Hormone Use in BRCA1 and BRCA2 Mutation Carriers

While many studies have examined the use of exogenous (produced outside of the body) hormones, such as birth control pills (oral contraceptives) and hormone replacement therapy, in women at general population risk for breast and/or ovarian cancer, a limited number of studies have analyzed their impact on BRCA1 and BRCA2 mutation carriers.

It has been well established that women who carry mutations in BRCA1 or BRCA2 have a high lifetime risk of developing breast and ovarian cancer. The lifetime risk for a mutation carrier to develop breast cancer ranges from 55-85% compared to the general population risk of 12-13%. The lifetime risk to develop ovarian cancer ranges from 15-60% compared to the general population risk of 1-2%.

Because of the increased risk for breast cancer, BRCA mutation carriers may have concerns about taking oral contraceptives or using hormone replacement therapy after a premenopausal prophylactic bilateral salpingo-oophorectomy (removal of the ovaries and fallopian tubes). Here we review the current literature about hormone use by BRCA mutation carriers.

Oral Contraceptives and BRCA Mutation Carriers

The use of oral contraceptives (OC) has been shown to reduce the risk of ovarian cancer in the general population as well as in BRCA mutation carriers.\(^1\)-\(^6\) The maximum reduction in ovarian cancer risk of up to 60% is reached after six or more years of use according to some studies, and with 3 to 5 years of use according to others.\(^3,7\) Therefore, one option available to BRCA mutation carriers who have never had cancer and are of childbearing age is to take OC to reduce their risk of developing ovarian cancer until they are able to have their ovaries removed.

A number of studies have analyzed potential risks for breast cancer in BRCA mutation carriers who have taken OC and the results have been somewhat mixed and controversial. A large, population-based study comparing breast cancer in BRCA mutation carriers and non-carriers showed that there is no evidence that the use of current, low-dose OC increases the risk for early-onset breast cancer in BRCA mutation carriers. Therefore, they concluded that OC use should not be contraindicated in this population. They also demonstrated that OC use may even decrease the risk for early-onset breast cancer in BRCA1 (not BRCA2) mutation carriers.\(^8\)

Another study of BRCA mutation carriers demonstrated that OC use was not associated with an increased risk of breast cancer in BRCA2 mutation carriers but was associated with a modest increase in breast cancer risk in BRCA1 mutation carriers. This is contrary to the results of the study mentioned above. This study concluded that BRCA1 mutation carriers who used OC before 1975 (when hormone doses were much higher than those used today), before the age of 30, and for at least 5 years may be at increased risk for early-onset breast cancer.\(^9\)
Three more recent meta-analyses of the available data suggest that there is no evidence that oral contraceptives (particularly recent formulations) increase the risk of breast cancer in women who carry a BRCA mutation.\textsuperscript{4, 5, 19}

While the exact risks for breast cancer associated with OC use in BRCA mutation carriers are unclear, the risk for early-onset breast cancer appears to be, at most, modestly increased, if it is increased at all. Therefore, the benefits of ovarian cancer risk reduction associated with OC appear to outweigh any potential breast cancer risks associated with use. Pre-menopausal BRCA mutation carriers with no previous history of cancer may consider using OC to reduce their risk of ovarian cancer. Pre-menopausal BRCA mutation carriers may also choose to take OC for other reasons, such as a form of birth control or for regulation of their menstrual cycle.

There are no data yet regarding the impact of different OC formulations and the effect on cancer risks in BRCA mutation carriers.

Ovarian cancer is difficult to detect at early stages and it is recommended that all female BRCA mutation carriers have a bilateral salpingo-oophorectomy (BSO) to reduce their risk of developing ovarian cancer when childbearing is complete or by age forty. BSO also significantly reduces the future risk of breast cancer, particularly in young women who have the surgery before they go through menopause.\textsuperscript{10}

**Hormone Replacement Therapy and BRCA Mutation Carriers**

The use of hormone replacement therapy (HRT) in healthy BRCA mutation carriers who have their ovaries removed before natural menopause is somewhat controversial because of the chance that these hormones may increase the risk for breast cancer. This concern largely stems from data from a large randomized trial of over 16,000 women, known as the Women’s Health Initiative (WHI), that demonstrated that HRT increases the risk of breast cancer.\textsuperscript{11} However, this study was of post-menopausal women who extended their life-long hormone exposure after menopause. This is much different than the use of HRT in pre-menopausal BRCA mutation carriers who choose BSO before natural menopause occurred.

A study of 462 BRCA mutation carriers compared the rate of breast cancer in women who had their ovaries removed and took HRT to women who never had their ovaries removed and had never taken HRT. Women who had their ovaries removed and took HRT had approximately a third of the risk to develop breast cancer as compared to those women who did not have their ovaries removed.\textsuperscript{12}

Therefore, short-term HRT does not appear to diminish the reduction in breast cancer risk with ovary removal in BRCA mutation carriers and should be an option for young women with no previous history of cancer who carry BRCA mutations and have their ovaries removed before natural menopause.
**Tamoxifen, raloxifene (Evista), and aromatase inhibitors (e.g. exemestane) and BRCA Mutation Carriers**

Some types of breast cancer grow more rapidly in the presence of estrogen. These cancers are called “estrogen receptor positive (ER+) tumors”. The majority of BRCA2-related breast cancers are ER+, while the majority of BRCA1-related breast cancers are estrogen receptor negative (ER-). Chemopreventative medications, such as tamoxifen and raloxifene, reduce the development of ER+ breast cancers. However, Tamoxifen is associated with a small, but increased risk of uterine cancer (<1%) (not ovarian cancer) and both tamoxifen and raloxifene are associated with other side effects.

It is well-known that tamoxifen and raloxifene can reduce the risk of breast cancer in women at increased risk for the disease due to age, family history, or high-risk findings on breast biopsy. Several studies have examined whether tamoxifen also decreases the risk for breast cancer in BRCA mutation carriers, although this area needs to be thoroughly examined via other study designs (i.e. a controlled study) and the effectiveness of raloxifene in BRCA mutation carriers also needs to be assessed.

In one study of 491 BRCA mutation carriers who were diagnosed with stage I or stage II breast cancer, tamoxifen reduced the risk of future breast cancers within the same breast of the original diagnosis (ipsilateral) and also cancers in the other breast (contralateral).\(^\text{13}\)

Another study compared 209 female BRCA mutation carriers with bilateral breast cancer to 384 female BRCA mutation carriers with unilateral breast cancer. This study demonstrated that the risk of a contralateral breast cancer was 50% lower in BRCA1 mutation carriers who used Tamoxifen as treatment for their initial breast cancer.\(^\text{14}\) A follow-up to this study, which included a larger sample size, found Tamoxifen equally effective in reducing the risk of a future breast cancer in both BRCA1 and BRCA2 breast cancer survivors who were pre-menopausal or had reached natural menopause.\(^\text{15}\)

A recent study of over 1500 women who carried a BRCA mutation and were diagnosed with breast cancer provided additional evidence that tamoxifen use is associated with a significant reduction in the risk of a contralateral breast cancer.\(^\text{16}\)

It is unclear whether tamoxifen further reduces the risk of breast cancer in women who have had a pre-menopausal BSO. Further studies are needed in this area.\(^\text{15}\)

There are little data regarding preventive tamoxifen or raloxifene use in BRCA1 and BRCA2 mutation carriers who have never been diagnosed with breast cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) is a well-known study which analyzed the effect of tamoxifen on breast cancer incidence in women never diagnosed with breast cancer; however, the end result of this trial did not look at the BRCA status of all of its participants making conclusions difficult.
Another well-known study, the STAR trial, demonstrated that raloxifene is also effective at reducing breast cancer risk and is associated with lower risks of side effects than tamoxifen. This study along with existing data confirmed that the benefits of both tamoxifen and raloxifene (in terms of breast cancer risk reduction) outweigh the risks (in terms of side effects) making both medications good options for women at increased risk for breast cancer. However, this study also did not assess BRCA status of participants making conclusions about effectiveness specifically in BRCA carriers difficult.

A different class of medications (called aromatase inhibitors) have also been used as treatment for ER+ breast cancers in post-menopausal women. One of these medications, exemestane, has recently been shown to be effective at reducing the risk of breast cancer in healthy postmenopausal women at increased risk for breast cancer. However, data are limited about the use of aromatase inhibitors in the primary prevention setting, in general, and this study did not assess BRCA status so there are currently no data specifically about the effectiveness of aromatase inhibitors for primary prevention of breast cancer in BRCA carriers.

Based on the available information, women who carry either a BRCA1 or BRCA2 mutation and have been diagnosed with an ER+ breast cancer may consider taking one of these medications to reduce their risk of a future breast cancer. BRCA2, and possibly BRCA1, mutation carriers who have never had a diagnosis of breast cancer may also consider using one of these medications prophylactically and should discuss the pros and cons of these medications further with their doctors.

References

18. Visvanathan K et al. JCO 2013; 31(23):2942-2963.