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## **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 oral contraceptives (birth control pills) 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 50-85% 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 pre-menopausal 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.<sup>1,2,3</sup> 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.<sup>3,4</sup> 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.

Several studies have analyzed potential risks for breast cancer in BRCA mutation carriers who have taken OC. A large, population-based study comparing breast cancer in BRCA mutation carriers and non-carriers in the general population 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.<sup>5</sup>

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.<sup>6</sup>

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 may outweigh the 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 is 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.<sup>7</sup>

### **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.<sup>8</sup> 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 occurs.

A recent 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.<sup>9</sup>

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 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, reduce the development of ER+ breast cancers. However, Tamoxifen is associated with a small, but increased risk of uterine cancer (<1%) (not ovarian cancer) amongst other side effects.

It is well-known that Tamoxifen 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 (e.g. a controlled study).

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).<sup>10</sup>

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.<sup>10</sup> A recent 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 positive breast cancer survivors who were pre-menopausal or had reached natural menopause.<sup>11</sup>

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.<sup>10,11,12</sup>

There are little data regarding preventive Tamoxifen 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, this trial did not examine the BRCA status of all of its participants, making conclusions difficult.

Therefore, women who carry either a BRCA1 or BRCA2 mutation and have been diagnosed with an ER+ breast cancer may consider taking Tamoxifen or another such medication 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 consider using Tamoxifen (or Raloxifene, a similar medication) prophylactically and should discuss the pros and cons of this medication further with their doctors.

## References

1. McGuire et al. *Am J Epidemiol* 2004; 160: 613-8.
2. Whittemore et al. *Br J Cancer* 2004; 91: 1911-5.
3. McLaughlin et al. *Lancet Oncol* 2007; 8: 26-34.
4. Narod et al. *N Engl J Med* 1998; 339(7): 424-8.
5. Milne et al. *Cancer Epidemiol Biomarkers Prev* 2005; 14(2): 350-6.
6. Narod et al. *J Natl Cancer Inst* 2002; 94(23): 1773-9.
7. Rebbeck et al. *N Engl J Med* 2002; 346(21): 1616-22.
8. *JAMA* 2002; 288(3): 321-33.
9. Rebbeck et al. *J Clin Oncol* 2005; 23(31): 7804-10.
10. Metcalfe et al. *J Clin Oncol* 2004; 22(12): 2328-35.
11. Gronwald J et al. *Int J Cancer* 2006; 118: 2281-84.
12. Narod et al. *Lancet* 2000; 356: 1876-81.