A REVIEW ON ORAL CONTRACEPTION AND BREAST CANCER

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ABSTRACT:

Oral contraception was introduced almost 50-60 years ago. Now a huge number of the female population use it as primary contraception across the globe as it is a convenient option available over the counter. However, contraceptive pills have several adverse effects on the female body as they cause hormonal imbalance. Oral contraceptive pills are of two types, the combined estrogen and progestin pill and the mini-pills, which contain only progestin. Recent research has shown that the hormone concentration in contraceptive pills is known to be a possible cause for cancer, specifically breast cancer, in females around 30-35 years of age-old. Women who consume contraceptive pills regularly are at high risk for breast cancer among other side effects like weight gain, mood swings, thyroid, PCOD, etc. The current work attempts to review the effects of oral contraceptives about breast cancer in women and its prevalence.

KEYWORDS: Oral contraceptive, breast cancer, estrogen, progestrin.

INTRODUCTION:

In the current times due to a busy lifestyle and high standard of living, women are turning to contraceptives as a convenient alternative to control their menstrual periods as well as a mode of contraception. Oral contraceptives were introduced in the 1960s, after which many women used them as their primary contraceptive method. Oral contraceptives are tablets made of hormones like progesterone and progestin that prevent pregnancy. In order to avoid conception, these artificial hormones alter your body's hormonal system. The body generally prevents ovulation when using hormonal contraceptives. A contraceptive pill or birth controlling pill helps to prevent ovulation and also change the mucosal lining of the cervix to make it more difficult for the sperm to pass through the cervix and fertilize the ova, thereby decreasing the likelihood that the fertilized egg will be implanted. (National cancer Institute, 2018) The hormonal oral contraceptive pill comprises synthetic derivatives of the female's natural hormones progesterone ($C_{21}H_{30}O_2$) and oestrogen ($C_{18}H_{24}O_2$). Most mixed preparations (second-generation tablets) contain ethinyloestradiol as the oestrogen. However, some preparations also contain mestranol. In third-generation pills, the newer chemicals desogestrel or gestodene, which are more effective, have less androgenic activity, and induce less modification in lipoprotein metabolism, may be used as the progestogen instead of norethisterone, levonorgestrel, ethynodiol, or any of the other older hormones. The estrogen content of the pill should be no more than 50µg of ethinyl-estradiol. Emergency contraceptive pills contain

progesterone and levonorgestrel ($C_{21}H_{28}O_2$), but combination oral pills comprising oestrogen (100 g) and levoestragestrel (250 g) must be taken within 72 hours following unprotected sex. Mifepristone is also administered as a single dosage. (FSRH-Faculty of Sexual and Reproductive Healthcare, 2019)

Furthermore, progestin—the synthetic equivalent of progesterone—is found in certain tablets. Non-steroidal and non-hormonal oral contraceptives include centchroman (Ormeloxifene). (Manual for Oral Contraceptives by Family Planning Division Ministry of Health and Family Welfare Govt. of India, 2016) Contraceptive pills have both contraceptive use and non-contraceptive use, as they also help with irregular menstruation, heavy menstruation, endometriosis, acne and premenstrual syndrome. In addition, it has other adverse effects including weight gain, mood swings, thyroid issues, obesity, cardiovascular issues, PCOD, Cancer, etc.

Breast cancers develop in women most commonly after age 40, but there are cases reported where women have developed breast cancer in their 30s. (Carey K. Anders et al., 2009). Research shows that there is a connection between breast cancer and a female's former reproductive history. Breast cancer is a multifaceted illness. The risk is increased due to several variables, including age, reproductive history, hormonal medication, exposure to radiation, family history, genetic mutations in BrCa1 & 2, and many more. Researchers have associated oral contraceptives with cancers related to the reproductive organs since they have been used and the same is reviewed in this study. The risk of cancer rises if the woman regularly uses hormonal contraception. There may be differences between oral contraceptive users and nonusers, which might raise the chance of developing cancer. According to Dr Lidegaard, the mechanism behind the link between hormonal contraception and breast cancer is that "exogenous hormones are expected to influence breast tissue as do the natural sex hormones, estrogen and progestin (Andrea S. Blevins Primeau, 2018). The goal of the current review is to comprehend and describe the risks related to using oral contraceptives and breast cancer.

MATERIAL AND METHODS:

We carried out an extensive search of the English Literature-related paper databases available in PubMed (Medline), Google Scholar, NCBI, Web of Science, and SCOPUS (from 1990 to 2022) to find studies examining the link between oral contraceptives and the risk of breast cancer. We used the MeSH phrases or keywords "breast cancer," "breast carcinoma," with "oral contraceptives," "combined pills," "contraceptive tablets," or "birth control pill" for computer searches. To find other relevant research, we also looked through various references of the papers that were discovered, earlier review articles, meta-analyses, and other relevant publications.

DISCUSSION:

1990-1995

During the period of 1990–1995, a lot of research was done to comprehend the connection between O.C. (oral contraceptives) and breast cancer. Various parameters and patterns of O.C. consumption was considered. Majority of the researchers found no elevated breast cancer risk among women who used the pills for a brief duration, but a slight increase in risk was associated with women

who were taking the pills for a longer period of time. (Romieu, I. et al., 1990)

The case-control study between 1983 and 1991 in Northern Italy concluded that there was no correlation between oral contraceptive pills use and parity, age at first delivery, or family medical history of breast cancer (Tavani, A., et al., 1993). After reviewing the epidemiologic literature, it was concluded that even after extensive usage, women who had ever used oral contraceptives did not have a higher incidence of breast cancer (Romieu et al., 1990). Overall, found a tendency of increased risk for women who started using them before full-term pregnancy (relative risk = 1.72) and in premenopausal women with breast cancer who took oral contraceptives for a longer period (Romieu et al., 1990). Similar to this, the meta-analysis by Hawley, W. B. et al., (1993) discovered that women who use oral contraceptives before their first full-term pregnancy have a higher chance of developing breast cancer, but no association between risk and length of use of the O.C. pill was observed. However, according to the study by McPherson, et al., (1994), breast cancer risk increased in women who began taking the O.C. pill before the age of 20 and continued to take it for more than 10 years; but the risk decreased if the consumption of O.C.s was discontinued.

1996-2000

Most research on the correlation between oral contraceptives and breast cancer between 1996 and 2000 concentrated on factors like frequency of use and the O.C. formulation women used. In a cohort study of four hundred and twenty-six families, a connection was observed between the usage of O.C. formulations and a family history of breast cancer among women diagnosed during 1944 and 1952. (Grabrick, D. M. M. 2000) arrived at the conclusion that women with first-degree relatives who had breast cancer and who consumed oral contraceptive formulations before 1975, which were probably to include higher doses of oestrogen and progestin, had a greater risk of developing breast cancer. Similar to this, The Collaborative Group on Hormonal Factors in Breast Cancer (1996), reviewed 54 epidemiological studies and found a marginally higher incidence of breast cancer in women using C.O.C (combined oral contraceptives). Women who continued using them for ten years after ceasing had a low relative risk (R.R = 1.24) as did those who continued using it for 1-4 years (R.R = 1.16) and 5-9 years (R.R = 1.07) after discontinuing. Breast cancer is not significantly more likely to be discovered 10 or more years after discontinuing consumption (R.R = 1.01) As compared to malignancies discovered among never-users of O.C., cancers diagnosed then are clinically less progressed (Calle, E. E., et al., 1996)

Rossing, M. A., et al., (1996) found no correlation between the use of oral contraceptives and the probability of getting breast cancer in middle age among the cohort of women who first took these medicines in their study of women residing in King County. Later, according to Chie, W., et al., (1998) post-menopausal patients who used O.C. before the age of 25 and for less than a year were at higher risk of developing OC-related adverse effects. The adjusted odds ratio (OR) was 3.4 when compared to never users of OC. Nevertheless, Van Hoften, C., et al., (2000) discovered that women over the age of 55 who used an oral contraceptive for more than ten years had a 2-fold increased risk of

breast cancer (OR= 2.1). They came to the conclusion that, while it does not affect younger women, long-term oral contraceptive use increases the chance of breast cancer in women over 55 years of age.

2001-2005

Between 2001 and 2005, more research was done at the genetic level; the association of O.C. use on Brca1/2 carriers and non-carriers was determined, as well as the types of new formulations. Milne, R. L., et al., (2005) found that the use of O.C. pills for at least 12 months was linked to a reduced risk of breast cancer for Caucasian women who are BRCA1 mutation carriers [odds ratio (OR)= 0.22]; but not for BRCA2 mutation carriers (OR, 1.02) or non-carriers (OR, 0.93). First use occurring in or before 1975 was associated with an increased risk for non-carriers (OR, 1.52 per year of usage before 1976). They concluded that while there may be a lower risk for BRCA1 mutation carriers, there is no proof that using the present low-dose O.C. formula elevate the likelihood of breast cancer with an early onset in mutation carriers. Women's Lifestyle and Health (2002) conducted a survey in which it was discovered that O.C. users who took O.C. for many years had an elevated risk of developing breast cancer than non-users (Merethe Kumle et al., 2002). As per the data recorded by Kumle and co-authors recent use of O.C.s is linked to a higher risk of breast cancer (R.R., 1.6). Both the usage of progestin-only tablets (R.R., 1.6) and combined OCs (R.R., 1.5) appear to raise the risk to a similar extent the overall, relative risk was 1.0 and previously it was 0.9 (Merethe Kumle et al., 2002). However, different outcomes were shown in the study by Marchbanks et al., (2002), which interviewed women between the ages of 35 and 64. It was found that using O.C. pills were not associated with considerably greater chances of breast cancer. The total health risks of combined oestrogen and progesterone usage, however, outweighed the advantages over a 5.2-year average follow-up among healthy postmenopausal American women. After the Women's Health Initiative study's findings were published by (Rossouw, J. E. et al., in 2002) there may have been a fall in the usage of H.R.T. (Hormonal Replacement Therapy), which could account for the observed decrease in incidence. Previous research dictates that factors like never being married, usage of oral contraceptives, the age at first delivery and number of deliveries in one's lifetime along with post menopause are directly related to breast cancer cases in a hospital-based case control study conducted Multiple analysis revealed that never married, use of O.C. pills, age at first delivery, number of deliveries and postmenopause, were directly correlated with breast cancer in study. (Yavari P., et al., 2005)

2006-2010

During 2006-2010, the study on BRCA1/2 was done concerning the various formulations of O.C., no direct relation between the use of O.C. and its association with the BRCA mutation carrier was observed. The International BRCA1/2 Carrier Cohort Study (IBCCS 2007), which included 1,593 BRCA1/2 mutation carriers, was conducted retrospectively. According to (Brohet., et al., 2007), there is no evidence that the current use of oral contraceptives elevates breast cancer risk beyond that seen in the general population. However, depending on the length of use, especially before the first full-term pregnancy, both BRCA1 and BRCA2 mutation carriers may be at an enhanced

probability of breast cancer. Similar findings were found by other researchers (Eunjung Lee et al., 2008) in their study of Los Angeles-based females between the ages of 20 and 49 who had recently been identified with breast cancer. The researchers came up with the conclusion that there was no correlation between the use of oral contraceptives in a general or minimal dose of oral contraceptives with an elevated risk of breast cancer in any category, including BRCA1/2 mutation carriers.

A statistically noteworthy correlation between the utility of the pill and the risk of breast malignancy was found by studies conducted by Muhammad Faheem, et al., (2007). Similarly to this, other researchers (Casey, et al., 2008) concluded in their review research, that while there was a slight increase in the risk of breast cancer linked to the use of previous O.C. formulations, more recent researches that included recent formulations have not found an increase in risk. The risk of breast cancer is quite low, even with the older formulations (Casey, et al., 2008). Yet, in contrast to the findings above, research done by Hunter et al., (2010) showed varied results. They examined the lifetime oral contraceptive use of 116,608 female nurses between the ages of 25 and 42, as well as the precise formulations used and discovered no link between previous oral contraceptive use and breast cancer risk (multivariate relative risk, 1.12). Any oral contraceptive currently being used was linked to slightly greater risk (multivariate relative risk, 1.33). The greater risk was significantly explained by the relative risk of triphasic preparations with levonorgestrel as the progestin, which was 3.05. There is an elevated risk of breast cancer associated with the present usage of oral contraceptives. The majority of this increase in risk may be attributed to levonorgestrel, which is utilised in triphasic preparations. Continuous monitoring of these linkages is necessary due to the diversity of oral contraceptive formulations. Different oral contraceptive formulations may provide varying breast cancer risks (Hunter et al., 2010).

2011-2015

From 2011 to 2015, various cohort studies & case-control studies were conducted considering various parameters concerning oral contraceptives, such as short-term, long term, variation in formulations, and also the association with respect to BRCA 1 and 2 mutations and triple-negative breast cancer.

In 2013, hospital-based, case-control research was carried out in north India by Bhadoria, et al., (2013). According to them breast cancer risk was found to be 9.50 times greater among women who had previously used oral contraceptives. The study's findings demonstrated a high correlation between breast cancer in the Indian population and reproductive aspects. Similar research was done in Bhopal, India in 2008–2009 (Lodha, R., et al., 2011). where a history of OCP usage and a family history of breast cancer may be epigenetic variables that increase the risk of breast cancer according to the findings of this study. In a case-control study using a questionnaire, (Soheila Ehsanpour et al., 2013) it was found that taking pills for 3-6 years increased breast cancer risk by 2.18 times, age at first use less than 20, the risk was increased by 3.28 times, and time since last use was less than 25 years, the risk was increased by 2.63 times. Demonstrating a substantial link between past usage of birth control pills and the likelihood of developing breast cancer Gierisch, et al.,

(2013) did a systematic study and came to identical conclusions, determining that users had a marginally but significantly higher risk of breast cancer (OR, 1.08). According to the findings, using oral contraceptives more recently is connected with a greater risk. Oral contraceptives may have a significant role in a significant number of incidences of breast cancer, even if the enhanced risk of the disease is quite low.

Beaber, et al., (2014) discovered that recent O.C. use (within the last year) was linked to an increased risk of breast cancer when compared to never or former O.C. use, research included women aged 20 to 49. Nevertheless, the recent usage of O.C.s with high doses of oestrogen (OR = 2.7), ethynodiol diacetate (OR = 2.6), or triphasic dosage with an average of 0.75 milligrammes of norethindrone was linked with significantly higher risks (OR = 1.0). This suggests that using contemporary O.C.s recently is associated with elevated risk of breast cancer, though the risk may vary based on formulations, according to a study on progestin-only formulations (Samson, M. E. et al., 2016). It was concluded that no correlation existed between the risk of breast cancer and the use of progestin-only formulations, such as oral contraceptives containing norethindrone, depot medroxyprogesterone acetate, injectable levonorgestrel system users, implantable devices, and intrauterine devices. This implies that breast cancer risk is not increased by progestin-only formulations (Samson, M. E. et al., 2016).

Zhu, H., et al., (2012) reported prospective cohort research on the use of oral contraceptives and breast cancer risk. The combined relative risk (R.R.) of breast cancer was 1.08, when comparing ever-OC users to never-OC users. A dose-response analysis based on five studies that met the criteria revealed a substantial 14% increase in breast cancer risk for every ten-year increase in O.C. usage. This implies that whereas long-term O.C. use is linked to a significantly greater risk of breast cancer, ever-occurring O.C. use is not significantly connected with an increased risk. Contrarily, (Vessey, M., & Yeates, D. K., 2013) from the Oxford-Family Planning Association contraceptive research concluded that the data regarding breast cancer (1087 cases) were completely negative; comparing ever users of O.C.s with never users the relative risk (R.R.) was 1.0.

According to Amanda I. et al., (2011) findings (H.R. = 0.80), oral contraceptives are not linked to triple-negative breast cancer. Corresponding to this, Moorman, P.G., et al., (2013) found in their comprehensive analysis a non-statistically significant link between breast cancer (OR, 1.21). Independent analyses of BRCA1 and BRCA2 mutant carriers produced similar outcomes.

2016-2022

In recent years, many studies have been conducted and reported that over the years the formulations of O.C. consumption pattern, and awareness about O.C. has changed since the time of discovery. Recent studies have mixed opinions on the risk of breast cancer wherein long-term consumption and specific formulation have a considerable rise in the risk of breast cancer.

In their study, Karlsson, T., et al., (2021) found that, while the follow-up was only extended to age 55, there was an elevated risk of breast cancer in women in general (OR = 1.10). For breast cancer, there was no particular pattern related to usage length. Only those who stopped using oral

contraceptives right away (within two years) after doing so were shown to have a higher Hazard Ratio (H.R.) for breast cancer (H.R. = 1.55). On the other hand, Park, J. and co-authors (2021) discovered in their research that O.C. use was consistently linked to an increased risk of breast cancer [odds ratio (OR), relative risk (RR), or hazard ratio (HR) = 1.24] and a decreased risk of ovarian cancer (OR/RR/HR = 0.53). When BRCA1 and BRCA2 mutant carriers were examined independently, similar results were seen. Only long-term (>5-year) O.C. users were shown to have an elevated risk of breast cancer. This means that the current research points to a strong correlation between BRCA mutation carriers' continued usage of O.C.s and an elevated risk of breast cancer (Park, J., et al 2021).

Niemeyer Hultstrand, J., et al., (2022) observed no higher risk of breast cancer among current users of any combination H.C (Hormonal Contraceptives), compared to never users of any H.C., but current users of progestogen-only techniques had an elevated risk of breast cancer, IRR 1.32. (1.20–1.45). Breast cancer risk was found to be highest in the first five years of usage across all H.C. types including combined H.C and progestogen-only. They concluded that progestogen-only methods are currently linked with a marginally higher risk of breast cancer, whereas combined H.C. users only showed an elevated risk during the first five years of use. Ten years after the women ceased using H.C., the risk was eliminated. In a study that was similar to this, (Nagykálnai, T., and Landherr, L., 2018) reviewed the literature and came to the conclusion that while the risk rose with longer usage duration, the absolute increase was extremely minor.

It was observed by researchers in their study that before the age of 25, there was a reduction in the risk of cancer in O.C. users nevertheless, using O.C.s before the first full-term pregnancy (OR= 1.14), and using them for more than five years (OR=1.09) both significantly elevated the risk of breast cancer (Kanadys, W., et al., 2021). Premenopausal women, postmenopausal women, and nulliparous women did not have a significant rise in risk. This means that using oral contraceptives does not seem to put consumers at an increased risk of breast cancer (Kanadys, W., et al., 2021). Nevertheless, study reports that taking O.C. before a first full-term pregnancy or for more than 5 years can affect the development of breast cancer (Kanadys, W., et al., 2021). Similar to this, Morch, L.S., et al., (2017) conducted a nationwide cohort study in Denmark of women between the ages of 15 and 49 years. They concluded that compared to women who had never used hormonal contraception, women who had recently used contemporary contraceptives had a greater chance of developing breast cancer, with a relative risk of 1.20. Also, risk increased for the women who used O.C. for longer durations; however, absolute raises in risk were minimal. In addition, the meta-analysis conducted by Baraska, A. et al., (2021) revealed that the use of O.C. in general was linked to a substantially higher risk of breast cancer. Following, in a meta-analysis, researchers (Baraska, A., and Kanadys, W. 2022) proposed a variety of effects of oral contraceptive usage against breast cancer in BRCA carriers. Overall, the results of the meta-analysis showed a statistically negligible decrease in risk. Conversely, O.C. usage before age 20 was linked to an increased risk of breast cancer. The risk of breast cancer was not

significantly affected by multivariable meta-regression including factors like age, duration of use and time since last OC use (Baraska, A., and Kanadys, W. 2022).

Huber, D., et al (2020) examined the breast cancer literature from 1995 to 2018, concluded that some studies suggested an elevated risk in breast cancer. In BRCA mutation bearers, other investigations did not discover a link between O.C. and breast cancer. Huber, D., et al (2020) concluded that previous researches only discovered a connection between young age at O.C. start and early-onset breast cancer. An elevation in breast cancer risk due to O.C. is hard to rule out. Women with the BRCA mutation who are considering using O.C. need to be aware of possible increases in breast cancer risk as well as other contraceptive methods. The research does not consistently support an elevated risk of breast cancer associated with C.O.C usage, according to (Kamani, M., et al., 2022). The findings vary from no increase in risk to an increase in the risk of 20%–30%, and the risk seems to be transient and restricted to recent or present frequent C.O.C use. Oral contraceptives and hormone replacement medication were found to be inversely linked with O.C. in recent research.

To summarize the review, it can be said that in the 1990s, studies found no correlation between oral contraception and breast cancer; however, studies concluded that women who use oral contraceptives before their pregnancy and use them for a longer duration may have an elevated risk. In early 2000, BRCA mutation 1 carriers had a reduced risk, but not for BRCA 2. The use of formulations like progestin-only pills or combined pills may increase the risk of breast cancer, but the disadvantages outweigh the advantages. Later, it was found that the old formulations of O.C. had increased risk, but the new and precise formulations did not increase the risk. However, the use of triphasic formulations of O.C. may elevate the risk of breast cancer. In the last decade, the studies have had inconsistent results. Studies have clearly shown that women who used oral contraceptives of particular formulations and used pills for an extended period are considerably more at risk. Additionally, there is a higher chance of breast cancer for women who used O.C. prior to a full-term pregnancy.

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Table 1: Summary of the effect of Oral Contraceptive use on the Breast cancer (1990-2022)

Study, Author, Year	Country	Study Period	Study Design	Age group	Number of Cases	Control	Relative risk 95% CI	Comments
Tavani. A. et al., (1993)	North Italy	1983-1991	Case-Control	Below 60	2309	1928	ever vs never user (RR= 1.2 CI=1.0-1.4) started 10> (RR = 1.3, 95% CI = 1.0-1.9) stopped in 5> (RR = 1.5, 95% CI = 1.1 -2.0) started when 25 (RR = 1.4, 95% CI = 1.1 -1.7) after first birth (RR = 1.2, 95% CI = 1.0- 1.5)	No Association
McPherson et al., (1994)	Developed Country		Review		373	456	> 10 years after stopping RR 1, Current user RR 1.24 (0.96-1.05) 1-5 years since stopping 1.16 1.08-1.2 5-9 years since stopping 1.07 1.02-1.13 below 40 (RR = 0.9, 95% CI = 0.6-1.2).	increased risk for women who used OC before the age of 20
Hawley et al., (1993)		1966-1990	Review				ever users (RR= 1.07, 95% CI =0.78 - 1.36) Current users (rs= -0.153, P = 0.189) before full term pregnancy (rs = +0.497, P = 0.011)	No association for ever users and long term user, Significant association for user before first full term pregnancy
Romieu, et al., (1990)		1966-1989	Review + Case Control				before first term pregnancy (RR = 1.72; 95% CI = 1.36 to 2.19)	Significant increase in risk for long term user and users for 4years before full term pregnancy

Grabrick, et al., (2000)	US	1944-1952,1991-1996	Cohort study + Interview			394 3002 2754	sister & daughter (RR=3.3; 95% [CI], 1.6-6.7) grand-daughter & nieces (RR= 1.2; 95% CI, 0.8-2.0) marry- in (RR= 1.2; 95% CI, 0.8-1.9) higher dose of estrogen and progestin (RR= 3.3; 95% CI, 1.5-7.2)	Association is significant for users of earlier formulation having first degree relative of breast cancer
Mary Anne Rossing, et al.,(1996)	King Country	1988-1990		50-64	537	492		no risk for use of OC in middle age
Collaborative Group on Hormonal Factors in Breast Cancer							(RR= 1-24 [1-15-1-33], 1 -4 years after stopping 1-16 [1-08-1-23] 5 -9 years after stopping 1-07 [1-02-1-13] 10 or more years after stopping use (RR= 1-01 [0.96-1.05]	risk for user of COC and log term users
Wei-Chu CHIE et al., (1998)	Taiwan	Feb 1993 to June 1994	case-control		174	453	odds ratio (OR) for OC use was 1.7 (95% CI 5 0.9–3.2). before 25 years old vs. never use was 3.4 (95%CI 5 1.2–9.7) OC use before 1971 vs. never use was 3.2 (95% CI 5 1.2–8.9) use ,25 years vs. never use was 5.8 (95% CI 5 1.5–22.1) > 5 years vs. never use was 3.5 (95% CI 5 0.9–14.3).	Risk is associated for those who use OC before the age of 25

Van Hoften, C., et al., (2000)	Netherlands	Nov 1982 to May1996	case-control	42-63	309	610	older then 55years, use more than 10 years odds ratio (OR) 2.1, 95% confidence interval (CI) 1.1–4.0)	Risk for long term users
Milne, R. L., et al., (2005)	San Francisco, California	1995-1998	case control	before age 40	316	124	use for at least 12 months [odds ratio (OR), 0.22; 95% confidence interval (CI), 0.10-0.49]	No association between curret OC user and BRCA mutation carrier
	Ontario, Canada	1996-1998			1119	504	r BRCA2 mutation carriers (OR, 1.02; 95% CI, 0.34-3.09)	
	Melbourne and Sydney, Australia	1992-1998			1208	913	(OR, 0.93; 95% CI, 0.69-1.24).	
Kumle, M., et al., (2002)	Norway & Sweden	1991-1992	case control	30-49	103027	1008	current user [RR, 1.6; 96% confidence interval(CI), 1.2–2.1] (RR, 1.5; 95% CI, 1.0–2.0) (RR, 1.6; 95% CI, 1.0–2.4) short term (RR, 1.3; 95% CI, 1.0–1.7) before full term pregnancy (RR, 1.4; 95% CI, 1.0–1.8)	Risk of use of OC for Current user as well as those who user COC and progestin only pill
Yavari, P., et al., (2005)	Iran	2004	Case-control		303	303	Current users RR=1.95 (95% CI 1.32-2.87)	OC is related to increase in risk for breast cancer
Marchbanks, P. A., et al., (2002)	Atlanta, Detroit, Philadelphia, Los Angeles, and Seattle		Case-control	35-64	4575	4682	current user RR= 1.0 (95% CI, 0.8 to 1.3) previous users 0.9 (95% CI, 0.8 to 1.0)	No risk associated
Rossouw, J. E et al., (2002)	US	1993-1998	Case-control	50-79	16608		HR= 1.26 (95% CI=1.00-1.59)	Health risk exceeds benefits from use of COC

Eunjung Lee et al., (2008)	Los Angeles	July 2000-March 2003	Case-Control	20-49	1469	444	BRCA1/2 mutation non-carrier OR=0.81 (95% CI,0.57-1.14) BRCA1/2 mutation carrier OR= 0.68 (95% CI,0.33-1.38) BRCA1/2 carrier cases vs non-carrier cases OR 0.82 (95% CI,0.46-1.46)	NO risk associated between user of OC and BRCA 1 & 2 mutation carrier
Muhammad Faheem et al., (2007)	Islamabad	January to July 2005	Case-control		300		use of contraceptive pill (p = 0.03)	No risk associated between OC user and breast cancer
David J. Hunter et al., (2010)	US	1989-2001	Case-control	25-42	1,344	1,246,967	Past Use of OC RR= 1.12; 95% CI (0.95–1.33) Current use RR =1.33; 95% CI, (1.03–1.73)	risk for current user of OC and use of levonorgestral in triphasic formulations
Bhadoria, A. S. et al., (2013)	India	2013	Case-control		320	320	Ever users OR=9.5(95% CI, 3.38- 26.7	risk is associated between OC user and breast cancer
Phipps, A. I., et al., (2011)	US	before 2010	Case-control		155723		ER+ and OC user HR=0.94 (95% CI,0.85 to 1.03) Triple negative HR= 0.98 (95% CI,0.73 to 1.32)	OC user risk is associated for ER+ but not triple negative breast cancer
Ehsanpour, S., et al., (2013)	Isfahan, Iran	2011	Case-control		175	350	OR=2.27 (95% CI,(1.53-3/33)	OC use can increase risk regardless of consumption pattern
Beaber, E. F., et al., (2014)	Washington	1990-2009	Case-control	20-49	1102	21952	Recent OC (OR=1.5, 95% CI=1.3–1.9) ER+ (OR=1.7, 95% CI=1.3– 2.1) ER− (OR=1.2, 95% CI=0.8–1.8) high dose estrogen (OR=2.7, 95% CI=1.1–6.2) ethynodiol diacetate (OR=2.6, 95% CI=1.4–4.7) triphasic dosing with an average of	Use of contemporary O.Cs is associated with increase in risk

							0.75 milligrams of norethindrone (OR=3.1, 95% CI=1.9–5.1 low dose estrogen OCs were not (OR=1.0, 95% CI=0.6–1.7)	
Mørch, L. S., et al.,	Denmark	1995-2012	cohort study	15-49	11,517	1,837,297	current user RR=1.20 (95% [CI], 1.14 to 1.26). within 1 year o use RR= 1.38 (95% CI, 1.26 to 1.51)	Increased risk for current users and long term user of OC
Niemeyer Hultstrand, J., et al., (2022)	Sweden	2005-2017	cohort study	15-34	3842		Current user IRR 1.03 (0.91−1.16) Progestogen only user IRR 1.32 (1.20−1.45) combined HC IRR 1.39 (1.14−1.69)	increased risk for current user of progestogen and increased risk for combined HC during first five years of use