Breast cancer chemoprophylaxis in high-risk women: How persistent is the impact of an aromatase inhibitor after 5 years of use?

Among postmenopausal women at high risk for breast cancer N = 3,864), **those treated with anastrozole (N = 1,920) compared with placebo (N = 1,944) for 5 years had a 49% reduction in breast cancer** (85 vs 165 cases; hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.39–0.66; *P*<.0001) **after a median follow-up of 131 months.** The reduction was larger in the first 5 years but remained significant after 5 years. Although the risk reduction from this endogenous estrogen-minimizing medication was persistent, no mortality benefit was observed.

Cuzick J, Sestak I, Forbes JF, et al; IBIS-II Investigators. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. Lancet. 2020;395;117-122.

EXPERT COMMENTARY
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A manufacturer-sponsored trial initiated in 2003, IBIS-II (International Breast Cancer Intervention Study II) included 3,864 menopausal women (mean age at baseline, 59.4 years) at elevated risk for breast cancer. The women were randomly assigned to 5-year treatment with either placebo (N = 1,944) or the aromatase inhibitor anastrozole 1 mg daily (N = 1,920).[1]

Reporting on the long-term follow-up results of the trial, Cuzick and colleagues found that anastrozole use substantially reduced the incidence of all breast cancer, including invasive breast cancer and ductal carcinoma in situ. Key adverse events associated with anastrozole were fractures, arthralgias, and menopausal symptoms (vasomotor symptoms and vaginal dryness).

To determine whether anastrozole had any persistent impact, the investigators continued to follow participants for all breast cancers and other outcomes.[2]

Details of the study

This randomized controlled trial that included 3,864 postmenopausal women had

Dr. Kaunitz reports serving on advisory boards for Pfizer.

FAST TRACK

In a long-term follow-up of the IBIS-II trial, investigators found that anastrozole use substantially reduced the incidence of all breast cancer, including invasive breast cancer and ductal carcinoma in situ

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The breast cancer chemoprophylactic efficacy of anastrozole compares favorably with that of tamoxifen. Furthermore, in women with an intact uterus, the increased risks of gynecologic problems, including endometrial cancer, associated with tamoxifen do not occur with aromatase inhibitors. However, the lack of any obvious mortality benefit means the ultimate value of estrogen deprivation breast cancer chemoprophylaxis continues to be uncertain, especially given other risks, including bone loss. In view of these new data, it will be important for high-risk women considering aromatase inhibitor prophylaxis to understand that these medications have not been associated with a mortality benefit.

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a median overall follow-up of 131 months; the primary outcome was all breast cancer. Random assignment to anastrozole use (1,920 women) was associated with a 49% reduction in all breast cancer (85 cases vs 165 cases in the placebo group [N = 1,944]; HR, 0.51; 95% CI, 0.39–0.66; *P*<.0001).

In the first 5 years, risk reduction was 61% with anastrozole (*P*<.0001 for overall and the first 5 years of follow-up). Subsequently, the magnitude of the risk reduction attenuated to 37% (*P* = .014). With 12 years of follow-up, the estimated risk of being diagnosed with breast cancer was 8.8% and 5.3% in the placebo and anastrozole groups, respectively. The number needed to treat for 5 years to prevent 1 breast cancer was 29.

With anastrozole, prevention of estrogen–receptor positive tumors was substantially more robust at 54% (HR, 0.46; 95% CI, 0.33–0.65; *P*<.0001) than for estrogen–receptor negative tumors at 27% (HR, 0.77; 95% CI, 0.41–1.44; *P* = .41).

Over the course of the long-term study, the incidence of fractures and cardiovascular events was similar in the placebo and anastrozole groups. Arthralgias and menopausal symptoms were not assessed after the trial's initial 5 years. Overall, the number of deaths (all cause as well as breast cancer related) were similar in the placebo and anastrozole groups.

Study strengths and limitations

The authors noted that this updated analysis of the IBIS-II trial data offers further support for the use of anastrozole in breast cancer prevention for high-risk postmenopausal women. The extended posttreatment follow-up showed a significant continuing reduction in breast cancer, and there was no evidence of new late adverse effects. A limitation of the analysis, however, is that very few deaths from breast cancer occurred during the study timeframe. Thus, additional follow-up would be needed to assess anastrozole's effect on breast cancer mortality. ●

References

1. Cuzick J, Sestak I, Forbes JF, et al; IBIS-II Investigators. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. *Lancet*. 2014;383:1041-1048.
2. Cuzick J, Sestak I, Forbes JF, et al; IBIS-II Investigators. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. *Lancet*. 2020;395;117-122.