Question
A 57-year-old woman with a history of modified radical mastectomy and reconstruction for breast cancer at age 36 presents with her daughter and sister to discuss their recent genetic testing results. The woman has no evidence of disease. Her BRCA testing was negative in the late 1990s and then again when repeat testing was performed.

More recently, an expanded panel revealed a CHEK2 mutation for which her daughter and sister are also positive. The woman is concerned about the risk of breast cancer recurrence, as well as any gynecologic cancer risks associated with the CHEK2 mutation. Her 52-year-old sister is unaffected, and is experiencing menopause symptoms. She is interested in management options, given the gene mutation.

The woman’s 25-year-old daughter is interested in discussing contraception options, specifically birth control pills. What are the safest options to treat menopause symptoms and for birth control in women with this gene mutation?

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The genes *BRCA1* and *BRCA2* are the most well-studied genes that correlate with risk of breast cancer. This family has another type of gene with mutations, *CHEK2*, a tumor-suppressor gene involved in pathways of DNA repair and cell cycle regulation.

Although *CHEK2* mutations are rare, in carriers with no affected relative, the risk of breast cancer is approximately 20%, and it increases up to 44% when both first- and second-degree relatives are affected.\(^1\)

All women testing positive for *CHEK2* mutation should be referred to a breast surveillance program for appropriate screening and discussion of a management plan. This interaction allows the woman and her gynecologist to discuss breast screening and initiate appropriate referrals.

There is no literature regarding *CHEK2* mutations and hormone therapy (HT) or oral contraception pill (OCP) use. As such, recommendations are extrapolated from *BRCA* literature, particularly from the unaffected, BRCA mutation-carrier population.

An unaffected woman with a *CHEK2* mutation who has menopause symptoms should review her management options with and without HT.

Results from the Women’s Health Initiative suggest a nonsignificant reduced risk of breast cancer for estrogen-only therapy (ET) and an increased risk with combination conjugated equine estrogens-medroxyprogesterone acetate therapy (EPT).\(^2\)

Extrapolating data from studies of *BRCA1* and *BRCA2* mutations, there is a theoretical increased risk of breast cancer in women with *CHEK2* mutations not undergoing risk-reducing mastectomy, but although limited, the data do not show an increased risk of breast cancer in carriers of the *BRCA* mutation who underwent risk-reducing bilateral salpingo-oophorectomy (RRSO), particularly with ET.\(^3-6\)

The Two-Sister Study evaluated more than 1,400 sister-matched cases of breast cancer and found no increased risk of breast cancer with use of EPT, whereas unopposed estrogen was associated with a reduced risk of young-onset breast cancer.\(^7\) Thus, young women undergoing RRSO do not appear to be at increased risk for breast cancer should they choose to start HT.

Ideally, any premenopausal woman will undergo counseling regarding symptoms she may experience, and options should be individualized to her as a “plan” before undergoing any risk-reducing surgery.

The choice of HT should be dictated by symptoms—generalized versus localized—and should be limited to the smallest dose for the shortest period. In addition, those undergoing concurrent mastectomy or who...
already have undergone prophylactic mastectomy are ideal candidates for HT.

Local vaginal estrogen is minimally absorbed and can be used for the management of the genitourinary syndrome of menopause in this population or in women who are survivors of breast cancer.\(^8,9\)

Although somewhat limited, existing data indicate that the risk of breast cancer is not increased with use of systemic HT by menopausal carriers of the \(BRCA\) mutation with intact breasts.\(^5\) Extrapolating again from unaffected carriers of the \(BRCA\) mutation, HT can be used in carriers of the \(CHEK2\) mutation.

It has long been acknowledged that oral contraceptives (OCs) reduce the risk of ovarian cancer in the general population\(^10-13\) as well as in the \(BRCA\)-mutation population. For this reason, unaffected \(BRCA\)-mutation carriers are often advised to use OCs regardless of whether they are undergoing RRSO.

This same benefit does not apply to carriers of the \(CHEK2\) mutation beyond the decreased risk attributed to the general population because there is no known increased risk of gynecologic cancers associated with \(CHEK2\) mutations. However, although there are some inconsistent data, there does not appear to be an increased risk of breast cancer in carriers of the \(BRCA\) mutation using OCs.\(^11,14\)

This 57-year-old woman is at risk for contralateral breast cancer and is discussing options with genetic counselors and her breast surgeon. Unlike with \(BRCA\) mutations, there is no known additional risk of gynecologic cancers in carriers of the \(CHEK2\) mutation. Thus, no additional intervention or evaluation is recommended to prevent gynecologic cancers.

The patient’s sister can safely use HT, but treatment should be individualized on the basis of her symptoms. As with the general population, it is recommended that symptoms be monitored and reassessed periodically so that treatment can be used for the shortest time possible and at the lowest possible dose.\(^14\)

The patient’s 25-year-old daughter should be counseled regarding contraception options as one would counsel any young woman who does not carry the \(CHEK2\) mutation. The OCs remain an option for her with little or no risk of breast cancer.

For affected women who are positive for the \(CHEK2\) mutation, as for affected women who are positive for the \(BRCA\) mutation, nonhormone options should be explored before initiating HT or OCs for quality-of-life issues. The benefits of therapy need to be weighed against the risks.

References
Have you ever encountered a patient in whom an expanded gene panel revealed a CHEK2 mutation? How did you proceed? Visit our Member Forum to discuss the May Menopause e-Consult.

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