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Is menopausal hormone therapy safe when your patient carries a BRCA mutation?

Data suggest that several years of systemic hormone therapy are safe in mutation carriers who have intact breasts and no personal history of breast cancer. If such mutation carriers have undergone risk-reducing bilateral mastectomy, systemic hormone therapy can be used without significantly elevating the risk of breast cancer.

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IN THIS ARTICLE

CASE **Disabling vasomotor symptoms in a BRCA1 mutation carrier**

Christine is a 39-year-old mother of 2 who underwent risk-reducing, minimally invasive bilateral salpingo-oophorectomy with hysterectomy 4 months ago for a BRCA1 mutation (with benign findings on pathology). Eighteen months before that surgery, she had risk-reducing bilateral mastectomy with reconstruction (implants) and was advised by her surgeon that she no longer needs breast imaging.

Today she reports disabling hot flashes, insomnia, vaginal dryness, and painful sex. Her previous ObGyn, who performed the hysterectomy, was unwilling to prescribe hormone therapy (HT) due to safety concerns. Christine tried venlafaxine at 37 to 75 mg but noted little relief of her vasomotor symptoms.

In discussing her symptoms with you during this initial visit, Christine, a practicing accountant, also reveals that she does not feel as intellectually "sharp" as she did before her gynecologic surgery.

What can you offer for relief of her symptoms?

More BRCA mutation carriers are being identified and choosing to undergo risk-reducing salpingo-oophorectomy and bilateral mastectomy. Accordingly, clinicians are likely to face more questions about the use of systemic HT in this population. Because mutation carriers may worry about the safety of HT, given their BRCA status, some may delay or avoid salpingo-oophorectomy—a surgery that not only reduces the risk of ovarian, fallopian

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Dr. Pinkerton and Dr. Simon provided peer review and comments for Dr. Kaunitz's case study.

tube, and peritoneal cancer by 80% but also decreases the risk of breast cancer by 48%.[1]

Surgically menopausal women in their 30s or 40s who are not treated with HT appear to have an elevated risk for dementia and Parkinsonism.[2] In addition, vasomotor symptoms are often more severe, and the risks for osteoporosis and, likely, cardiovascular disease are elevated in women with early menopause who are not treated with HT. For these reasons, systemic HT is recommended for women with early menopause, and generally should be continued at least until the normal age of menopause unless specific contraindications are present.[3]

Because Christine not only has had risk-reducing gynecologic surgery but also risk-reducing bilateral mastectomy, her current risk for breast cancer is very low whether or not she uses HT. Because she does not have a uterus, her symptoms can effectively and safely be treated with systemic estrogen-only therapy.

Among clinicians with special expertise in the management of BRCA mutation carriers, the use of systemic HT would be considered appropriate—and not controversial—in this setting.[4]

Angelina Jolie details her surgeries

In March 2015, 39-year-old Oscar-winning actress and filmmaker Angelina Jolie Pitt published an opinion piece in the *New York Times* detailing her recent laparoscopic salpingo-oophorectomy and initiation of HT.[5] Ms. Jolie Pitt, who carries the BRCA1 mutation, lost her mother, grandmother, and aunt to hereditary breast/ovarian cancer. Two years earlier, Ms. Jolie Pitt made news by describing her decision to move ahead with risk-reducing bilateral mastectomy.

Following her risk-reducing salpingo-oophorectomy, she initiated systemic HT using transdermal estradiol and off-label use of a levonorgestrel-releasing intrauterine system for endometrial protection.

Her courageous decision to publicly describe her surgery and subsequent initiation of systemic HT will likely encourage women with ominous family histories to seek out genetic counseling and testing. Her decision to "go public" regarding surgery should help mutation carriers without a history of cancer (known in the BRCA community as "previvors") who have completed their families to move forward with risk-reducing gynecologic surgery and, when appropriate, use of systemic HT.[6]

The outlook for previvors with intact breasts

Three studies address the risk of breast cancer with use of systemic HT among previvors with intact breasts. A 2005 study followed a cohort of BRCA1 and BRCA2 carriers with intact breasts, 155 of whom had undergone risk-reducing salpingo-oophorectomy, for a mean of 3.6 years. Of these women, 60% and 7%, respectively, of those who had and had not undergone salpingo-oophorectomy used HT. The authors noted that bilateral salpingo-oophorectomy reduced the risk of breast cancer by some 60%, whether or not women used HT.[7]

A 2008 case-control study focused on 472 menopausal BRCA1 carriers, half of whom had been diagnosed with breast cancer (cases); the other half had not received this diagnosis (controls). A 43% *reduction* in the risk of breast cancer was associated with prior use of HT.[8]

A 2011 presentation described a cohort study in which 1,299 BRCA1 and BRCA2 carriers with intact breasts who had undergone salpingo-oophorectomy were followed for a mean of 5.4 years postoperatively. In this population, use of HT was not associated with an increased risk of breast cancer. Among women with BRCA1 mutations, use of systemic HT was associated with a reduced risk of breast cancer.[9]

Viewed in aggregate, these studies reassure us that short-term use of systemic HT does not increase breast cancer risk in women with BRCA1 or BRCA2 mutations and intact breasts.

DR. SIMON *Nevertheless, I think it is important to point out that a properly powered*

FAST TRACK

Short-term use of systemic HT does not increase breast cancer risk in women with BRCA1 or BRCA2 mutations and intact breasts

study to assess actual risk in this setting is not available in the literature.

When a patient refuses HT

DR. PINKERTON *Some BRCA mutation carriers may refuse HT despite reassurance that it is safe. Nonhormonal therapies are not as effective at relieving severe menopausal symptoms. Almost all selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) can be offered, although only low-dose paroxetine salt is approved for treatment of postmenopausal hot flashes.*[10,11] *Gabapentin also has shown efficacy in relieving hot flashes.*

For genitourinary syndrome of menopause (GSM; formerly known as vulvovaginal atrophy), lubricants and moisturizers may provide some benefit, but they don't improve the vaginal superficial cells and, therefore, are not as effective as hormonal options. There is now a selective estrogen receptor modulator (SERM) approved to treat GSM—ospemifene. However, in clinical trials, ospemifene has been shown to increase hot flashes, so it would not be a good option for our patient.[12]

CASE Continued

Christine follows up 3 months after initiating estrogen therapy (oral estradiol 2 mg daily). She reports significant improvement in her hot flashes, with improved sleep and fewer sleep disruptions. In addition, she feels that her "mental sharpness" has returned.

DR. PINKERTON *What if this patient had an intact uterus? Then she would not be a candidate for estrogen-only therapy because she would need continued endometrial protection. Options then would include low-dose continuous or cyclic progestogen therapy, often starting with micronized progesterone, as the E3N Study suggested it has a less negative effect on the uterus.*[13] *Or she could use a levonorgestrel-releasing intrauterine system off label, as Ms. Jolie Pitt elected to do.*

Another option would be combining estrogen with a SERM. The only estrogen/SERM combination currently approved by the US Food and Drug Administration (FDA) is conjugated estrogen/bazedoxefine, which showed no increase in breast tenderness, breast density, or bleeding rates, compared with placebo, in multiple trials up to 5 years in duration.[14]

CASE Resolved

Christine says she would like to continue HT, although she still experiences dryness and discomfort when sexually active with her husband, despite use of a vaginal lubricant. A pelvic examination is consistent with early changes of GSM.[15]

You discuss GSM with Christine and suggest that she consider 1 of 2 strategies:

- Switch from daily use of oral estradiol to the 3-month systemic 0.1-mg estradiol ring (Femring), which would address both her vasomotor symptoms and her GSM.
- Continue oral estradiol and add low-dose vaginal estrogen (cream, tablets, or Estring 2 mg).

Christine chooses Option 2. When she returns 6 months later for her well-woman visit, she reports that all of her menopausal symptoms have resolved, and a pelvic examination no longer reveals changes of GSM.

FAST TRACK

Because lubricants and moisturizers don't improve vaginal superficial cells, they aren't as effective as hormonal options for genitourinary syndrome of menopause

Disclosures

Dr. Kaunitz reports that within the past 36 months, he has received or is currently receiving grant or research support from Bayer, Teva, and TherapeuticsMD, and has served or is currently serving as a consultant to Actavis, Bayer, and Teva.

Dr. Pinkerton reports that within the past 36 months, she has received or is currently receiving grant or research support from TherapeuticsMD and has served or is currently serving as a consultant to Noven, Inc., Pfizer, Shionogi, and TherapeuticsMD.

Dr. Simon reports that within the past 36 months, he has been a consultant to or served on the advisory boards of AbbVie, Actavis, Amgen, Amneal, Apotex, Ascend Therapeutics, BioSante, Depomed, Dr. Reddy Laboratories, Everett Laboratories, Intimina by Lelo, Lupin, Meda, Merck, Novartis, Noven, Novo Nordisk, Nuelle, Pfizer, Regeneron, Sanofi SA, Sermonix, Shionogi, Shippan Point Advisors, Sprout, Teva, TherapeuticsMD, Warner Chilcott, and Watson.

In the past 36 months, Dr. Simon has received grant/research support from AbbVie, Actavis, Agile Therapeutics, Bayer Healthcare, EndoCeutics, New England Research Institute, Novo Nordisk, Palatin Technologies, Teva, and TherapeuticsMD.

Within the past 36 months, Dr. Simon has also served on the speaker's bureaus of Amgen, Eisai, Merck, Novartis, Noven, Novo Nordisk, Shionogi, Teva, and Warner Chilcott.

Dr. Simon served as Chief Medical Officer of Sprout Pharmaceuticals until April 1, 2013.

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