–200.
[19] Wentzensen N, Berrington de Gonzalez A. The Pill's gestation: From birth control to cancer prevention. Lancet Oncol. 2015;16(9):1004–1006.
[20] National Cancer Institute. Oral Contraceptives and Cancer Risk. Available from: https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones/oral-contraceptives-fact-sheet (accessed on 25 July 2025).
[21] Menon G, Alkabban FM, Ferguson T. Breast Cancer. 2024 Feb 25. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025.
[22] Finlay-Schultz J, Sartorius CA. Steroid hormones, steroid receptors, and breast cancer stem cells. J Mammary Gland Biol Neoplasia. 2015;20(1–2):39–50.
[23] Cavalieri E, Rogan E. The molecular etiology and prevention of estrogen-initiated cancers: Ockham's Razor: Pluralitas non est ponenda sine necessitate. Plurality should not be posited without necessity. Mol Aspects Med. 2014;36:1–55.
[24] Cancer Council. Combined oral contraceptives and cancer risk. Available from: https://www.cancer.org.au/about-us/policy-and-advocacy/treatment-care/medicines-devices/combined-oral-contraceptives-and-cancer-risk#benefits (accessed on 25 July 2025).
[25] Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Lancet. 1996;347(9017):1713-1727.
[26] Hunter DJ, Colditz GA, Hankinson SE, Malspeis S, Spiegelman D, Chen W, Stampfer MJ, Willett WC. Oral contraceptive use and breast cancer: a prospective study of young women. Cancer Epidemiol Biomarkers Prev. 2010;19(10):2496-2502.
[27] Bhupathiraju SN, Grodstein F, Stampfer MJ, Willett WC, Hu FB, Manson JE. Exogenous Hormone Use: Oral Contraceptives, Postmenopausal Hormone Therapy, and Health Outcomes in the Nurses' Health Study. Am J Public Health. 2016;106(9):1631-1637.
[28] Charlton BM, Rich-Edwards JW, Colditz GA, Missmer SA, Rosner BA, Hankinson SE, Speizer FE, Michels KB. Oral contraceptive use and mortality after 36 years of follow-up in the Nurses' Health Study: prospective cohort study. BMJ. 2014;349:g6356.
[29] Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard Ø. Contemporary Hormonal Contraception and the Risk of Breast Cancer. N Engl J Med. 2017;377(23):2228-2239.
[30] Beaber EF, Buist DS, Barlow WE, Malone KE, Reed SD, Li CI. Recent oral contraceptive use by formulation and breast cancer risk among women 20 to 49 years of age. Cancer Res. 2014;74(15):4078-4089.

[31] Burchardt NA, Eliassen AH, Shafrir AL, Rosner B, Tamimi RM, Kaaks R, Tworoger SS, Fortner RT. Oral contraceptive use by formulation and breast cancer risk by subtype in the Nurses' Health Study II: a prospective cohort study. Am J Obstet Gynecol. 2022;226(6):821.e1-821.e26.
[32] Hannaford PC, Selvaraj S, Elliott AM, Angus V, Iversen L, Lee AJ. Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraception study. BMJ. 2007;335(7621):651.
[33] Milne RL, Knight JA, John EM, Dite GS, Balbuena R, Ziogas A, Andrulis IL, West DW, Li FP, Southey MC, Giles GG, McCredie MR, Hopper JL, Whittemore AS. Oral contraceptive use and risk of early-onset breast cancer in carriers and noncarriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Biomarkers Prev. 2005;14(2):350-356.
[34] Smith JS, Green J, Berrington de Gonzalez A, Appleby P, Peto J, Plummer M, Franceschi S, Beral V. Cervical cancer and use of hormonal contraceptives: a systematic review. Lancet. 2003;361(9364):1159-1167.
[35] Roura E, Travier N, Waterboer T, de Sanjosé S, Bosch FX, Pawlita M, Pala V, Weiderpass E, Margall N, Dillner J, Gram IT, Tjønneland A, Munk C, Palli D, Khaw KT, Overvad K, Clavel-Chapelon F, Mesrine S, Fournier A, Fortner RT, Ose J, Steffen A, Trichopoulou A, Lagiou P, Orfanos P, Masala G, Tumino R, Sacerdote C, Polidoro S, Mattiello A, Lund E, Peeters PH, Bueno-de-Mesquita HB, Quirós JR, Sánchez MJ, Navarro C, Barricarte A, Larrañaga N, Ekström J, Lindquist D, Idahl A, Travis RC, Merritt MA, Gunter MJ, Rinaldi S, Tommasino M, Franceschi S, Riboli E, Castellsagué X. The Influence of Hormonal Factors on the Risk of Developing Cervical Cancer and Pre-Cancer: Results from the EPIC Cohort. PLoS One. 2016;11(1):e0147029.
[36] Iversen L, Fielding S, Lidegaard Ø, Hannaford PC. Contemporary hormonal contraception and cervical cancer in women of reproductive age. Int J Cancer. 2021.
[37] International Collaboration of Epidemiological Studies of Cervical Cancer; Appleby P, Beral V, Berrington de González A, Colin D, Franceschi S, Goodhill A, Green J, Peto J, Plummer M, Sweetland S. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. Lancet. 2007;370(9599):1609-1621.
[38] Gadducci A, Barsotti C, Cosio S, Domenici L, Riccardo Genazzani A. Smoking habit, immune suppression, oral contraceptive use, and hormone replacement therapy use and cervical carcinogenesis: a review of the literature. Gynecol Endocrinol. 2011;27(8):597-604.
[39] Moodley M, Moodley J, Chetty R, Herrington CS. The role of steroid contraceptive hormones in the pathogenesis of invasive cervical cancer: a review. Int J Gynecol Cancer. 2003;13(2):103-110.
[40] Rinaldi S, Plummer M, Biessy C, Castellsagué X, Overvad K, Krüger Kjær S, Tjønneland A, Clavel-Chapelon F, Chabbert-Buffet N, Mesrine S, Lukanova A, Kaaks R, Weikert C, Boeing H, Trichopoulou A, Lagiou P, Trichopoulos D, Palli D, Agnoli C, Tumino R, Vineis P, Panico S, Bueno-de-Mesquita B, van Kranen HJ, Peeters PH, Bakken K, Lund E, Gram IT, Rodríguez L, Bosch FX, Sánchez MJ, Dorronsoro M, Navarro C, Gurrea AB, Kjellberg L, Dillner J, Manjer J, Butt S, Khaw KT, Wareham N, Allen NE, Travis R, Romieu I, Ferrari P, Riboli E, Franceschi S. Endogenous sex steroids and risk of cervical carcinoma: results from the EPIC study. Cancer Epidemiol Biomarkers Prev. 2011;20(12):2532-2540.
[41] Altekruse SF, Kosary CL, Krapcho M. SEER Cancer Statistics Review, 1975–2007. Bethesda: National Cancer Institute; 2010.
[42] Beral V, Million Women Study Collaborators, Bull D, Green J, Reeves G. Ovarian cancer and hormone replacement therapy in the Million Women Study. Lancet. 2007;369(9574):1703-1710.
[43] Bosetti C, Negri E, Trichopoulos D, Franceschi S, Beral V, Tzonou A, Parazzini F, Greggi S, La Vecchia C. Long-term effects of oral contraceptives on ovarian cancer risk. Int J Cancer. 2002;102(3):262-265.
[44] Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet. 2008;371(9609):303-314.
[45] Michels KA, Pfeiffer RM, Brinton LA, Trabert B. Modification of the associations between duration of oral contraceptive use and ovarian, endometrial, breast, and colorectal cancers. JAMA Oncol. 2018;4(4):516–521.

[46] Havrilesky LJ, Moorman PG, Lowery WJ, Gierisch JM, Coeytaux RR, Urrutia RP, Dinan M, McBroom AJ, Hasselblad V, Sanders GD, Myers ER. Oral contraceptive pills as primary prevention for ovarian cancer: a systematic review and meta-analysis. Obstet Gynecol. 2013;122(1):139-147.
[47] Iodice S, Barile M, Rotmensz N, Feroce I, Bonanni B, Radice P, Bernard L, Maisonneuve P, Gandini S. Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: a meta-analysis. Eur J Cancer. 2010;46(12):2275-2284.
[48] Moorman PG, Havrilesky LJ, Gierisch JM, Coeytaux RR, Lowery WJ, Peragallo Urrutia R, Dinan M, McBroom AJ, Hasselblad V, Sanders GD, Myers ER. Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. J Clin Oncol. 2013;31(33):4188-4198.
[49] Friebel TM, Domchek SM, Rebbeck TR. Modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: systematic review and meta-analysis. J Natl Cancer Inst. 2014;106(6):dju091.
[50] Mahdy H, Vadakekut ES, Crotzer D. Endometrial Cancer. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025.
[51] Collaborative Group on Epidemiological Studies on Endometrial Cancer. Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. Lancet Oncol. 2015;16(9):1061–1070.
[52] Gierisch JM, Coeytaux RR, Urrutia RP, Havrilesky LJ, Moorman PG, Lowery WJ, Dinan M, McBroom AJ, Hasselblad V, Sanders GD, Myers ER. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer Epidemiol Biomarkers Prev. 2013;22(11):1931-1943.
[53] Luan NN, Wu L, Gong TT, Wang YL, Lin B, Wu QJ. Nonlinear reduction in risk for colorectal cancer by oral contraceptive use: a meta-analysis of epidemiological studies. Cancer Causes Control. 2015;26(1):65-78.
[54] Bosetti C, Bravi F, Negri E, La Vecchia C. Oral contraceptives and colorectal cancer risk: a systematic review and meta-analysis. Hum Reprod Update. 2009;15(5):489-498.
[55] Murphy N, Xu L, Zervoudakis A, Xue X, Kabat G, Rohan TE, Wassertheil-Smoller S, O'Sullivan MJ, Thomson C, Messina C, Strickler HD, Gunter MJ. Reproductive and menstrual factors and colorectal cancer incidence in the Women's Health Initiative Observational Study. Br J Cancer. 2017;116(1):117-125.
[56] Kabat GC, Miller AB, Rohan TE. Oral contraceptive use, hormone replacement therapy, reproductive history and risk of colorectal cancer in women. Int J Cancer. 2008;122(3):643–646.
[57] Brändstedt J, Wangefjord S, Nodin B, Eberhard J, Jirström K, Manjer J. Associations of hormone replacement therapy and oral contraceptives with risk of colorectal cancer defined by clinicopathological factors, beta-catenin alterations, expression of cyclin D1, p53, and microsatellite-instability. BMC Cancer. 2014;14:371.
[58] Charlton BM, Wu K, Zhang X, Giovannucci EL, Fuchs CS, Missmer SA, Rosner B, Hankinson SE, Willett WC, Michels KB. Oral contraceptive use and colorectal cancer in the Nurses' Health Study I and II. Cancer Epidemiol Biomarkers Prev. 2015;24(8):1214-1221.
[59] Coffey K, Beral V, Green J, Reeves G, Barnes I; Million Women Study Collaborators. Lifestyle and reproductive risk factors associated with anal cancer in women aged over 50 years. Br J Cancer. 2015;112(9):1568-1574.
[60] La Vecchia C, Tavani A, Franceschi S, Parazzini F. Oral contraceptives and cancer. A review of the evidence. Drug Saf. 1996;14(04):260–272.
[61] Khoo S K. Cancer risks and the contraceptive pill. What is the evidence after nearly 25 years of use? Med J Aust. 1986;144(04):185–190.
[62] IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Sex hormones (II) IARC Monogr Eval Carcinog Risk Chem Hum. 1979;21:11–561.
[63] Bovo AC, Pedrão PG, Guimarães YM, Godoy LR, Resende JCP, Longatto-Filho A, Reis RD. Combined Oral Contraceptive Use and the Risk of Cervical Cancer: Literature Review. Rev Bras Ginecol Obstet. 2023;45(12):e818-e824.
[64] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Pharmaceuticals. IARC Monogr Eval Carcinog Risks Hum. 2012;100(Pt A):1-401.

[65] Schlesselman JJ. Net effect of oral contraceptive use on the risk of cancer in women in the United States. Obstet Gynecol. 1995;85(5 Pt 1):793-801.
[66] Moreno V, Bosch FX, Muñoz N, Meijer CJ, Shah KV, Walboomers JM, Herrero R, Franceschi S; International Agency for Research on Cancer. Multicentric Cervical Cancer Study Group. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. Lancet. 2002;359(9312):1085-1092.
[67] Ning Y, Wang L, Giovannucci EL. A quantitative analysis of body mass index and colorectal cancer: findings from 56 observational studies. Obes Rev. 2010;11(1):19-30.
[68] Kotsopoulos J, Lubinski J, Moller P, Lynch HT, Singer CF, Eng C, Neuhausen SL, Karlan B, Kim-Sing C, Huzarski T, Gronwald J, McCuaig J, Senter L, Tung N, Ghadirian P, Eisen A, Gilchrist D, Blum JL, Zakalik D, Pal T, Sun P, Narod SA; Hereditary Breast Cancer Clinical Study Group. Timing of oral contraceptive use and the risk of breast cancer in BRCA1 mutation carriers. Breast Cancer Res Treat. 2014;143(3):579-586.
[69] Kotsopoulos J. BRCA Mutations and Breast Cancer Prevention. Cancers (Basel). 2018;10(12):524.
[70] Fruzzetti F, Fidecicchi T, Montt Guevara MM, Simoncini T. Estetrol: A New Choice for Contraception. J Clin Med. 2021;10(23):5625.
[71] Stanczyk FZ, Hapgood JP, Winer S, Mishell DR Jr. Progestogens used in postmenopausal hormone therapy: differences in their pharmacological properties, intracellular actions, and clinical effects. Endocr Rev. 2013;34(2):171-208.
[72] Richardson AR, Maltz FN. Ulipristal acetate: review of the efficacy and safety of a newly approved agent for emergency contraception. Clin Ther. 2012;34(1):24-36.
[73] Marinaro JA, Goldstein M. Non-hormonal Contraception: Current and Emerging Targets. Adv Exp Med Biol. 2025;1469:245-272.
[74] Sitruk-Ware R, Nath A. The use of newer progestins for contraception. Contraception. 2010;82(5):410-417.
[75] Skovlund CW, Mørch LS, Kessing LV, Lidegaard Ø. Association of Hormonal Contraception With Depression. JAMA Psychiatry. 2016;73(11):1154-1162.