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REVIEW ARTICLE

Combined Oral Contraceptives and Breast Cancer: an Unsolved Conundrum

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Abstract

Purpose This article's purpose is to evaluate the quality of evidence and the magnitude of risk of breast cancer attributed to combined oral contraceptives (COCs). This is because whilst a number of studies have been done to assess this risk, evidence has been inconclusive and contradictory. This article is expected to aid clinicians when counselling women about COC and develop strategies to mitigate risk, if any, especially to women with pre-existing risk factors for breast cancer.

Materials and methods Thirteen recent studies of diverse levels of evidence which attempt to assess the risk of breast cancer in COC users have been critically appraised. Six were systematic reviews/meta-analyses, and three were prospective cohort studies. Two case–control studies, a literature review and an observational study comprised the remaining four. Sample sizes of prospective cohort studies ranged from 46,022 to 1.8 million. Populations of various nationalities were included.

Results There appears to be a marginal increase in risk of breast cancer with a relative risk ranging from 1.19 to 1.5. The risk increased with duration of use, particularly when exceeding 5 years. More recent studies have indicated higher risk when compared to studies before 1994.

Conclusion The available evidence highlights the importance of adequate counselling when helping decide suitable contraceptive methods or hormonal therapy in general. It also suggests that short-term use may be safe in the absence of other risk factors for breast cancer. Caution needs to be exercised in women with pre-existing risk factors such as high BMI, smoking, family history of breast cancer or when there is a need to use it for longer than 5 years.

Keywords Combined oral contraceptives · Breast cancer · Hormonal contraception · Oestrogen

Background

Breast cancer is the second most common cancer in the world and the most common cancer among women. One woman out of every eight is at risk of developing breast cancer in her lifetime [1]. Aetio-pathology of breast cancer development is poorly understood in vast majority of sufferers. There could be several contributing factors such as genetic predisposition, diet, lifestyle, obesity and smoking (Fig. 1). Various hormonal therapies, to which women are exposed, are increasingly coming under scrutiny as possible contributing factors. This is because COC containing oestrogen with progesterone as well as progestin-containing devices/implants and hormonal replacement therapy (HRT) are being increasingly prescribed for various indications.

COC, since its inception in 1957, has turned out to be a very popular contraceptive choice because of ease of use, high efficacy and several non-contraceptive benefits such as protection from endometrial/ovarian cancers, endometriosis and reduction of menstrual blood loss and regularisation of cycles [2]. Moreover, it is increasingly being used for managing endocrine disturbances such as poly-cystic ovarian syndrome, acne and hirsuitism.

It is important to examine whether women are indeed exposed to a higher risk of breast cancer when using COC. This concern may, in part, be due to the theoretical

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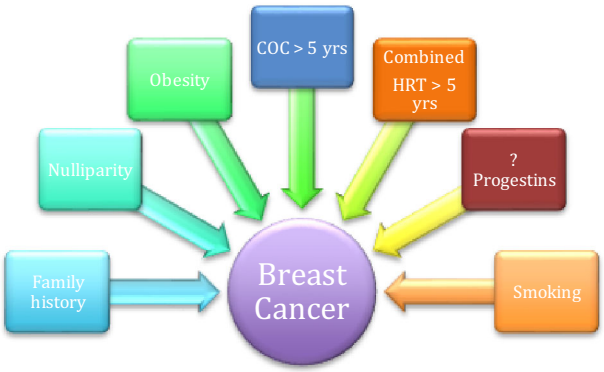

Fig. 1 Possible risk factors for breast cancer

possibility that exogenous oestrogen may stimulate oestrogen receptors in breast tissue, thereby increasing the risk of carcinogenesis [3]. If so, we need to assess the magnitude of risk and whether benefits of use outweigh the theoretical risk. It is also important to evaluate whether it is possible to modify the purported risk whilst allowing women to enjoy the benefits summarised above.

Current guidelines by several reputed organisations have not addressed this issue in a comprehensive manner. Faculty of Sexual and Reproductive Healthcare (FSRH) of UK [4] states in its guidelines that there is an increase in the risk of breast cancer but it does not clarify in unambiguous terms, the magnitude of this risk and relation to the duration of use. Interestingly, FSRH provides much better data on the positive effects of COC in reducing the incidence of uterine and ovarian cancers [3].

Objectives of our review are summarised as follows:

- To assess the quality of evidence on effect of COC use on incidence of breast cancer.
- If there is an increased risk, to understand the magnitude of this risk.
- To assess the possible strategies to mitigate this risk as applicable.
- To identify lacunae in evidence base and assess key areas for future research.

Review of Evidence

A thorough literature search of evidence base was performed using the key words "Oral Contraceptive Pills", "Combined Oral Contraceptives", "Hormonal Contraception", "Breast Cancer" and "oestrogen" on the EBSCO search engine. It revealed at least 13 studies (Table 1) addressing the relative risk of breast cancer with COC use. Prospective studies, systematic reviews and meta-analyses with large sample sizes were chosen for an in-depth review.

The FSRH, in its guidelines published in 2019, suggested that women be advised that current use of COC is associated with a small increased risk of breast cancer which reduces with time after stopping COC, and there is no risk due to COC after 10 years of stopping usage [4].

The most significant of studies cited by FSRH in its guidelines is a large Danish prospective cohort study [5] published in 2017 by Mørch L S et al. Using Nationwide registries, 1.8 million Danish women were followed up on average for 10.9 years (a total of 19.6 million person-years). The relative risk of breast cancer among current/recent users of COC was 1.2 (95% CI 1.14–1.26). This risk increased from 1.09 with less than one year of use to 1.38 with more than 10 years of use. After discontinuation of COC, the risk continued to be higher in women who had used pills for more than 5 years as compared to those who did not. The study found one extra breast cancer for every 7690 women using hormonal contraception. No major differences in risk were observed between COCs containing different progestogens. The study is significant because of robust study design and methodology, large sample size and standardisation for potential confounding factors.

A systematic review by Jennifer M Gierisch et al. [6] that included 44 observational studies studying the effect of COC on the risk of breast cancer observed an RR of 1.08 (95% CI 1.00–1.17) for ever users of pills. Due to the constantly changing oestrogen dose in COC, the publication years of included studies were limited to those published from 2000, to maximise the proportion of subjects who used oral contraceptive formulations similar to those currently on the market. It was also observed that though the RR seemed small, it was very significant due to the overall high rate of breast cancer diagnosis in women. No relation to the duration of use was seen, and the increased risk in recent COC users was lost after 10 years of stopping use.

A prospective cohort study published by Lisa Iversen et al. [7] in 2017 observed 46,022 women for a period of 44 years. Cancer incidence rates in ever and never users of COC were also calculated, and data were standardised for age, parity, social class and smoking. It was observed that the insignificant increased risk of breast cancer in women using COCs (RR 1.02 [95% CI 0.91–1.17]) appeared to be lost after 5 years of stopping use. The study thus concluded that not only did COC use not have any long-term effects on risk of breast cancer, but many women would benefit from the important reduction in risks to other types of cancers.

A meta-analysis by Ali Soroush et al. [8] published in 2017 observed an RR of 1.521 (95% CI 1.25–1.85) in women who used COCs as compared to non-users. The STROBE criteria were used whilst choosing the 26 studies for this review, which assessed risk for a total of 460,260

Table 1 Summary of studies included in the literature review

Year	Studies	Type of study	Level of evidence	Results	95% CI	Sample size
1990	Gast et al. [17]	Systematic review	1	No risk associated with COC use	–	–
1994	Mishell [16]	Literature review	5	No risk associated with COC use and in fact stated that COC use protected against breast cancer when used at a young age	–	–
1994	Tomasson et al. [15]	Prospective case–control study	3	No risk associated with COC use	–	–
1995	La Vecchia C et al. [14]	Case–control study	3	Increased risk with an RR of 1.1	0.9–1.4	3890 participants
1996	Collaborative group on Hormonal Factors in Breast Cancer [9]	Meta-analysis	1	Increased risk with an RR of 1.24 in current COC users, which decreased with the number of years of stopping use	1.15–1.33	54 case–control studies, 153,536 participants
2006	Kahlenborn C et al. [11]	Meta-analysis	1	Increased risk with an RR of 1.19	1.09–1.29	34 studies of varying evidence
2007	Hannaford PC et al. [10]	Observational study	3	An increased risk with an RR of 1.22 with more than 97 months of COC use	0.97–1.52	1,830,000 participants
2012	Zhu H et al. [13]	Meta-analysis	1	Increased risk with an RR of 1.09. 10 years of use contributed a 14% increase to the risk	0.99–1.17	13 cohort studies 871,616 participants
2013	Jennifer M Gierisch et al. [6]	Systematic review	1	Increased risk with an RR of 1.08	1.00–1.17	44 observational studies
2014	Poosari A et al. [12]	Prospective cohort study	2	Increased risk with an RR of 1.31	0.65–2.65	11,414 participants
2016	Soroush, Ali et al. [8]	Meta-analysis	1	Increased risk with an RR of 1.5	1.25–1.85	26 studies, 460,260 participants
2017	Mørch LS et al. [5]	Prospective cohort study	2	An increased risk with an RR of 1.2 in current/recent users, and 1.38 in women who used COC for more than 10 years	1.14–1.26	1.8 million participants
2017	Lisa Eversen et al. [7]	Prospective cohort study	2	Increased risk with an RR of 1.02	1.00–1.17	46,022 participants

Iranian women. It was postulated that the attributed risk may be directly due to an increase in oestrogen levels in the body and indirectly due to the oestrogen-induced weight gain.

The Collaborative Group on Hormonal Factors in Breast cancer [9] conducted a meta-analysis (1996) of 54 case–control studies involving 153,536 women to assess the relation between breast cancer and COC use. Current users had an RR of 1.24 (95% CI 1.15–1.33) which reduced to 1.16 (95% CI 1.08–1.23) 1–4 years after stopping and 1.07 (95% CI 1.02–1.13) 5–9 years after stopping. Interestingly, breast cancers diagnosed in ever users were less clinically advanced than those in never users.

An observational study done by Hannaford PC et al. [10] including 1,830,000 British women did not state any significant risk associated with the use of COC. Interestingly, however, an RR of 0.95 (95% CI 0.81–1.23) for COC use of less than 97 months increased to 1.22 (95% CI 0.97–1.52) for COC of equal to or more than 97 months. The significantly increased risk of breast and cervical cancer that was seen in current and recent users, however, appeared to be lost within approximately 5 years of stopping oral contraception, with no evidence of either cancer recurring at increased risk in ever users with time.

One particularly interesting observation is the increased risk of breast cancer seen with COC use in newer studies, particularly those published in the last decade, compared to the older ones. This may be due to better surveillance of COC users as well as highly sensitive diagnostic methods and rigorous testing for the early detection of cancer. There may be other confounding factors such as increased BMI, but this will remain a conjecture without directed research.

The Danish cohort study [4] also suggested the contribution of progestins to the risk of breast cancer, although

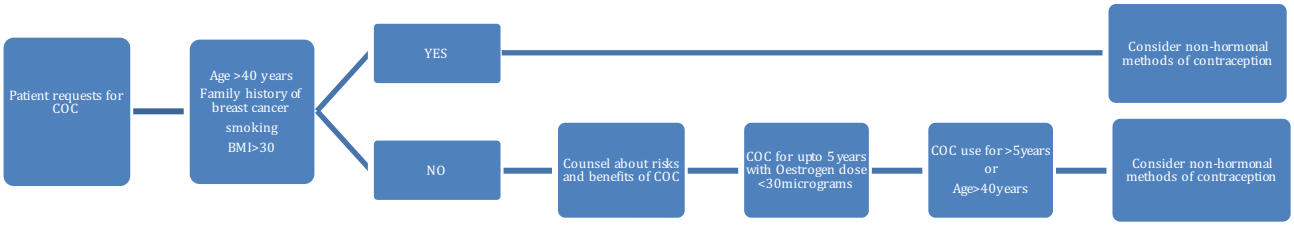

Fig. 2 An algorithm for prescribing COC without increasing risk of breast cancer

the data were insufficient to make a definite connection between the two. Interestingly, NICE guidelines on Hormone Replacement Therapy in postmenopausal women [18] published in 2015 cited low-quality evidence from 1 RCT that found that the risk of developing breast cancer is significantly higher for women who received oestrogen plus progestogen compared with those on placebo during 13 years of treatment and follow-up, but not for women on oestrogen alone.

The possibility of role progestogens is corroborated by a new meta-analysis of participant data from the Collaborative Group on Hormonal Factors in Breast Cancer published in The Lancet [19] in August 2019. The analysis included 108,647 cases of breast cancer in prospective studies. The study included long-term follow-up of women who used hormonal replacement therapy (HRT) and those who discontinued HRT, mostly in the early 2000s. Among women with complete information, mean HRT duration was 10 years in current users and 7 years in past users.

It was found that RRs were greater for oestrogen–progestin than oestrogen-only preparations, were greater in current than in past users and (in both current and past users) increased steadily with duration of use. There was a significant excess risk during 1–4 years of current use: the RRs were 1.60 (95% CI 1.52–1.69) for oestrogen–progestin and 1.17 (95% CI 1.10–1.26) for oestrogen-only HRT. For 5–14 years of current use, the RRs were 2.08 (95% CI 2.02–2.15) for oestrogen–progestin and 1.33 (95% CI 1.28–1.37) for oestrogen-only HRT. Risk due to HRT also persisted more than 10 years after stopping.

Considering the fact that progestins are being extensively used as a form of contraception both in combination with oestrogen and on its own (intra-uterine devices, pills, depot and implants), it is imperative to determine its contribution (if any) on the risk of breast cancer.

Conclusion

More recent studies, particularly published in the last decade, do observe an increased risk of developing breast cancer among women using COC, when compared to those prior to 1994. This risk showed an increase with duration of use, mainly when used over 5 years. An increase in risk was also observed when COC was taken by women younger than 30 years, in the majority of studies. This risk gradually reduced to a minimum after 5–10 years of stopping usage of oral contraceptives. There was also a significant increase in risk to ever users who either had a family history of breast cancer or had mutations that predisposed to breast cancer in some studies.

Based on the evidence, it may be advisable to educate women about the potential risk that may be there when using COC whilst emphasising that this risk has to be weighed against many of the potential benefits of using COC (refer Fig. 2 for an algorithm for prescription of COC). COC use of 5 or more years has a significant residual increase in the risk of developing breast cancer, and therefore, it may not be advisable to use COC for more than 5 years.

In women who have either a family history or a mutation in a gene that may predispose to developing breast cancer, the increased risk over and above the background risk may mean that it is more advisable to use other methods of contraception. There are no sufficient data available that assess the risk of recurrence of breast cancer due to COC use, but it makes eminent sense to avoid any form of hormonal contraception in this group.

Research recommendations are as follows:

(A) Evaluate whether discontinuation of COC for short intervals of 3 to 6 months would reduce the risk of developing breast cancer long term.
(B) Evaluate the role of progesterone in augmenting the risk of breast cancer.
(C) Evaluate the feasibility of developing a national registry of cancer to profile the magnitude of cancer incidence in developing countries and understand the possible risk factors in the context of developing countries.

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Availability of Data and Material All data and materials as well as software applications support their published claims and comply with field standards.

Code Availability Not applicable.

Declaration

Conflict of interest None.

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