Associated Risk Between Use of Oral Contraceptive Pills and Three Types of Breast Cancer: ER+, ER-, and TN

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ABSTRACT

Around 9.5 million women between the ages of 15 and 44 use some form of oral contraceptives. Oral contraceptive pills typically consist of progestin and estrogens, synthetic versions of the hormones that a female-bodied person naturally produces and are used by many people for a various number of reasons; such reasons include regulating acne, controlling hormone production, and preventing pregnancy. One in eight women in the US is diagnosed with breast cancer over the course of her lifetime, and many of these cancers have hormone-related causes. However, there are three types of breast cancer specifically linked to the hormones that are found in oral contraceptive pills: estrogen receptor-positive, estrogen receptor-negative, and triple-negative. While the potential of oral contraceptive-related causes for these breast cancers have been studied at great length, researchers are often unable to confirm their finding of an associated risk between synthetic hormones in oral contraceptives and certain types of breast cancer. Many studies agree that this associated risk exists, but stress the need for more involved research with more detailed and specific objectives. This literature review will provide insight into limitations of current research on the associated risk between oral contraceptives and breast cancer in order to fill research gaps and evaluate the certainty of current findings.

INTRODUCTION

Oral contraceptives, also known as birth control pills, have gained popularity as they have become more accessible over the last several years. The pill is used for many reasons, including reducing the appearance of acne, controlling hormone production, preventing pregnancy, managing irregularities with menstruation, and controlling the symptoms of Polycystic Ovarian Syndrome or endometriosis-related pain (Cooper et al., 2019). Oral contraceptive pills typically consist of progestin and estrogens, which are synthetic versions of the hormones that female bodies naturally produce. Based on the specific reason for which a woman uses oral contraceptives, the concentration of these hormones varies. As a result, there are different types of oral contraceptive pills with different compositions of hormones depending on a woman’s needs: the combined pill, which contains both progestin and estrogens; the progestin-only pill; and the estrogens-only pill (CDC, 2018a). There is no limit on the length of time during which a woman can use these three types of oral contraceptive pills. In fact choosing to take oral contraceptives for many years or until reaching menopause is seen as acceptable as long as the person is healthy (CDC, 2017).

Almost 9.5 million women in the United States, aged 15 to 44, use some form of oral contraceptives (“Contraceptive use in the united states,” 2018). This statistic highlights the magnitude of women, within a range of ages, who use oral birth control. One in eight American women are diagnosed with breast cancer over the course of their lifetime (“U.S. breast cancer statistics,” 2018). Breast cancer has become increasingly common, hence more effort is being made to find its cause and expand treatment options. Recently, many studies have linked the use of oral contraceptives with breast cancer.

Many types of breast cancers exist, but the three specific types that are associated with estrogen and progesterone hormone levels in the female body are estrogen receptor-positive (ER+), estrogen receptor-negative (ER-), and triple-negative breast cancer (TNBC). Growth of cancerous cells is known to be promoted when the hormones progesterone and estrogen bind to receptors on breast tissue (American Cancer Society, 2017). Knowing whether or not the specific case of breast cancer is connected to either of these two types of receptor-related cancers is key to understanding and prescribing...
the best treatment option. ER+ breast cancer means that the cancer has occurred due to the binding of estrogen to the receptor, whereas ER- breast cancer refers to breast cancer not caused by estrogen, but rather from another hormone (like progesterone) binding to different hormone receptors. Another kind of breast cancer is TNBC, wherein breast tissue does not have estrogen, progesterone, or HER2 hormone receptors (CDC, 2018b). TNBC research is important because TNBC cells do not have the hormone receptors related with the ingestion of synthetic hormones, yet can have an associated risk with their use (“Breast cancer hormone receptor status,” 2017).

This review will examine existing research done on the correlation between the use of oral contraceptives and an associated risk for three types of breast cancer: ER+, ER-, and TNBC. Gaps in research need to be filled in order to allow more people in need of oral contraceptives to be able to use them without fear of potentially increasing their risk of breast cancer.

**ESTROGEN RECEPTOR-POSITIVE (ER+) BREAST CANCER**

Many studies have found a significant relationship between estrogen receptor-positive breast cancer and oral contraceptives through odds ratio and hazard ratio values. A prospective study (a type of study that includes similar participants who only differ by certain attributes) conducted by Bethea et al. specifically looked at 1,848 African American women in the United States with ER+ breast cancer. Geographic location and age were controlled in this study, but the type of specific oral contraceptive used by the participants was not mentioned. For women who had used some form of general oral contraceptive in the last five years, the odds ratio was 1.46 (Bethea et al., 2015). An odds ratio value is a measure of association between an outcome and an exposure. It represents the odds of a certain outcome in relation to a certain or multiple exposures. The odds of a particular situation are then compared to the odds of the outcome occurring without that exposure to produce an odds ratio value (Szumilas, 2010). In the study by Bethea et al., the odds ratio value is 1.46; a value higher than 1 means that the exposure is associated with higher odds of that outcome. In the context of Bethea et al., there appears to be an association between ER+ breast cancer and oral contraceptives.

Busund et al. looked specifically at the use of progestin-only oral contraceptives in correlation with ER+ breast cancer in a cohort study. A total of 74,862 Norwegian women, aged 30–70, participated in the study over the span of 16 years. The researchers followed up repeatedly after seven or eight years, and a total 1,245 cases of premenopausal breast cancer were indicated. The researchers depicted their findings through hazard ratio values. A hazard ratio also measures for association between the likeliness of an outcome and exposure; however, it is represented through a number which establishes if the association is present in the group focus in comparison with a control group (Spruance et al., 2004). Women who exclusively used the progestin-only oral contraceptives for more than five years had a hazard ratio of 1.87 (Busund et al., 2018). The hazard ratio value is above 1, which indicates an increased risk and association between the outcome and exposure, or breast cancer and progestin-only oral contraceptives.

A case-control study conducted by Beaber et al. in Cancer Research looked at the recent use of oral contraceptives and its association with breast cancer in women aged 20 to 49. There were approximately 1,120 participants that were studied over a period of 19 years. The women studied were exclusive to the Seattle area and used different forms of oral contraceptive pills, which had varying dosages of estrogen or progestin only. Beaber et al. came to the conclusion that the use of a high estrogen oral contraceptive pill (50 µg ethinyl estradiol or 80 µg mestranol) led to an odds ratio value of 3.9; this high value indicates a present association between high estrogen oral contraceptive pills and ER+ breast cancer. This study also looked at progestin-only oral contraceptives and found increased odds ratios for estrane progestin, norethindrone, and ethynodiol diacetate, with odds ratios of 2.1, 2.1, and 6.7 respectively (Beaber et al., 2014a). Such odd ratio values for the multiple types of progestin-only oral contraceptive pills show an association with ER+ breast cancer since they are all greater than 1. Limitations of this study include a lack of precise information regarding the duration of oral contraceptive use. Beaber et al. also only categorized the women by having “recently used” and “never/former used” without providing the specific number of years. They simply mentioned that the women who received at least one oral contraceptive prescription before the reference date qualified for having “recently used” the pill (2014a).

Rosenberg et al. studied 907 women on the East Coast of the United States in a case-control study. These women were either Caucasian or African American, aged between 25 and 69, and used some type of oral contraceptive pill. For ER+ breast cancer, the odds ratio for women who used an oral contraceptive pill for at least one year and who were under the age of 35 was 1.7, which indicates an increased association between ER+ breast cancer and oral contraceptive pills (Rosenberg et al., 2009). Rosenberg et al. did not mention the precise duration of oral contraceptive use, while also imprecisely grouping their classification of use to more than one year (2009).
ESTROGEN RECEPTOR-NEGATIVE (ER-) BREAST CANCER

Studies have also found that there is an association, through odds ratio and hazard ratio values, between estrogen receptor-negative breast cancer and oral contraceptives. A study conducted by Bethea et al. looked at oral contraceptives in correlation with ER- breast cancer, specifically in African American women. For women who had used some form of general oral contraceptive, the odds ratio was 1.57 for ER- breast cancer (Bethea et al., 2015), indicating an association between both the exposure and outcome.

A case-control, population-based study conducted by Beaber et al., featured in Cancer Epidemiology, Biomarkers and Prevention, studied 943 women aged 20 to 44 residing in the Seattle area over a six year time period. These women used a combined version of the oral contraceptive pill, containing both estrogen and progestin. The study also assessed a dose-response for each type of combined oral contraceptive pill. All of the women participating in the study used the contraceptive pill for more than six months and knew the specific type of pill they were taking. Overall, this study found an odds ratio value of 2.0 in correlation with ER- breast cancer for women aged 20 to 44, all of whom used the combined oral contraceptive at the time of the study or in the last five years. The odds ratio increased to 3.5 for women aged 20 to 39, who used the combined oral contraceptive pill within the same time period (Beaber et al., 2014b). The difference in odds ratio values depending on age shows that there is a higher association between the combined oral contraceptive pill and ER- breast cancer for women who are aged 20 to 39.

A study published by Rosenberg et al. studied women who were Caucasian or African American and were aged between 25 and 69. All of the participants used some type of oral contraceptive pill. The odds ratio was 1.7, indicating a present association between ER- breast cancer for women under the age of 35 who used an oral contraceptive pill for more than one year (Rosenberg et al., 2009).

Busund et al. looked at both progestin-only and combined oral contraceptives in correlation with ER-breast cancer in their study. This study specifically looked at Norwegian women over a span of 16 years. Women who exclusively used the progestin-only oral contraceptive and those who exclusively used the combined oral contraceptive pill for more than five years had a hazard ratio value of 1.54 and 1.73, respectively (Busund et al., 2018). Since the hazard ratio values are both above one, they indicate a greater association between the combined oral contraceptive pill than the progestin-only oral contraceptive with ER- breast cancer since 1.73 is larger than 1.54.

As detailed above, the studies mentioned are all in agreement regarding an association between some form of oral contraceptive and ER- breast cancer. However, a study published by Beaber et al. in Cancer Research arrived at a different consensus than the studies previously mentioned. Their results indicated that there was not an associated risk between ER- breast cancer and combined oral contraceptives (Beaber et al., 2014a). The most significant difference between this study and the other studies discussed above is their data collection method. Beaber et al. looked at prescriptions and detailed accounts of oral contraceptive use (Beaber et al., 2014a), while the study published in Cancer Epidemiology, Biomarkers and Prevention by Beaber et al. based their data collection on participants’ verbal recall (2014b). Differences like these, which are critical in achieving an accurate finding, indicate that qualified and detailed information from participants are necessary.

TRIPLE NEGATIVE BREAST CANCER (TNBC)

An informative case-control and meta-analysis study by Li et al. published in Molecular and Clinical Oncology observed 15,427 women, 3,279 of which were diagnosed with TNBC. The study included women of different ethnic and racial backgrounds and took place over different time frames from 1993 to 2015. No specific information on the type of oral contraceptives used by the women in the study is available, but all of the women must have been on some form of oral contraceptive pill for at least one year to be considered an oral contraceptive user. This study identified an odds ratio value of 1.21 (Li et al., 2017), indicating an association between TNBC and oral contraceptives used by women for at least a year, regardless of specific race or ethnicity.

In another study, Bethea et al. specifically looked for a correlation between oral contraceptives and TNBC in African American women. The odds ratio for women who used some form of general oral contraceptive in the last five years was 1.78 (Bethea et al., 2015). Being above 1, this odds ratio value expresses an association between TNBC and oral contraceptives in African American women who used contraceptive pills in the last five years.

A study in Cancer Epidemiology, Biomarkers, and Prevention, conducted by Beaber et al., looked specifically at women in the Seattle area over a six year time period, and focused on the association between different doses of the combined oral contraceptive pill and TNBC. An odds ratio value of 2.2 was found for women aged 20 to 44 who used the combined oral contraceptive at the time of the study or in the last five years. The odds ratio increased to 3.7 for women aged 20 to 39 who used the combined oral contraceptive pill within the aforementioned time period (Beaber et al., 2014b). An increase in the odds ratio values indicates that there is a stronger association between combined oral contraceptive pill usage for more than five years.
years and TNBC in women aged 20 to 39, as opposed to the broader age range of 20 to 44.

FUTURE AREAS OF STUDY

There are many inconsistencies in different aspects of the reviewed studies, most of which pertain to data collection and classification of oral contraceptive use. In order for there to be a definitive answer regarding a clear association between oral contraceptive use and ER+, ER−, or TN breast cancer, certain improvements need to take place while conducting such studies.

Firstly, a case-control study looked at oral contraceptives in association with cancerous tumors of the milk ducts in the breast; this is referred to as breast cancer in situ, a type of breast cancer excluded from the studies previously mentioned. Conducted by Gill et al., this study offers insight regarding prospective improvements for cancer research, the foremost being to assess the use and chemical makeup of oral contraceptives (2006). With this information, the factors that make oral contraceptives harmful can be pinpointed and new formulations of the pill can be produced, allowing women to continue using oral contraceptives with fewer risks.

Secondly, a study by Beaber et al. proposed the need for a more thorough history check on the women in these trials, using sources such as pharmaceutical records, which would allow doctors to be able to prescribe them birth control that would not harm them. This improvement would prevent miscalculations in association between breast cancer and oral contraceptive use, as well as aid in the formation of better and unique treatment plans for women depending on the contraceptive they use (2014b).

Lastly, one case-control and meta-analysis study criticized all of the assumptions that different experiments make in associating the use of oral contraceptives, specifically the consumption of synthetic estrogens, in relation to breast cancer. In the end, the study mentions the importance of understanding the specific type of oral contraceptive used by the women in the study, the exact time they used it and what stages in their lives, as well as looking more closely into their life history and ethnicity (Soroush et al., 2016). By gathering more information on factors that potentially influence both variables, more directed studies can be performed in order to confirm whether there is an associated risk between oral contraceptives and breast cancer.

Using these recommendations for improvement will allow more women to be aware of potential risks so that they can make healthy decisions regarding their oral contraceptives. Additionally, promoting research is necessary to create healthier forms of oral contraceptives, which will allow women to benefit from a commonly used medication without fear of its potential correlation with certain types of breast cancer.

CONCLUSION

Estrogen receptor-positive, estrogen receptor-negative, and triple-negative breast cancer all express odds ratio and hazard ratio values above one, indicating that there is an association between these types of breast cancers and oral contraceptive pills. All of the studies mentioned specify different types of oral contraceptives; however, the association between the outcome and exposure is still very much present between the oral contraceptives and ER+, ER−, and TN breast cancers. Some values were considerably greater than one, while others were only slightly above. Regardless, the value being above one expresses how there is an increased positive association.

In order to provide clearer and more definitive results, it is necessary for future experiments to focus more on data collection methods, chemical makeup of oral contraceptives and their influence, personal histories of participants, and the overall need for specificity when looking for an association. By following these suggestions, researchers will be able to better understand the relationship between oral contraceptives and estrogen receptor-positive, estrogen receptor-negative, and triple-negative breast cancer, allowing more women to use this resource without facing potential harm.

REFERENCES

1. Beaber, E. F., Buist, D. S. M., Barlow, W. E., Malone, K. E., Reed, S. D., & Li, C. I. (2014a).
2. Recent oral contraceptive use by formulation and breast cancer risk among women 20–49 years of age. Cancer Research, 74(15), 4078–4089. http://doi.org/10.1158/0008-5472.CAN-13-3400
3. Beaber, E. F., Malone, K. E., Tang, M. T., Barlow, W. E., Porter, P. L., Daling, J. R., & Li, C. I. (2014b). Oral contraceptives and breast cancer risk overall and by molecular subtype among young women. Cancer Epidemiology, Biomarkers & Prevention, 23(5), 755–764. http://doi.org/10.1158/1055-9965.EPI-13-0944
4. Bethea, T. N., Rosenberg, L., Hong, C. C., Troester, M.A., Lunetta, K. L., Bandera, E. V., Schedin, P., Kolonel, L. N., Olshan, A. F., Ambrosone, C. B., ... Palmer, J. R. (2015). A case-control analysis of oral contraceptive use and breast cancer subtypes in the african american breast cancer epidemiology and risk consortium. Breast Cancer Research, 17(1), 22. https://doi.org/10.1186/s13058-015-0535-x
5. Breast cancer hormone receptor status. (2017). Retrieved from https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-hormone-receptor-status.html

6. Busund, M., Bugge N. S., Braaten, T., Waaseth, M., Rylander, C., & Lund, E. (2018). A progestin-only and combined oral contraceptives and receptor-defined premenopausal breast cancer risk: The Norwegian women and cancer society. International Journal of Cancer, 142(11), 2293-2302. https://doi.org/10.1002/ijc.31266

7. CDC. Contraception. (2018a). Retrieved from https://www.cdc.gov/reproductivehealth/contraception/index.htm

8. CDC. Triple-negative breast cancer. (2018b). Retrieved from https://www.cdc.gov/cancer/breast/triple-negative.htm

9. CDC. When women can stop using contraceptives. (2017). Retrieved from https://www.cdc.gov/reproductivehealth/contraception/mmwr/spr/stop_using_contraceptives.html

10. Contraceptive use in the United States. (2018). Retrieved from https://www.guttmacher.org/factsheet/contraceptive-use-united-states

11. Cooper, B. D., Adigun, R., & Bhimji, S. S. (2019). Stat Pearls. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK430882/#_NBK430882_pubdet_

12. Gill, K. J., Press, F. M., Patle, V. A., & Bernstein, L. (2006). Oral contraceptive use and risk of breast carcinoma in situ (United States). Cancer Causes & Control, 17(9), 1155-1162. https://doi.org/10.1007/s00552-006-0056-0

13. Li, L., Zhong, Y., Zhang, H., Yu, H., Huang, Y., Li, Z., Chen, G., ... Hua, X. (2017). Association between oral contraceptive use as a risk factor and triple-negative breast cancer: A systematic review and meta-analysis. Molecular and Clinical Oncology, 7(1), 76-80. https://doi.org/10.3892/mco.2017.1259

14. Oral contraceptives and cancer risk. (2018). Retrieved from https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones/oral-contraceptives-fact-sheet)

15. Rosenberg, L., Zhang, Y., Coogan, P. F., Strom, B. L., & Palmer, J. R. (2009). A case-control study of oral contraceptive use and incident breast cancer. American Journal of Epidemiology, 169(4), 473-479. https://doi.org/10.1093/aje/kwn360

16. Soroush, A., Farshchian, N., Komasi, S., Izadi, N., Amirifard, N., & Shahmohammadi, A. (2016). The role of oral contraceptive pills on increased risk of breast cancer in Iranian populations: A meta-analysis. Journal of Cancer Prevention, 21(4), 294-301. https://doi.org/10.15430/JCP.2016.21.4.294

17. Spruance, S. L., Reid, J. E., Grace, M., & Samore, M. (2004). Hazard ratio in clinical trials. Antimicrobial agents and chemotherapy, 48(8), 2787-2792. https://doi.org/10.1128/AAC.48.8.2787-2792.2004

18. Szumilas M. (2010). Explaining odds ratios. Journal of the Canadian Academy of Child and Adolescent Psychiatry, 19(3), 227-229. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2938757/

19. U.S. breast cancer statistics. (2018). Retrieved from https://www.breastcancer.org/symptoms/understand_bc/statistics

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Mentor Details

This paper was written with the mentorship of Dr. Carly Jordan.

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