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To interview Jack Cuzick, contact Julia Gunther at julia.gunther@aacr.org or 215-446-6896. For a photo of Cuzick, click here.

# Breast Cancer Preventive Effects of Anastrozole Persist Long After Stopping Treatment

SAN ANTONIO — Breast cancer incidence among postmenopausal women at high risk for developing the disease continued to be significantly reduced 5.9 years after stopping five years of the aromatase inhibitor anastrozole, according to data from the International Breast Cancer Intervention Study II (IBIS-II) Prevention trial presented at the 2019 San Antonio Breast Cancer Symposium, held Dec. 10–14. The study is being simultaneously published in the *The Lancet*.

"IBIS-II Prevention was designed to investigate whether five years of anastrozole can safely and effectively prevent breast cancer in postmenopausal women who are at high risk for the disease," said Jack Cuzick, PhD, cochairman of the International Breast Cancer Intervention Studies. "In 2013, we reported that in the first seven years of follow-up, anastrozole significantly reduced breast cancer incidence compared with placebo and that it did so with very few side effects.

"Our new data show that after a median of 10.9 years of follow-up there continues to be a significant reduction in breast cancer incidence," continued Cuzick, who is also director of the Wolfson Institute of Preventive Medicine, head of the Centre for Cancer Prevention, and the John Snow Professor of Epidemiology at Queen Mary University of London. "It is exciting to see that anastrozole has a continued impact on breast cancer incidence even after stopping treatment, as this strengthens the case for its use as a breast cancer prevention therapy."

Cuzick and colleagues enrolled 3,864 postmenopausal women at increased risk for developing breast cancer in the IBIS-II Prevention study from 2003 to 2012. Women were considered to be at high risk for breast cancer if they fulfilled any one of a number of criteria, including having two or more blood relatives with breast cancer, having a mother or sister who developed breast cancer before the age of 50, and having a mother or sister who had breast cancer in both breasts. Among the participants, 1,920 were randomly assigned to anastrozole for five years and 1,944 to placebo. Five-year adherence to treatment was 74.6 percent for anastrozole and 77.0 percent for placebo, which is not significantly different.

After a median follow-up of 10.9 years, the researchers found that women assigned to anastrozole were 50 percent less likely to have developed breast cancer compared with women assigned to the placebo.

Cuzick explained that there were no new adverse side effects to add to those reported in 2013, which were mostly small increases in muscle aches and pains, and hot flashes. "No excess of fractures or other serious side effects were seen with anastrozole," he said.

"The 50 percent reduction in likelihood of breast cancer incidence after 10.9 years of follow-up is slightly less than the 53 percent reduction we reported after the first seven years of follow-up,

but it is still a significant effect and larger than that seen for tamoxifen," said Cuzick. "Another way to consider the data is that it translates into an estimated 29 women needing to be treated with anastrozole for five years to prevent one breast cancer during treatment and in the next five years.

"This is far fewer women than the estimated 49 women that need to be treated with tamoxifen for five years to prevent one breast cancer in the same time period," added Cuzick. "Therefore, our new results strongly suggest that anastrozole should be the preferred therapy for breast cancer prevention in postmenopausal women at increased risk for the disease, with tamoxifen used for women who experience severe side effects from anastrozole."

Cuzick cautioned that the preventive benefits of anastrozole are seen for estrogen receptor–positive breast cancer and for ductal carcinoma in situ but not for estrogen receptor–negative breast cancer. This is to be expected, he says, because anastrozole targets the estrogen pathway.

At the time of analysis, 129 deaths had been reported, with no significant difference in all-cause mortality between the anastrozole and placebo groups. There had been only five deaths from breast cancer, two among those assigned anastrozole and three among those assigned placebo.

"This is too few breast cancer deaths to determine if anastrozole reduces breast cancer mortality, so we are planning to follow the IBIS-II Prevention participants for longer to investigate this," Cuzick concluded.

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**ABSTRACT**

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Ten year results of the international breast cancer intervention study II

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**Background:** Two large clinical trials have shown the benefit of aromatase inhibitors in healthy women to reduce the risk of developing breast cancer (MAP.3 and IBIS-II). Here, we report blinded 10-year median follow-up efficacy data for the IBIS-II trial, which compared anastrozole to placebo in women at increased risk of developing breast cancer.
**Material and Methods:** 3864 postmenopausal women at increased risk of developing breast cancer were recruited into a double-blind trial of anastrozole (N=1920) versus matching placebo (N=1944) for 5 years. The primary objective of this study was to determine the efficacy of anastrozole in preventing breast cancer (both invasive and ductal carcinoma in situ (DCIS)), overall and particularly for the post 5-year time period. Secondary endpoints included prevention of oestrogen receptor positive breast cancer, breast cancer mortality, non-breast cancer deaths, other cancers, cardiovascular disease, fractures, and musculoskeletal events.
**Results:** After a median follow-up of 10.9 years (IQR 8.8-13.0), a total of 241 breast cancers have been reported (HR=0.50 (0.38-0.65), P<0.0001) (Table). The reduction was larger in the first 5 years (HR=0.39 (0.27-0.58), P<0.0001), but still significant after 5 years (117 (49%) new cases; HR=0.63 (0.43-0.91), P=0.015) (Table). The effects in the two time periods

were not significantly different (P=0.11). Invasive oestrogen receptor (ER) positive breast cancer was reduced by 54% with anastrozole (HR=0.46 (0.33-0.65), P<0.0001), with a continued significant effect observed in the post treatment follow-up period (Table). A non-significant effect was observed in invasive ER-negative breast cancer (HR=0.76 (0.39-1.45), P=0.4). A reduction in DCIS overall was observed (Table), with a very large reduction in those known to be ER-positive (HR=0.23 (0.08-0.69), P<0.0001). A total of 129 deaths have been reported, with no significant difference in all-cause mortality between the two treatment arms (63 vs. 66; HR=0.93 (0.66-1.32), P=0.7). Only 5 deaths from breast cancer (2 vs. 3) were reported, but number of events are very small and longer follow-up is needed. 321 cancers other than breast were reported, with a significant decrease observed with anastrozole (129 vs. 192, OR=0.66 (0.52-0.83), P=0.0004). Specifically, fewer endometrial cancers (4 vs. 8), ovarian cancers (5 vs. 9), lung cancers (5 vs. 12), and melanomas (9 vs. 18) were observed with anastrozole. A comprehensive adverse event profile will be reported.
**Conclusion:** This updated analysis of the IBIS-II trial confirms the significant reduction in breast cancer occurrence with anastrozole in the post-treatment follow-up period. These results indicate a long-term preventive benefit with anastrozole for ER-positive breast cancer in postmenopausal women.

Number of events and Hazard Ratios (95% CI) according to followup period.

| | **Number of events** | **HR (95% CI)** | **P-value** |
|---|---|---|---|
| **Overall** | 241 (81 vs. 160) | 0.50 (0.38-0.65) | <0.0001 |
| 0-5 years | 124 (35 vs. 89) | 0.39 (0.27-0.58) | <0.0001 |
| 5+ years | 117 (46 vs. 71) | 0.63 (0.43-0.91) | 0.015 |
| **Invasive ER-positive** | 151 (48 vs. 103) | 0.46 (0.33-0.65) | <0.0001 |
| 0-5 years | 72 (20 vs. 52) | 0.38 (0.23-0.64) | <0.0001 |
| 5+ years | 79 (28 vs. 51) | 0.53 (0.34-0.84) | 0.007 |
| **All DCIS** | 42 (13 vs. 29) | 0.44 (0.23-0.85) | 0.015 |
| 0-5 years | 22 (5 vs. 17) | 0.29 (0.11-0.80) | 0.011 |
| 5+ years | 20 (8 vs. 12) | 0.65 (0.26-1.59) | 0.34 |

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