

Does hormone therapy increase breast cancer risk in *BRCA1* mutation carriers?

No. In a prospective study that followed 872 *BRCA1* carriers after oophorectomy for a mean follow-up of 7.6 years, the hazard ratio was 0.97 (95% confidence interval, 0.62–1.52; $P = .89$) for ever use of any type of hormone therapy versus no use. The use of estrogen therapy compared with estrogen plus progestogen therapy *reduced* the subsequent risk of breast cancer (10-year actuarial risk of breast cancer of 12% vs 22%, respectively; $P = .04$).

EXPERT COMMENTARY

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Kotsopoulos J, Gronwald J, Karlan BY, et al; Hereditary Breast Cancer Clinical Study Group. Hormone replacement therapy after oophorectomy and breast cancer risk among BRCA1 mutation carriers [published online ahead of print April 19, 2018]. JAMA Oncol. doi:10.1001/jamaoncol.2018.0211.

Prophylactic bilateral oophorectomy (BO) reduces the risk of future ovarian cancer in women who have *BRCA1* gene mutations. Women in this high-risk population may be reluctant, however, to use menopausal hormone therapy (HT) to mitigate the symptoms of surgical menopause because of concerns that it might elevate their risk of breast cancer.

To determine the relationship between

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HT use and *BRCA1*-associated breast cancer, Kotsopoulos and colleagues conducted a multicenter international cohort study. They prospectively followed women with *BRCA1* mutations who had undergone BO and had intact breasts and no history of breast cancer.

Details of the study

The study included women who had a *BRCA1* mutation and considered HT use following BO. Women were excluded from the analysis if they had a prior diagnosis of breast cancer or had BO prior to study enrollment. Study participants completed a questionnaire at baseline and a follow-up questionnaire every 2 years thereafter. The primary end point was invasive breast cancer.

Among 872 participating *BRCA1* carriers, 43% ($n = 377$) used HT following BO. Mean duration of HT use following BO was 3.9 years, with 69% of users taking estrogen therapy alone (ET) and 19% using estrogen plus progestogen therapy (EPT). Those who used HT were younger at the time of BO compared with women who never used HT (mean age, 43.0 vs 48.4 years).

During follow-up (mean, 7.6 years; range, 0.4–22.1), invasive breast cancer was diagnosed in similar proportions of HT users

FAST TRACK

BRCA1 carriers who undergo prophylactic oophorectomy may be reluctant to use HT for surgical menopause symptoms due to concerns it might increase their risk of breast cancer

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and nonusers—10.3% and 10.7%, respectively ($P = .86$). The hazard ratio was 0.97 (95% confidence interval, 0.62–1.52; $P = .89$) for ever use of any type of hormone therapy versus no use.

When the type of HT used was examined, the 10-year actuarial risk of breast cancer was significantly lower with ET than with EPT (12% vs 22%, respectively; $P = .04$); this difference was more marked for women who underwent BO prior to age 45 (9% vs 24%; $P = .009$).

Study strengths and weaknesses

This investigation had several strengths, including the large number of *BRCA1* mutation carriers studied, the relatively long follow-up, and the detailed exposure data obtained.

The use of self-administered questionnaires for collecting information on lifetime HT use and breast cancer diagnoses may be a limitation. In addition, the HT route, regimen, and dose were not considered in the analysis, and the effect of intrauterine devices as progestational endometrial protection was not evaluated. Finally, the

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Because women with *BRCA1* mutations have an elevated risk of ovarian cancer, risk-reducing gynecologic surgery is recommended for these women who have completed childbearing. In young women, BO without HT is associated with severe vasomotor symptoms, osteoporosis, cardiovascular disease, and cognitive decline. The clear reduction in breast cancer risk associated with ET (vs EPT) following BO suggests that in *BRCA1* carriers who have completed childbearing, hysterectomy (which precludes the need for progestogen therapy) should be considered as part of risk-reducing gynecologic surgery. Further, the findings of this prospective study in high-risk women parallels the findings of the large randomized Women's Health Initiative trial (performed in the general population of menopausal women), which found that ET (conjugated equine estrogen) reduces the risk.¹

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relationship between HT and breast cancer risk in women with intact ovaries was not evaluated. ●

Reference

1. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA*. 2013;310(13):1353–1368.