EBP Paper: BRCA Positive Mutations and Incidence of Breast Cancer in Patients that Use Hormone Replacement Therapy

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Introduction

Cancer screening has clinically evolved from just the simple question of do you have a family history of breast cancer, to has any family member had genetic testing done to determine the type of genetic mutation involved in breast cancer or breast cancer risk. Women who carry the BRCA 1 mutation have a 44% risk of developing ovarian cancer and a 72% risk of breast cancer, whereas women who carry the BRCA2 mutation have a 17% risk of ovarian cancer and a 69% risk of breast cancer (Loizzi et al., 2023). Because of the significance of these statistics, practice has shifted in preventative actions like prophylactic salpingo-oophorectomy (RRSO) in pre-menopausal women between the ages of 35-40 years for the BRCA1 mutation, and 40-45 years of age for the BRCA2 mutation (Loizzi et al., 2023). Removing the ovaries causes premature ovarian failure resulting in secondary menopausal syndromes. This hormonal deficiency leads to neuromotor, cardiovascular, cognitive, and urogenital symptoms (Loizzi et al., 2023). To further break this down, the deficiency in estrogen and progesterone leads to metabolic and endocrine imbalances leading to cardiovascular and urogenital symptoms, affects the ability for bones to continue to become denser, and affects cognitive impairment and risk for dementia (Loizzi et al., 2023). Hormone replacement therapy (HRT) can aid in these premature symptoms and play a role in the prevention of cardiovascular disease and osteoporosis, however, there is conflicting research on the increased risk of breast, ovarian, and endometrial cancer with its use. This evidence-based practice paper aims to break down the literature and understand where research meets clinical decision making and comprehending the significance of what hormone therapy can do for patients while understanding the risks and benefits specific to those with BRCA1 or BRCA2 mutations.

PICO Question

The development of a clinical question using the PICO framework was used to guide the integration of the best research findings to establish clinical expertise. The PICO framework reflects the population, intervention, comparison, and outcome. The population of research is premenopausal women positive for the BRCA1 or BRCA2 mutation. The intervention is the use of hormone replacement therapy, specifically estrogen-only hormone replacement. The comparison is those who do not use hormone replacement therapy. The outcome is a reduction in the incidence of breast cancer. The PICO question for this research is as follows: in premenopausal women with a positive BRCA1 or BRCA2 mutation, does the use of estrogen-only hormone replacement therapy compared to no hormone therapy reduce the incidence of breast cancer?

Literature Search

A literature search was conducted with suggested general databases of EBSCO Megafile, Academic Search Premier, and Masterfile from the University of Mary librarians. Academic Search Ultimate was used in this literature search in hopes of eliminating any missed data or biases on the subject. Research was conducted using MEDLINE and CINAHL Complete. These were accessed through the University of Mary-Welder library. The Cochrane Handbook recommends starting with the population as the keyword and moving forward with the intervention (Melnyk & Fineout-Overholt, 2019). Keywords and their variations that were emphasized in the search regarding this topic were: pre-menopausal women, BRCA mutation, hormone replacement therapy, and breast cancer. See the literature search table below for these combinations. Several studies were provided after request through the University of Mary library for research in hopes of narrowing down the three articles selected to best support the PICO

question of study. Results were reviewed and deemed a primary resource, a high level of evidence, and relevant to the PICO question.

Literature Matrix Grid [Table 1].

Table 1

Literature Search Table

MEDLINE	Subject Heading Search	Search Results	Limits	Total	Total articles reviewed	Total articles included excluding duplicates
1	BRCA mutation AND hormone replacement therapy	41	English; Human, published last 10 years, All Adults (19+ years)	39	9	0
2	BRCA mutation AND hormone replacement therapy AND breast cancer	43	English; Human, published last 10 years, All Adults (19+ years)	29	2	2
CINAHL complete						
1	BRCA mutation AND hormone replacement therapy	16	English; Human, published last 10 years, All Adults (19+ years)	14	4	0
2	BRCA mutation	17	English; Human,	9	3	0

	AND hormone replacement therapy AND breast cancer		published last 10 years, All Adults (19+ years)			
Academic Search Ultimate						
1	BRCA mutation AND hormone replacement therapy	35	English; Human, published last 10 years, All Adults (19+ years)	33	4	0
2	BRCA mutation AND hormone replacement therapy AND breast cancer	26	English; Human, published last 10 years, All Adults (19+ years)	18	7	0

Annotated Bibliography

Annotation One

Kotsopoulos, J., Gronwald, J., Karlan, B. Y., Huzarski, T., Tung, N., Moller, P., Armel, S., Lynch, H. T., Senter, L., Eisen, A., Singer, C. F., Foulkes, W. D., Jacobson, M. R., Sun, P., Lubinski, J., & Narod, S. A. (2018). Hormone Replacement Therapy After Oophorectomy and Breast Cancer Risk Among BRCA1 Mutation Carriers. *JAMA Oncology*, *4*(8), 1059–1065. https://doi-org.ezproxy.umary.edu/10.1001/jamaoncol.2018.0211

Addressing questions within each design of evidence-based research, study validity, reliability, and applicability can allow clinicians to develop a body of evidence supporting the PICO question (Melnyk & Fineout-Overholt, 2019). Kotsopoulos et al (2018) research design is a prospective, longitudinal cohort study. The study's purpose is to evaluate hormone replacement therapy (HRT) use and breast cancer incidence among women with a BRCA1 mutation after bilateral saphingo-oophorectomy (RRSO). The study population was vast with 17 participating countries (Poland, Canada, United States, and *other*) and 80 participating healthcare centers within these countries. Participants that were included were those who had sought genetic testing for the BRCA1 or BRCA2 mutations due to family history, and individuals who tested positive for BRCA1 mutation with no personal history of cancer, who also had undergone an RRSO following the enrollment were eligible to be a part of the population of study between the years of 1995 to 2017. A baseline questionnaire was done with follow-up questionnaires administered every two years after to gather detailed information on history of cancer, reproductive, and medical histories. Women who did use HRT were asked to identify estrogen or progesterone or both, starting year of HRT, ending year, length of time used in years, and method of administration. These questionnaires were either mailed or administered over the phone by a genetic counselor or research assistant. Disqualifying factors to the research are critical pieces, and for this study included a previous diagnosis of cancer, did not have an oophorectomy during the follow-up period, and did not complete at least one follow-up questionnaire. Of the 13,087 women with the BRCA1 mutation, 872 were eligible for the analysis.

To critically analyze scholarly resources, it is critical to use a model in which evidence-based practice is rated. The John Hopkins Nursing Evidence-Based Practice model was chosen

for this analysis. Kotsopoulos et al (2018) research falls under the level III criteria being a well-designed cohort study with a B quality rating. The CRAAP (currency, relevancy, authority, accuracy, and purpose) tool is an available tool to evaluate research in a systematic way. The research was released in 2018 with research between the years of 1995 and 2017 giving it currency while eliminating the data retrieved after 2017 for relevance of the study. The mean of 7.6 years for follow-up surveys adds to the validity of the results given that the women were followed for a long enough time period to show that the variable of breast cancer incidence was of significance. Furthermore, relevancy is recognized through the study sample being BRCA1 positive in genetic testing and being placed on HRT (average of 3.9 years of HRT) after having had their ovaries removed. The range of HRT throughout the sample population was 0.5-19 years. The authors are all PhD and MD certified, with this research working toward the *Hereditary Breast Cancer Clinical Study Group*. The accuracy of the information is supported by the design of the study while Kotsopoulos et al. (2018) encompasses other supporting literature comparing study results with large prospective studies and randomized control trials. The authors have listed these in the references with working links in the paper. The purpose of this evidence-based research is to understand the risks of HRT on breast cancer, along with the window of time HRT benefit outweigh the risks (Kotsopoulos et al., 2018).

Validity and reliability rely on the study's measurement of major variables. Although Kotsopoulos et al. (2018) include survey questions and their specificity, the survey itself is not included in the research which would have proven the yielding results of more value. The authors state that after 10 years of follow-up, the cumulative incidence of breast cancer among women who used estrogen-alone HRT was 12%, and 22% who used estrogen-plus-progesterone HRT. External validity is exemplified with the population characteristics being specific to

BRCA1 mutations, where most studies do not differentiate between the two mutations, or include both mutations in one study. The intervention in the study is HRT, and the population of study was almost split down the middle with 377 (43%) women who used HRT after oophorectomy and 495 (57%) of women who did not use HRT after oophorectomy. Age was not a variable measured factor in this study. Reliability is established using the Cox proportional hazards regression to estimate the hazard ratio and 95% CIs of breast cancer associated with each HRT exposure. Statistical significance was given if P< or equal to .05. Kotsopoulos et al. (2018) mention that there was not a limitation in the use of subjects ever using HRT versus never using HRT, however, they do mention there was a small effect. The authors do include a limitation section stating that the type of hormone therapy (bio-identical or synthetic) is not specified, which can be of significance for evidence supporting clinician decision-making in this specific area. Furthermore, a limitation of the study was that the subjects had all had bilateral oophorectomies performed, so the evaluation between HRT and breast cancer risk in women with intact ovaries was not studied. The study concluded that the use of estrogen-alone HRT after an oophorectomy does not increase the risk of breast cancer in women with the BRCA1 mutation, but can actually decrease the incidence of breast cancer when compared to combination therapy of estrogen-progesterone (Kotsopoulos et al., 2018).

Annotation Two

Michaelson-Cohen, R., Gabizon, P. S., Armon, S., Srebnik-Moshe, N., Mor, P., Tomer, A., Levy-Lahad, E., & Paluch-Shimon, S. (2021). Breast cancer risk and hormone replacement therapy among BRCA carriers after risk-reducing salpingo-oophorectomy. *European Journal of Cancer*, *148*, 95–102. https://doi-org.ezproxy.umary.edu/10.1016/j.ejca.2021.02.007

Michaelson-Cohen et al. (2021) did a retrospective cohort study of 306 healthy BRCA1 and BRCA2 mutation carriers who had an RRSO comparing HRT use and breast cancer risk. The mean follow-up period was 7.26 years, sample subjects were followed up until diagnosis of breast cancer, a bilateral mastectomy, or end of the collection period in 2019. Data was collected from 2012 to 2019, with sample collection done at a high-risk clinic whom gene tests for the BRCA mutation. Data was collected from medical records and by self-administered questionnaires. Questions included on the questionaries included age at RRSO, ethnicity, gene mutation positive for, and family history including 1st, 2nd, and/or 3rd-degree relatives with breast cancer diagnosed before 50 years of age. If there was any missing data, follow-up calls were made to the subject. The researchers used the cutoff age of 45 for age of surgery, as evidenced by other publications on this topic. The authors listed this research which was years 2008, 2016, and 2018 supporting their reasoning. The purpose of this study was to assess the breast cancer risk of healthy BRCA1/BRCA2 mutation carriers using short-term HRT.

According to the Johns Hopkins Nursing Evidence-Based Practice model, this research falls into level III with a quality rating of B. Analyzing Michaelson-Cohen et al. (2021) research via the CRAAP method reveals that currency is excellent given it was written in the last three years, with research conducted from 2012 to 2019. Links within the paper are functional and cited appropriately. Relevance to the PICO question revolves around the axis of BRCA-positive mutations among pre-menopausal women, however, does not address the population that has not undergone RRSO. The author's credentials are listed with an array of specialties including gynecology, oncology, and internal fetal medicine. The information is supported by evidence of research and literature, while also recognizing limitations of the sample. The authors made the

goal of the research clear without yielding opinions. The research aimed at determining the safety of HRT in women who have a positive BRCA mutation (Michaelson-Cohen et al. 2021).

Validity and reliability were evident in the research with statistical analysis highlighting both quantitative variables and qualitative variables. Kaplan-Meier survival with log-rank test was used for comparing breast cancer incidence. Analysis of multiple variables is available including age of RRSO, ethnicity, and the specific gene mutation. The sample size is small, but variable in that it was almost 50/50 for HRT users compared to those that did not use HRT. Limitations include that the authors' sample came from a high-risk clinic, not randomly from the general population. Michaelson-Cohen et al. (2021) found that HRT use and the incidence of breast cancer was increased in women who were older than 45 years of age at the time of RRSO (surgery). A P value of 0.04 was identified, comparing the two variables, and considered significant. Conflicting statements are made by the authors because they do state there was not an increased risk of breast cancer in the overall cohort. This coincides with other research findings of increased risk of breast cancer and HRT in the older population, although the authors do not specifically state what "older" means, they only infer above 45 years of age. Although not listed as a limitation, Michaelson-Cohen et al. (2021) report that a possible reason for increased breast cancer risk in the older population taking HRT could be because of combined therapy. The authors conclude that HRT use in women 45 years and younger at the time of RRSO does not increase breast cancer risk, while those older than 45 years of age at the time of RRSO and use of HRT does increase breast cancer risk.

Annotation Three

Kim, H. Y., Park, J., Moon, S. J., Jeong, S., Hong J. H., Lee, J. K., Cho, G. J., & Cho, H. (2024). Short-term Impact of Hormone Replacement Therapy on Risk of Breast Cancer in BRCA

Mutation Carriers: A Nationwide Study in South Korea. *Cancer Research & Treatment*, *56*(1), 143–148. https://doi-org.ezproxy.umary.edu/10.4143/crt.2023.653

Kim et al. (2024) did a retrospective study focusing on HRT in 151 BRCA mutation carriers that underwent RRSO. In South Korea, The Health Insurance Review and Assessment Service (HIRA) is an organization through the government that has access to the information on all claims of approximately 50 million Koreans. These claims include patient diagnosis, treatment, procedures, surgical history, and prescription drugs, but do not include laboratory results or cancer stage. This study sample included all Korean women who were diagnosed with the BRCA mutation and underwent an RRSO between January 1, 2013, and December 31, 2021. Women were excluded if they had a diagnosis of breast cancer before the RRSO or underwent mastectomy for any reason. This study falls into level III of the Johns Hopkins Nursing Evidence-Based Practice Model, with a quality rating of C due to the small sample size with the control being HRT. The study sample that received HRT after RRSO was 33 individuals and those that did not receive HRT was 118 individuals. Comparison was done with the incidence of breast cancer over time between the two groups.

Analyzing Kim et al. (2024) research with the CRAAP method, currency is very recent being published this year. Referenced literature ranges from 1994-2019 with all literature being pertinent to the subject of research. The relevance to the PICO question is well-rounded and appropriate given it analyzes BRCA mutation carriers and the incidence of breast cancer using hormone replacement therapy. The study specifically highlights the categories of hormone use being estrogen-only, progesterone-only, tibolone, and estrogen-progesterone combination. The authors' credentials and graduating medical schools are listed, with email and telephone numbers available for contact. Accuracy is supported by the resource from which the information was

drawn as the medical system in South Korea is government-controlled and country-wide. Language through the study is unbiased. The purpose was well defined and defended with the authors' discussion and concluding remarks.

Validity and reliability were recognized as this study offered the type of HRT the individuals in the sample were taking, providing there was no significant risk of breast cancer according to the type (mainly referencing progesterone). Distinguishing between synthetic and non-synthetic hormones was not done in this study, nor listed as a limitation. Limitations reported include the small sample size and short follow-up period to develop breast cancer (3.03 years). Although not noted as a limitation but noted by the authors, the study showed that only 21.9% of patients received HRT, while 83.1% of patients did not receive it due to personal concerns about developing breast cancer. The strengths the authors mentioned were that data was taken from the database and not patient-reported, eliminating recall bias, which the authors note as a large advantage. The method of statistical analysis was a t-test for continuous variables and a chi-square test for categorical variables. 95% confidence intervals of occurrence of breast cancer were used adding to the validity of the study. Added external validity was identified in the exclusion of those diagnosed with the BRCA mutation in the years 2021-2022 as the follow-up was too short. Kim et al. (2024) conclude that the use of HRT post-RRSO is an appropriate resource to alleviate menopausal symptoms and does not increase breast cancer risk in BRCA mutation-positive women.

Literature Synthesis Summary

The theme of these three longitudinal studies was to evaluate the use of hormone replacement therapy on pre-menopausal women who tested positive for the BRCA mutation and underwent preventative surgery (RRSO) for increased risk of ovarian and breast cancer. Due to

secondary menopause from the removal of the ovaries, women's quality of life, along with increased risk for osteoporosis, heart disease, and dementia with the shift in hormones without ovaries were key introductory pieces of each research study. To convey this importance the articles sought out the incidence of breast cancer with HRT in hopes to alleviate the concerns in HRT that were yielded from the Women's Health Initiative study (increased breast cancer risk with the use of HRT). As mentioned by Kim et al. (2024) in the study population only 21.9% of patients received HRT after RRSO, with the other percentage of patients not accepting the therapy due to fear of breast cancer risk. This stigma of HRT was mentioned in all three research articles. Kim et al. (2024) go on to note that with the findings of their research, clinicians have the ability to provide the risks and benefits of HRT with specific knowledge around positive genetic testing of the BRCA mutation. These three studies were focused on the short-term use of HRT, a key theme, specifically, an average of 4 years of use of HRT in Michaelson-Cohen et al.'s (2021) study, mean use of 3.03 years in Kim et al.'s (2023) study, and mean range of 3.9 years in Kotsopoulos et al.'s (2018) study.

Kim et al. (2023), Kotsopoulos et al. (2018), and Michaelson-Cohen et al. (2021) thematically support the use of HRT in genetically tested BRCA-positive women who have had RRSO. None of the three studies look at HRT in BRCA positive mutation and those who have not undergone RRSO, but report that this is a necessary area of study. Of these three articles, in addition to supporting claims of other articles listed within, Kotsopoulus et al. (2018) yielded safety of estrogen-only HRT by showing an 8% reduction in breast cancer risk per year of use; Michaelson-Cohen et al. (2021) supports the use of HRT therapy with RRSO being performed at 45 years of age or younger; and Kim et al. (2023) supports the use of short term HRT following an RRSO. There was a correlation between Kim et al. (2023) and Michaelson-Cohen et al.

(2021) as Kim et al. (2023) recognized in the results section referring to multivariate logistics of age and parity that there was no significant risk in breast cancer between those that used HRT and those that did not.

While Kotsopoulos et al. (2018) found that estrogen alone HRT actually decreases the risk of breast cancer risk, all three studies state the limitation of not distinguishing between synthetic HRT and bio-identical HRT. One question all studies pose is the increase in breast cancer risk with the use of combined therapy of estrogen and progesterone, which is specific to this PICO question as it specifically highlights the use of estrogen-only therapy. Kim et al. (2023) pose that progesterone has no impact on increasing the risk of breast cancer (small sample), while Kotsopoulos et al. (2018) study claims that although non-significant, the difference in 10-year risk of breast cancer in estrogen-only use is 12%, where combined therapy of estrogen plus progesterone yielded a 22% risk (RRSO completed 45 years of age and younger in this study). These themes help guide safe and educational care on the benefits versus the risks of HRT in BRCA-positive patients that have had an RRSO.

Application

Critical appraisal of evidence from a variety of sources is one of the most important skills clinicians can possess, whilst differentiating the best evidence from unreliable evidence. Producing positive outcomes for patients, but also recognizing posing risks needs to be understood through the most current and up-to-date research. When taking an EBP decision into actual practice, this involves clinical expertise, patient values and preferences, and the most current applicable research evidence (Melnyk & Fineout-Overholt, 2019). Specific guidelines in HRT are critical to develop given the research of these three articles, education on benefits and risks related to age, and duration in which is safe for the patient.

To be able to safely practice hormone replacement therapy in practice, with hopes of decreasing breast cancer incidence with estrogen-only therapy, or perhaps combined bio-identical hormone therapy, clinicians need to understand what the research is posing. The risk of breast cancer in BRCA1 mutation-positive patients is 72% and 69% in BRCA2-positive patients (Huber et al., 2021). Bilateral salpingo-oophorectomy reduces this risk but leads to early menopausal symptoms. HRT, specifically estrogen-only can aid in these symptoms, while also positively impacting bone, cardiac, and cognitive health. If a woman has an intact uterus, progesterone is necessary with the use of estrogen to ensure the endometrial lining does not get too thick, posing a concern with some significant findings in two of the studies analyzed (Kotsopoulos et al., 2018; Michaelson-Cohen et al., 2021). HRT can improve quality of life for women going through menopause and has some links to the prevention of cancer as evidenced by Kotsopoulos et al. (2018). Clinicians have the ability to educate patients on the risks and benefits of HRT with current research, however, more research is necessary on bio-identical hormone replacement therapy and the patient population positive for BRCA mutation who do not elect to do bilateral salpingo-oophorectomy and would like to pursue HRT for menopausal symptoms. Clinicians should continue to follow research closely while considering the risks specific to each patient, specifically to those with the BRCA1 or BRCA2 mutation. Every single woman goes through menopause, elective salpingo-oophorectomy causes early menopause exposing additional risks of osteoporosis, cardiovascular decline, and cognitive risk factors. It is essential to support every woman, their choices, and shared decision-making based on research to endorse the best healthcare outcomes and quality of life measures.

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