NAMS Practice Pearl

Use of Systemic Hormone Therapy in BRCA *Mutation Carriers*

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As more women are being counseled and tested, clinicians increasingly encounter women with identified* BRCA1 *and* BRCA2 *gene mutations. Existing, albeit limited, data indicate that risks of breast cancer are not increased with use of systemic hormone therapy by menopausal* BRCA *mutation carriers with intact breasts. Young mutation carriers with or without intact breasts should not defer or avoid risk-reducing (and lifesaving) bilateral salpingo-oophorectomy because of concerns that subsequent use of systemic hormone therapy will elevate breast cancer risk.

As more *BRCA* mutation carriers are being identified, clinicians increasingly encounter patients with such mutations seeking advice regarding the use of systemic hormone therapy (HT). In *BRCA1* carriers, the estimated cumulative risks of breast and ovarian cancer by age 70 range from 60% to 65% and 39% to 59%, respectively, and these risks range from 45% to 55% and 11% to 17%, respectively, in women who harbor *BRCA2* mutations.[1,2] When performed in premenopausal women, bilateral salpingo-oophorectomy (BSO) reduces ovarian, fallopian tube, and peritoneal cancer risks by 72% to 80% and breast cancer risks by 46% to 48%.[3,4] Women mutation carriers with no personal history of breast or ovarian cancer (known as *previvors* in the *BRCA* community) should be encouraged to complete childbearing and undergo risk-reducing BSO by age 35 to 40 years. Women who carry a *BRCA1* mutation have an estimated 4% risk of being diagnosed with ovarian cancer clinically or at the time of surgery before age 40. This risk increases to 14.2% if such women defer BSO until age 50.[4]

Without use of systemic HT, young surgically menopausal women in observational studies appear to have an elevated risk for cognitive impairment or dementia.[5] In addition, vasomotor symptoms are often more severe, and risks for osteoporosis and cardiovascular disease may be elevated in women with early menopause who are not treated with HT. Accordingly, in the absence of contraindications, use of systemic HT should be considered for women with early menopause and generally should be continued at least until the normal age of menopause.[6] However, mutation carriers may delay or avoid risk-reducing (and lifesaving) BSO because of concerns regarding the safety of systemic HT.[7]

Assessing the safety of hormone therapy in previvors with intact breasts. Randomized trials to inform decision making regarding use of HT in previvors have not been performed. However,

three observational studies address the risk of breast cancer with use of systemic HT in menopausal previvors *with intact breasts*.

A 2005 study followed a cohort of 462 women with *BRCA1* or *BRCA2* mutations, 155 of whom had undergone risk-reducing BSO. Among these women, 60% of those who had undergone BSO used HT; 7% of those who had not undergone BSO used HT.[7] With a mean follow-up of 3.6 years, the researchers observed that BSO was associated with a 60% reduced risk of breast cancer ($P < 0.05$), with similar risk reduction noted whether women used HT or not. Similar trends were noted with use of estrogen-only therapy (ET) and estrogen-progestogen therapy (EPT). However, few women in this study used EPT, reflecting that many of these women had undergone prior hysterectomy. Although the researchers did not report on duration of HT use, this duration presumably was similar to a mean follow-up of 3.6 years because most HT was initiated after risk-reducing BSO.

A case-control study published in 2008 assessed 472 menopausal *BRCA1* carriers, half of whom had been diagnosed with breast cancer (cases); the other half of this study population were previvors (controls).[8] Approximately three-quarters of cases and controls had undergone spontaneous menopause. There was a history of prior and current HT use in 20% and 29% of cases and controls, respectively. Accordingly, HT use was associated with a 43% *reduction* ($P = 0.02$) in the risk of breast cancer. Mean duration of HT use was 4.0 and 3.7 years in cases and controls, respectively. Duration of HT use was not significantly associated with risk of breast cancer. Likewise, use of ET versus EPT was not associated with differences in risk for breast cancer.

A 2011 presentation described an expansion and follow-up of a study by Rebbeck and associates[7] that assessed risk of breast cancer in 1,299 previvors carrying *BRCA1* or *BRCA2* mutations who had undergone risk-reducing BSO and compared this risk with mutation carriers who had not.[9] Women using HT were followed postoperatively for a mean of 5.4 years (range, 0.6-24.4 y). Compared with nonusers who had not undergone BSO, HT use among women who had undergone BSO was not associated with an elevated risk for breast cancer. As with the case-control study, in women with *BRCA1* mutations, use of systemic HT was associated with a 48% reduced risk of breast cancer ($P < 0.05$).

The three studies that have addressed the effect of HT use by previvors are limited by their observational design, size, and limited duration of follow-up. Nonetheless, these reports provide some reassurance for clinicians and previvors that use of systemic HT (whether ET or EPT) does not substantially increase breast cancer risk in *BRCA1* or *BRCA2* mutation carriers with intact breasts.

***Angelina Jolie Pitt, risk-reducing surgery, and use of hormone therapy*.** Many women with the *BRCA* gene mutation come to the clinic with some information about the public statements made by Angelina Jolie, the 39-year-old actress and filmmaker and *BRCA1* mutation carrier. It can be clinically useful to discuss her statements and experience with women. In 2015, she authored an Op-Ed piece in the *New York Times* detailing her risk-reducing BSO. Two years earlier, Jolie Pitt had described her risk-reducing bilateral mastectomy in the same newspaper. After her risk-reducing gynecologic surgery, she initiated EPT.[10]

By publicly describing her experience, she has likely encouraged previvors to proceed with risk-reducing mastectomy and gynecologic surgery and, on an individualized basis, initiate systemic HT.

Menopausal previvors who decline to use hormone therapy. Some menopausal previvors refuse HT despite guidance from their clinicians that, in limited observational studies, it appears safe for *BRCA* mutation carriers. In this setting, previvors with bothersome vasomotor symptoms should be encouraged to use nonhormone therapies. Although not as effective as standard-dose HT, the selective serotonin reuptake inhibitor paroxetine and serotonin-norepinephrine reuptake inhibitor venlafaxine are more effective than placebo and represent the best-studied nonhormone agents for relieving menopause symptoms. In contrast with venlafaxine, low-dose paroxetine salt 7.5 mg tablets are approved for treatment of postmenopausal hot flashes. In addition to low-dose paroxetine salt and venlafaxine, off-label use of gabapentin is more effective than placebo in relieving hot flashes.[11]

Clinical recommendations for menopausal previvors. Existing albeit limited data indicate that risks of breast cancer are not increased with use of systemic HT by menopausal *BRCA* mutation carriers with intact breasts. Young previvors with or without intact breasts should not defer or avoid risk-reducing BSO because of concerns that subsequent use of systemic HT will elevate breast cancer risk.

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