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Long-Term Oral Contraceptive Use and Incidence of Breast Cancer

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## Long-Term Oral Contraceptive Use and Incidence of Breast Cancer

### Abstract

Breast cancer is the most frequent occurring malignancy in American women and the second leading cause of cancer deaths (Lovett et al., 2017). Combination oral contraceptives (OCs) are taken by more than 100 million women worldwide making them the most commonly used birth control method (Stewart & Black, 2015). The use of OCs has been well studied in relation to breast cancer risk, however the impact of its use in relation to breast cancer risk has been inconsistent (Smith, Brinton, Kramer, Jemal, DeSantis, 2011).

A 31-year-old woman, N.S., with no current concerns presented to establish care. She was a healthy appearing woman of stated age, with no known medical comorbidities, who has used long-term (>10 years) OCs for birth control. Upon further inquiry, her family medical history is significant for breast and ovarian cancers. Her mother developed breast cancer in her 40s and is deceased. The patient was unsure if her mother had completed genetic testing and had not visited with a genetic counselor nor initiated genetic testing. This case illustrates the potential relationship of breast cancer with long-term use of OCs, especially in high-risk women.

A literature review was completed to determine the incidence of breast cancer with long-term use of OCs. The databases of CINAHL (Cumulative Index of Nursing and Allied Health Literature), PubMed, and ClinicalKey were utilized to search the literature. Results were limited to the past five years, with a total of 1,059 results. After a thorough literature review was conducted, eight articles were deemed relevant to the clinical question. A thorough discussion of findings is discussed in the literature review section.

## Background

The average age of women at their first birth continues to rise over the past four decades, with women in their 30s having more children as compared to those in their 20s (Caplan-Bricker, 2017; Sifferlin, 2014). Therefore, there is a potential for an increase in the duration of OC use. Since its first introduction in the United States in the 1950s, several different forms of birth control are available today with an estimated 100-150 million women using OCs (Iverson, Sivasubramaniam, Lee, Fielding, Hannaford, 2017). A variety of reasons may necessitate the use of OCs including: birth control, menstrual pain, menstrual regulation, acne, and/or endometriosis, with the highest percentage of women using OCs for birth control (95%) (Gutmacher Institute, 2018).

The prevalence of breast cancer today has led to large public health burden, prompting further investigation into this phenomenon. Naturally occurring estrogen and progesterone have been shown to influence the development of certain breast cancers (National Cancer Institute, 2012). Since the introduction of OCs, the amount of estrogen and progesterone has decreased, however breast cancer continues to remain the second leading cause of death in women (Lovett et al., 2017). A multitude of confounding factors other than exogenous estrogen and progesterone exposure may contribute to this finding including environmental and dietary factors, advancing age, and longer duration of exposure to endogenous estrogen influenced by lower parity (Lovett et al., 2017).

As presented, N.S. is a nulliparous 31-year-old-women with a history of OC use and a significant family history of malignancy, including breast and ovarian carcinomas. The relationship between OC use and breast cancer incidence has been studied; however, results have been largely inconsistent (National Cancer Institute, 2012). As women continue to utilize OCs

for a longer duration of time, the purpose of this paper is to determine if a relationship exists between long-term OC use and the incidence of breast cancer.

### **Case Report**

N.S., a 31-year-old single, nulliparous Caucasian woman without significant medical history, presented to establish care. She had routine care with a previous physician and denies any questions or concerns today. She has been using long-term OCs, unsure of the name, for birth control. She is in a monogamous relationship and desires to have a family in the future. She takes a multivitamin occasionally and denies use of herbs/supplements. She has an allergy to penicillin (hives) that occurred when she was young. Surgical history is significant for an appendectomy when she was young. Her immunizations are up-to-date per current CDC (Center for Disease Control and Prevention) recommendations. She is a grade-school teacher in the community. She exercises approximately once per week, and typically follows a healthy diet.

Her family history is significant for breast cancer in her mother, maternal aunt, and cousin. Her mother acquired breast cancer in her 40s and is deceased; she does not know if genetic testing was completed. Her father is adopted, without significant medical history, and with unknown family history. Her brother is without significant medical history.

Her physical exam is without abnormal findings. She declined a full physical exam and does not perform regular self-breast examinations. No lab tests or imaging were indicated. She was agreeable to return for a well-woman appointment and examination. Given her strong family history of breast cancer, we discussed the importance of visiting with a genetic counselor and/or receiving genetic testing. She was agreeable to this treatment plan and plan-of-care will be modified based on genetic results, if obtained (see Appendix A).

### **Literature Review**

A thorough literature review was conducted to determine the incidence of breast cancer and long-term use of OCs. An online literature search was conducted using the Harley E. French Library at the University of North Dakota to find supportive evidence for the PICOT question: how does the use of long-term (> 10 years) of OC use, as compared with short-term or no use, affect the incidence of breast cancer? Several databases were utilized to compile a thorough review of the literature. Initial databases utilized were CINAHL and PubMed as they are considered essential databases for the health sciences (Mateo & Foreman, 2014). Additionally, the database ClinicalKey was utilized to include Elsevier's medical and surgical journals. Based on the clinical question, the search focused on the terms long-term OCs and breast cancer.

The literature search was first conducted utilizing the CINAHL database. According to Mateo and Foreman (2014), CINAHL is a "comprehensive source for nursing and allied health journals" with over 5,000 journals available (p. 23). The literature search was conducted using the CINAHL headings "long term oral contraceptives" and "breast cancer." Results were filtered to the English language, human subject, and publication with five years resulting in seven articles. One article was deemed relevant to the clinical question.

The next database utilized was PubMed. According to Mateo & Foreman (2014), PubMed is the ideal choice for initial searches and is the largest biomedical database. The literature search was conducted using the medical subject heading (MeSH) terms of "long term oral contraceptives" and "breast cancer." Results were filtered to the human subject and publication within five years resulting in 22 articles. Two articles were deemed relevant to the clinical question; however, one article was a duplicate of a study previously found and was not included for review.

Lastly, the database of ClinicalKey was utilized to further substantiate the literature review. The literature search was conducted utilizing the following keywords “long term oral contraceptive use” and “breast cancer.” Results were filtered to include randomized control trials, meta-analyses, systematic reviews, books, clinical trials, and publication within the past five years. This resulted in 147 results, of which five articles were deemed relevant to the clinical question. One of the five articles included duplicate information from a previous study, and lead to findings of an alternate study that was retrieved utilizing PubMed and included for review.

A brief search for grey literature was conducted to reduce publication bias. The search engine of Google was utilized to look for unpublished studies and conference proceedings using the keywords “long term oral contraceptives” and “breast cancer.” No ongoing studies were identified; however, one newspaper article was deemed relevant, but was a duplicate of a study previously found and was not included for review. After the literature search was completed, eight articles were deemed relevant to the clinical question. It is important to note, the brand and strength of OC utilized throughout the studies were reported in two of the eight articles included for review, and another study classified OC estrogen content as low, medium, or high. Studies utilized did not include women defined as high-risk for development of breast cancer.

### **Summary of Findings**

Levels of evidence included in the literature review range from level I-V with: one study compromising level I evidence (Zhu, Lei, Feng, & Weng, 2012), one level II evidence (Freund, Kelsberg, & Safranek, 3014), four level III evidence (Morch et al., 2017; Iversen, Sivasubramaniam, Lee, Fielding, & Hannaford, 2017; Aronson, 2016; Beaber et al., 2014), and two level V evidence (Smith, Brinton, Kramer, Jemal, & DeSantis, 2017; Bhupathiraju et al., 2016) . Studies reviewed showed inconsistent findings from no elevation in risk to a 50 percent



increased risk. Of the three studies that identified a positive correlation between long-term OC use and breast cancer development: risk increased from 1.09 (95% CI, 0.96 to 1.23) with less than one year of use to 1.38 (95% CI, 1.26 to 1.51) with more than ten years of use ( $P=0.002$ ), and for every ten-years' increment of OC use, risk increased to 14% (95% CI, 1.05-1.23) (Mørch et al., 2017; Zhu et al., 2012). Additionally, current and recent users were found to be at an increased risk of developing breast cancer regardless of duration of use (RR, 1.24; 95% CI, 1.15 to 1.33) (Smith et al., 2017). It should be noted however, the increased risk associated with recent use subsided within ten years of cessation of OC use; therefore, the risk associated with long-term use may primarily be due to recent usage (Smith et al., 2017).

Three of the eight studies did not find a statistically significant correlation between long-term OC use and development of breast cancer (Aronson, 2016; Freund et al., 2014; Iversen et al., 2017). A systematic review conducted by Freund et al., (2014), "found no significant difference in breast cancer risk between OCP users and nonusers, regardless of age or duration of use" (p. 548). Similar results were found by Aronson (2016). Neither recent OC use (<10 years, RR=0.77; 95% CI, 0.54-1.11) nor past OC use (>10 years, RR=1.01; 95% CI, 0.80-1.28) affected risk of developing breast cancer (Freund et al., 2014).

Similarly, a prospective cohort study conducted by Iversen et al., (2017), observed women for 44 years. There was no evidence of new cancer risks appearing later in life among women who had used OCs. It should be noted, the mean duration of OC use was approximately three years, however this study was still included as incidence of cancer was followed for 44 years. Additionally, the study also concluded the increased risk of breast cancer seen with current and recent users appears to be lost within approximately five years of stopping OC (Iversen et al., 2017).

Lastly, two of the eight studies founded mixed results. Lifetime duration of OC use greater than or equal to 15 years was associated with a 50 percent increased breast cancer risk (OR=1.5, 95% CI, 1.1-2.2) however, this risk was not found among women with less than 15 years of lifetime OC use (Beaber et al., 2014). Bhupathiraju et al. (2016), concluded the use of OC for ten or more years, and past OC use before a first full-term pregnancy, did not significantly increase the risk of breast cancer. However, duration of use for greater than ten years was associated with a higher risk of death from breast cancer (HR=1.39; 95% CI, 1.13-1.71) (Bhupathiraju et al., 2016).

### **Learning Points**

- There are inconclusive results comparing long-term OC use and the incidence of breast cancer.
- Studies reviewed showed inconsistent findings from no elevation in risk to a 50 percent increased risk.
- Several studies correlated an increased risk of breast cancer development with current and recent OC use. Future studies are needed to further quantify and demonstrate this effect.
- Two of the eight studies included for review differentiated between brand and strength of OC formulation utilized. One study included noted OC estrogen strength as low, moderate, or high. The remaining five studies did not differentiate between formulations of OC utilized, nor if users had only utilized one preparation for ten years or longer. Future studies are needed to determine the potential effects.

- Clinical recommendations for the use of OCs use should include an informed discussion between the provider and the patient about the inconsistent correlation between the use of long-term OCs and the development of breast cancer.
- The strongest study included for review was a meta-analysis conducted by Zhu et al. (2012), demonstrating a statistically significant correlation between OC use and development of breast cancer for every ten-years increment of use (14%: 95% CI, 1.05-1.23).

Breast cancer is the second leading cause of death in women (Lovett et al., 2017). As women continue to have their first child at a later age, the potential for OC use throughout a lifetime has increased in duration (Caplan-Bricker, 2017). More than 100 million women in the United States utilize OCs making them the most commonly utilized birth control method (Stewart & Black, 2015). This paper has demonstrated the inconsistent correlations found between the use of OCs for greater than ten years duration and the development of breast cancer. Further studies are warranted to continue to monitor these effects. Clinical recommendations for the use of OCs should included an informed conversation between the provider and patient about the inconsistent correlation between the use of long-term OCs and the development of breast cancer.

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## Appendix A

## Case Report

*Subjective*

**CC:** Establish Care

**HPI:** N.S. is a 31-year-old, single female here to establish care. She has just moved from Fargo and is grade-school teacher. She had routine care with a previous physician and a release of information form will be signed. She states she is currently healthy and does not have any questions or concerns today.

**PMH:** None

**Surgical:** Appendectomy when young, does not remember date.

**Allergies:** Penicillin-rash when young.

**Immunizations:** Up to date per current CDC recommendations. Has received influenza vaccine for this season.

**Current medications:** Oral Contraceptive daily (does not remember the name). OTC multivitamin occasionally.

**FH:** Mother-deceased: breast cancer (40s). Does not know if she had genetic testing completed. Father-alive: adopted, unknown family history. Brother-alive: healthy. Maternal Grandmother-deceased: ovarian cancer. Maternal Aunt-alive: breast cancer. Cousin-alive: breast cancer.

**SH:** School grade teacher. Exercises approximately once per week. Tries to follow a healthy diet. In a monogamous relationship with boyfriend. Desires to have a family in the future.

**ROS:**

**Constitutional:** Denies fevers, unintentional weight loss, chills or night sweats.

**Neuro:** Denies headaches, double vision.

**Cardiac:** Denies chest pain, shortness of breath.

**GI/GU:** Denies constipation, diarrhea, urinary frequency, hesitancy, or blood in urine/stool.

**Musculoskeletal:** Denies myalgias or pain.

*Objective*

**Vitals:** BP 110/66, P 82, R 14, Weight 155 lbs. Denies pain.

**PE:** General: Alert, in no acute distress. Well nourished.

**Head:** Normocephalic, atraumatic. Upright, midline, without tics or tremors.

**Ears:** The external auditory canals are clear. Tympanic membranes are translucent, grey, bony landmarks noted.

**Throat:** Pink, moist, without lesions or tonsillar exudate.

**Neck:** Supple without lymphadenopathy. Thyroid without nodules.

**Lymph nodes:** No adenopathy noted.

**Lungs:** Clear to auscultation without vesicular sounds.

**Heart:** Regular rate and rhythm. S1 and S2. No murmurs present.



**Musculoskeletal:** Gait appropriate. Strength symmetrical without weakness. Back without curvature.

**Labs/Diagnostics:** None indicated.

*Assessment*

31-year-old presenting to establish care.

ICD 10: Z00.00 Encounter for general adult examination

Z80.3 Family history of malignant neoplasm of breast

CPT 10: 99204 New patient, comprehensive patient examination

*Plan*

1. Patient agreeable to visit with genetic counselor given family history of breast and ovarian cancer. Plan of care will be modified based on genetic results. Referral placed.
2. Patient to schedule appointment for well-women exam to obtain labs and complete physical examination.
3. Continue to get 150 minutes of moderate activity per week and follow a heart healthy diet.
4. Follow-up as needed. Call with any questions or concerns.