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Rebecca Pulkrabek

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Oral Contraceptive Use and Risk for Development of Breast Cancer in Women with High-Risk

Breast Cancer Genes: A Case Study.

Rebecca Pulkrabek, BSN, RN

University of North Dakota

March 8, 2018

PERMISSION

Title: Oral Contraceptive Use and Risk for Development of Breast Cancer in Women with High-Risk Breast Cancer Genes: A Case Study.

Department: Nursing

Degree: Master of Science

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Abstract

Oral combined contraceptive pills (OCP's) are commonly utilized by women of childbearing age for the prevention of pregnancy, and for other non-reproductive purposes. Women with an inherited high-risk for breast cancer development and who may be utilizing OCP's need to understand their potential risk versus benefit. However, the association between use of OCP's in high-risk women and breast cancer risk has been conflicting and unclear. The following case study identifies how women with increased risks of breast cancer due to hereditary and genetic mutations must consider modifiable risks that can impact their future risk for development of cancer. Providers need to understand what the current evidence based practice recommendations are in order to provide women with personalized care that is also associated with the best possible outcome. A 31-year-old Caucasian female presents to establish care with no significant personal current or past medical history, who's only current prescription medication is Apri (an OCP). Her family history presents significant concerns for hereditary and/or genetic breast cancer risk due to breast cancer diagnosis and mortality in a first degree relative at age 40, and multiple second-degree relatives with associated cancers. She expresses concern to the provider about the safety of continuing to use OCP's related to her family history and probable increased risk for breast cancer. A search of the available literature was conducted utilizing the University of North Dakota's Harley French Medical Library. Cochrane Library, PubMed, CINAHL, and SCOPUS databases were searched. Keywords utilized in the search focused on breast cancer risk, combined oral contraceptives, familial breast cancers, BRCA1 and BRCA2.

Keywords: Breast Cancer, Oral Contraceptives, BRCA1 and BRCA2, Family History of Breast Cancer, Case Study.

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Breast cancer remains the single most common form of cancer occurring in American women today, is the second leading cause of mortality, and accounts for roughly 15% of all newly diagnosed cancer cases in the United States (Centers for Disease Control and Prevention (CDC), 2017; National Cancer Institute (NCI), n.d.). Lifetime risk for the general American female population remains roughly about 10% to 12%. Yet, for women who may have an inherited predisposition to certain gene mutations or changes such as BRCA1 or BRCA2, lifetime risk for development of breast cancer may be as high as 40% to 85% (Grenader, Peretz, Lifchitz, & Shavit, 2005). Primary care providers are expected to assess an individual's risk for cancer based on obtaining a comprehensive personal history, family history, and physical exam. Providers must be knowledgeable of available testing for clarification of a patient's risk for development of cancer, and should understand key clinical findings that may warrant recommendation for further testing of certain individuals. Additionally, providers should understand the impact of potential risk reduction strategies to educate and counsel individuals appropriately who have been identified with an increased risk profile.

Background

While there have been many advances in the study of breast cancer, treatments, and risk assessment of a women's potential for development of breast cancer, conflicting data exists related to the potentially modifiable risk associated with use of oral contraception in this population (Grenader, Peretz, Lifchitz, & Shavit, 2005; Kotsopoulos et al., 2014; Moorman et al., 2013). OCP's are frequently used by women of childbearing age as an effective and reversible form of contraception for the prevention of pregnancy, as well as for numerous other reasons

unrelated to the prevention of pregnancy (Ross & Shulman, 2017). Women with inherited gene mutation risks need to understand what their associated risk versus benefit of continued use of OCP's are, so that they may make informed personalized decisions regarding their medical care.

Women look to their primary care providers to help them find personalized answers to these questions. Therefore, primary care providers must navigate through the conflicting data with the intent of providing individualized and appropriate care for these women. They must do so all while attempting to clearly present the actual risk and/or benefits of oral contraceptive use in these women based on the most current scientific data. The following case demonstrates the need to review the current scientific literature to address if the risks outweigh the benefits for the use of OCP's in these high-risk women. A literature review was conducted to assess the available scientific evidence to determine if there is indeed an increased risk associated with the use of OCP's for women with an identified higher breast cancer risk.

Case Presentation

“Nicole” is a healthy 31-year-old single, G0P0, Caucasian women who presented to her local family practice clinic to establish care with a new primary care provider. She denied any significant medical history or concerns. She denied any previous personal history of cancer or other chronic health conditions. Her only surgical history was an appendectomy as an eight-year-old child. Her current medications included: an oral contraceptive (Apro: desogestrel/ethinyl/estradiol 0.15mg/30 mcg tab) taken by mouth daily; and inconsistent use of a once daily multi-vitamin. She denied use of any herbal or other over the counter medications. Her only indicated allergy is to oral penicillin, which she stated caused a generalized rash in childhood. All her vaccinations were current and up-to-date. She did receive an influenza vaccine

in October 2017. She was current and up to date for all age appropriate preventative care and screenings, including having had a PAP Smear with normal results in July 2017.

Nicole is a teacher and works with children in the third grade. She hoped to one day have children of her own with her significant other of two years, but indicated that they are planning to wait until sometime after they are married in the next few years. She denied any tobacco or illicit drug use presently or in the past, and indicated very rare alcohol consumption.

Upon discussion of family medical history, Nicole shared that she does have some concern about her family history of cancers. Nicole indicated that her mother died of breast cancer at the age of 40. She was unable to recall what type of breast cancer her mother had, but indicated that her mother died within about 7 months of her initial diagnosis. Upon further discussion, Nicole recalled that her maternal grandmother had ovarian cancer at an unknown age of diagnosis. Additionally, she also identified that one maternal aunt and a maternal first cousin have been diagnosed with breast cancer at fairly-young ages. She indicated that she did not believe that anyone in her family ever had any genetic screenings related to this increased hereditary cancer pattern. She further indicated she has been performing monthly self-breast exams, but never had any formal breast screenings or testing completed. She stated that she is concerned that she may be at increased risk for breast cancer and would consider genetic testing in the future.

Nicole represents a commonly seen newly establishing patient in the primary care setting. She is a generally healthy young woman with no significant past medical history. Her review of systems, and physical exam were unremarkable and negative. Yet, it is through further exploration of her family history that an understanding of Nicole's significant red flags for potential hereditary and/or genetic cancer risk leads to an appropriate referral for genetic testing

which is scheduled for the following week (NCI, 2018). Additionally, based on her mother's age of diagnosis and mortality, Nicole was also scheduled for an initial screening mammogram (Grenader, Peretz, Lifchitz, & Shavit, 2005).

Discussion and education about Nicole's potential modifiable lifestyle factors included reviewing her alcohol consumption, physical activity level, reproductive history, and use of oral contraceptives (NCI, 2018). Nicole expressed concern about remaining on her oral contraceptive while awaiting further testing, stating that she has heard it may increase her risk of breast cancer, but is concerned about pregnancy if she discontinues it. This represents a dilemma for the provider, what is the best recommendation for Nicole regarding ongoing use of oral contraceptives with her high potential for increased breast cancer risk? It is difficult to determine what is best to advise her without reviewing the current scientific literature.

Literature Review

Search Strategies

A systematic search of the literature was conducted through utilization of the University of North Dakota's Harley French Medical Library website. Four separate databases were explored to conduct the literature search and included the following; CINAHL, the Cochrane Library, PubMed, and SCOPUS. Keywords and terms utilized for this review focused on the clinical question presented by the case study and included; *familial breast cancer risk, combined oral contraceptives, use of oral contraception in BRCA1 or BRCA2, breast cancer and birth control, breast neoplasms*. Determination of appropriate articles for inclusion related to the purpose for this review included articles that identified oral birth control pill use in women identified with high-risk factors for breast cancer development due to either a positive family history or BRCA1/2 germ-lines without consideration of any further specific genetic mutation.

Additionally, specific formulation of OCP's or duration of OCP use were not specifically defined or limited in order to provide for a broader search of the available literature.

Initially, the Cochrane Library was searched due to the established quality and strong level of evidence presented within the database. The initial search attempt utilized the search term *familial breast cancer risk* resulted in finding 1 article. Review of this article deemed it irrelevant to the purpose of this review, as it focused primarily on genetic risk factors of breast cancer. A second search was conducted utilizing the terms *combined oral contraceptive AND breast cancer* resulted in 7 articles, none of which were relevant to the clinical question in this study. A final search was attempted utilizing the terms *oral contraception use AND BRCA1 or BRCA2* resulted in one article that did not meet criteria for inclusion. These searches resulted in no appropriate articles for inclusion in this review, so the decision was made to move on to a different search approach.

The Cumulative Index to Nursing and Allied Health Literature (CINAHL) database was then searched as it is considered the most specific database for nursing related studies and articles. An initial quick search of keywords in the CINAHL database utilizing the terms *familial breast cancer risk* (1,169), *contraceptives use in breast cancer risk* (1,918) and *use of oral contraception in BRCA1 or BRCA2* (265) resulted in 6 usable articles. A search utilizing the terms *combined oral contraceptives AND breast cancer risk* identified 7 articles, 2 were possibly appropriate but not accessible, and the other 5 were not applicable for this review. A final search in the CINAHL database was attempted utilizing the terms *use of oral contraception in BRCA1 or BRCA2* resulted in 265 articles. However, when filters were applied to English only and limited to the years of 2011 to 2018, this number was reduced to 101 articles and only 1 was appropriate, but was a duplicate.

Search of the PubMed database utilizing the medical subject heading (MeSH) terms *combined oral contraceptives AND familial breast cancer* resulted in 243 articles. Further filtering was completed to limiting studies available in English, and to the years of 2010 to 2018, and free full text option when available resulted in 10 articles. Upon more in-depth review 1 article was identified as appropriate and 1 additional article was found through review of the referenced articles associated to the first article. The search was repeated except the terms were limited to *contraceptives AND familial breast cancer* which resulted in 127 articles. After further review 6 additional articles were identified as relevant, but 2 were duplicates, leaving 3 additional applicable articles. A search using the MeSH terms *contraceptives and familial breast cancer risk* resulted in 2 more appropriate articles. Additional searches conducted utilizing the MeSH terms *contraceptive use AND BRCA1 or BRCA2; oral contraceptive use AND breast neoplasms* resulted in numerous additional articles, but ultimately did not result in any additional articles appropriate for this review.

Additional search was conducted in the SCOPUS database utilizing the terms *combined oral contraceptives AND familial breast cancer* with dates limited to 2011-2018 resulted in 8 articles, 6 were excluded, 1 was a duplicate article previously identified, and 1 was considered appropriate for use in this review. One additional article was identified from review of the reference list from the previously identified article. After intensive review of available full text studies, a final count of 11 articles met inclusion criteria and were included in this literature review.

Summary of Findings

The case study presented demonstrates the important role that primary care providers may play in the provision of care, assessment, and knowledge required to assist women who face

difficult medical decisions related to their future risk for breast cancer so they may be empowered to make well informed personalized medical decisions. Women need to be provided with the appropriate knowledge to make these vital decisions. These women cannot change their family history or their inherited genes however, they can be educated on their potentially modifiable risks.

The body of evidence compiled in this search demonstrates two conflicting conclusions regarding the overall safety and potential impact that use of combined oral contraceptives may have in women identified as having increased risk for breast cancer development due to family history or genetic mutation inheritance. Several of the studies included in this review were meta-analysis which included data from multiple countries, women of various ages, and types of inherited risk. Three meta-analysis studies found no increased risk associated with OCP use in the populations studied (Gaffield, Culwell, & Ravi, 2009; Iodice et al., 2010; Moorman et al., 2013). Limitations of these studies included lack of case controlled studies, different definitions of familial history or risk factors that were considered for inclusion, and limitations related to unknown duration of use and dosages might allow for potential unexpected or unidentified bias.

Conversely, two nationwide prospective cohort studies conducted in Denmark and Norway involving over 90,000 women concluded a small but potentially significant increase in breast cancer risk due to the use of OCP's (Busund et al., 2018; Morch et al., 2017). Limitations to these studies include findings may apply to the specific population, but may not apply to other geographic areas or populations; as well as unknown impacts of pre-study exposure to OCP's, OCP formulations which may vary significantly from country to country, and ages included in the cohorts. However, findings from two additional case control studies that involved women from the U.S. and 13 other countries also found similar results of a slight increase in risk of

breast cancer associated with OCP use in women with known increased risk due to genetic factors (Beaber et al., 2014; Kotsopoulos et al., 2014). Three studies specifically discussed OCP use related to increased risk of breast cancer development in known BRCA1 or BRCA 2 carriers and found an increased risk associated with current OCP use in BRCA1 carriers specifically (Cibula, Zikan, Dusek, & Majek, 2011; Grenader et al., 2005; Kotsopoulos et al., 2014).

An unexpected finding related to this review was the fact that many of the studies concluded a statistically significant reduction in risk of ovarian cancer related to OCP use in women with known inherited genetic risk factors (Cibula, Zikan, Dusek, & Majek, 2011; Grenader et al., 2005; Iodice et al., 2010; Moorman et al., 2013; Morch et al., 2017; Vessey & Yates, 2013). While the previously discussed limitation related to these studies may result in potential bias. The fact that the benefit was established in so many studies, across various countries, populations, and ages suggests a strong association.

In addition to the previously identified databases a focused Google search was conducted with the intent to identify relevant current U.S. clinical practice guidelines for inclusion in this review. Clinical guidelines serve as invaluable tools utilized by primary care providers in determination of the most appropriate course of action for specific patient situations and care and are pertinent to the clinical question identified by our case study. Two clinical guidelines were identified as appropriate for inclusion in the review. Available data from these clinical practice guidelines in addition to two systematic reviews suggest that there is not an increased risk for potential breast cancer development in high-risk women who utilize modern formulations of combined oral contraceptives and OCP use should not be considered contraindicated for these women (CDC, 2016; Freund, Kelsberg, & Safranek, 2014; Grenader, et al., 2005; NCI, 2018).

Learning Points

Based on the case study presented and the review of the relevant current scientific evidence four main recommendations may be made. The Strength of Recommendation Taxonomy (SORT) system from the American Academy of Family Physician's (AAFP) was utilized to determine the strengths of the following recommendations.

- Use of OCP's in women identified as high-risk based on family history or those known to carry genetic mutations may have a slight statistical risk to no statistically increased risk for development of breast cancer. Data is inclusive and the evidence is inconsistent to make a strong recommendation that no risks exist without defining further variables. Based on the inconsistency within the body of evidence this recommendation receives a SOR grade of B.
- Oral combined contraceptive pills are not absolutely contraindicated for use in women that have been identified at higher risk for breast cancer. Personalized decision making should be encouraged with thoughtful consideration of all potential risks and benefits. Based on some inconsistency within the body of evidence of this literature review this recommendation receives a SOR grade of B.
- Risk for development of breast cancer related to OCP use may be different based on the type of inherited genetic mutation and may therefore require special consideration based on genetic screening information to make an appropriate clinical recommendation. Based on inconsistent findings and lack of clearly supporting evidence this recommendation receives a SOR grade of C.
- Use of OCP's have been found to provide significant risk reduction for ovarian cancer development in women identified with inherited genetic mutations. Based on consistent evidence this recommendation receives a SOR grade of A.

Conclusion

Primary care providers are entrusted to provide personalized and knowledgeable health care to women identified with having an increased hereditary risk for development of breast cancer. The decision to continue or discontinue the use of OCP's for women with increased breast cancer risk is a very personal and individualized decision. Providers can foster and promote well-informed decisions by providing non-biased, evidence based care. Review of the current available literature conducted in this study finds inconclusive evidence related to a slight potential increase in risk for breast cancer development with continued use of OCP's in young women like Nicole, who have an established hereditary risk of breast cancer. Risk may vary for women based on what specific genetic mutation they have inherited and will require individualized counseling and education accordingly. One significant benefit for continued use of OCP's was noted throughout much of the literature. Ovarian cancer risk is reduced directly related to use of OCP's in women, including those who have been identified with hereditary risk. Additionally, it is important to also consider that current literature indicates OCP use is not contraindicated in cases like Nicole's, but requires careful personalized consideration of all potential modifiable benefits and risks.

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