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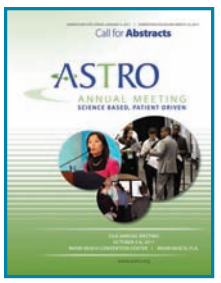

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AACR Meeting Highlights Progress against Breast Cancer in Very High-Risk Women

BY PEGGY EASTMAN

WASHINGTON, DC — Breast cancers in very high-risk women, especially the 10% to 15% who are triple negative — i.e., negative for estrogen, progesterone, and HER2 — continue to present major challenges for oncologists. Presentations here at the fourth AACR Science of Cancer Health Disparities conference suggest ways to detect and treat breast cancer in these patients in order to optimize their prognosis.

Early breast cancer diagnosis in high-risk uninsured or underinsured women — who are disproportionately younger, African American, and more likely to have triple-negative breast cancer (TNBC) — is improved by magnetic resonance imaging (MRI) screening specifically targeted to this high-risk group, according to a study from Duke University Medical Center.

The study, conducted between 2004 and 2011, compared rates of breast cancer mammography screening in 299 underserved women who had a general risk for breast cancer with the rates for 299 high-risk, underserved women who received combined mammogram and MRI screening.

The average age of women undergoing mammography was 50; the average age of those undergoing MRI was 47. In the general-risk mammography group, 40% of women were African American, 25% were white, 25% were Hispanic, and 1% "other," while in the MRI group the rates were 33%, 62%, 3% Hispanic, and 2% other.

Mammography screening detected one breast cancer, while MRI screening detected nine. The cost per diagnosis was $37,375.00 for MRI, vs $21,561.22 for mammography. The number of benign breast biopsies/total biopsies was seven out

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VICTORIA L. SEEWALDT, MD, found that although the Warburg effect is generally thought to be a late event in breast cancer, in high-risk African American women the effect occurs during cancer initiation.

of eight (88%) for mammography screening, vs 31 out of 40 (78%) for MRI.

Compliance with follow-up studies was higher for MRI than for mammography screening: 90% vs 75%, and was aided by breast patient navigators recruited at health and screening fairs in North Carolina.

Lead author Anne C. Ford, MD, Assistant Professor of Obstetrics and Gynecology at Duke University Medical Center, said targeted breast MRI screening is cost-effective in this high-risk group because it detects more breast cancers than mammography screening.

JUDY E. GARBER, MD, MPH, said that women with triple-negative breast cancer are candidates for neoadjuvant chemotherapy, but that they have a poor prognosis if the drugs don't produce a pathological response.

"If you truly target high-risk women with MRIs, you can find the cancers, and you can find them early," she said.

In this study, a grant helped to lower the cost of breast MRI screening, and Dr. Ford said she hopes the high cost of breast MRI screening will come down with more frequent use.

One of her coauthors on the study, Victoria L. Seewaldt, MD, Professor of Medicine and co-leader of the Breast and Ovarian Cancer Program at Duke, pointed out that only 14% of African American women with TNBC will be alive at one year, and thus early detection is greatly needed.

Warburg Effect Found in Precancerous Cells

The study she reported at the meeting

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assessed whether activation of biologic pathways that predict aggressive TNBCs are also activated in atypia in high-risk African American women. The researchers used spectroscopy to track glucose metabolism in live mammary epithelial cells from high-risk women. A "glucose addiction" was found in precancerous mammary epithelial cells in African American women, an important finding given that aggressive cancers consume glucose avidly and produce lactic acid, she explained.

"If you truly target high-risk women with MRIs, you can find the cancers, and you can find them early," said ANNE C. FORD, MD, who added that she hopes the high cost of breast MRI screening will come down with more frequent use."

This shift toward lactate production, even in the presence of adequate oxygen, is known as the Warburg effect–"a very ancient observation," said Dr. Seewaldt. "This is something that is a hallmark of aggressive cancers; it is something that we can target. We were very excited to find it in precancerous cells."

The Duke team concluded that although the Warburg effect is generally thought to be a late event in breast cancer, in high-risk African American women the effect occurs during cancer initiation. Asked by *OT* about the clinical significance of these findings in precancerous cells, Dr. Seewaldt said that since the study defined the ability to identify abnormal glucose and activated signaling

networks, she hopes the study results ultimately will lead to advances in early detection and prevention in women at an elevated risk for breast cancer.

Determine Subtype

At diagnosis, it is very important to determine the subtype of breast cancer in a high-risk woman, especially whether she has TNBC, several speakers at the AACR meeting emphasized, noting, though that TNBC has a range of histology—"We're talking here about the basal-like subtype," said AACR President Judy E. Garber, MD, MPH, Director of the Center for Cancer Genetics and Prevention at Dana-Farber Cancer Institute and Professor of Medicine at Harvard Medical School.

LISA A. NEWMAN, MD, MPH, noted that women in Ghana tend to develop breast cancer at a younger age, and that they have a very high incidence of triple-negative breast cancer.

If women with TNBC are not cured, "they recur quickly," with metastases tending to go to the liver and brain. "Their biology is really quite different," Dr. Garber noted of women with TNBC. These women are candidates for neoadjuvant chemotherapy, she said, but they have a poor prognosis if the drugs don't produce a pathological response.

Dr. Garber said that platinum chemotherapy is a treatment option for TNBC and HER2+ breast cancer, and can be used as an early agent in metastatic TNBC, especially if there is central nervous system involvement.

Platinum agents can be used for

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TNBC in combination with an investigational PARP inhibitor in a clinical trial. (PARP inhibitors target poly (ADP-ribose) polymerase, a key enzyme in cell proliferation and DNA repair.)

Dr. Garber cited several promising PARP inhibitors, including olaparib and iniparib. High-risk women whose breast cancer is caused by BRCA1 or BRCA2 mutations appear to be especially responsive to PARP inhibitors, she said.

There are now 129 trials focusing on TNBC listed in the federal government's clinicaltrials.gov database, she noted, some of which are investigating neoadjuvant therapy. These include: carboplatin and eribulin mesylate; sunitinib and carboplatin/paclitaxel; and carboplatin/paclitaxel and the gamma secretase inhibitor RO4929097.

Dr. Garber also cited an ongoing trial of neoadjuvant cisplatin in breast cancer patients with BRCA1 mutations. She said there has been recent interest in treating TNBC patients and HER2+ patients with cisplatin.

Other Research Areas for Clinical Trials

Dr. Garber suggested the following other topics ripe for clinical trials:

- Novel TNBC prevention strategies;
- Novel early-detection strategies;
- Biopsying metastatic lesions to understand chemotherapy resistance or to help choose a targeted therapy;
- Studying circulating tumor cells;
- Investigating how to minimize treatment toxicities;
- Studying how best to treat TNBC metastases to the brain.

Heritable Marker?

As of now, in addition to surgery, "we have to rely on general chemotherapy for TNBC," said Lisa A. Newman, MD, MPH, Director of the Breast Care Center and Professor of Surgery in the Division of Surgical Oncology at the University of Michigan Comprehensive Cancer Center in Ann Arbor.

She warned that recommendations to defer mammography screening until age 50 could have dire consequences for black women, who are more likely to develop high-risk breast cancer at a younger age even when data are adjusted for socioeconomic variables.

"Is African ancestry associated with a heritable marker for high-risk breast cancer subtypes?" asked Dr. Newman, who is participating in a University of

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Lazanda Fentanyl Nasal Spray for Breakthrough Pain Now Available

Lazanda (fentanyl) nasal spray is now available by prescription in US pharmacies. The drug, which received FDA approval at the end of June, is indicated for the management of in cancer patients age 18 and older who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

"Even though the incidence of breakthrough pain is high in cancer patients, it is often not correctly identified or reported," Nash Gabrail, MD, MRCP, a clinical investigator for the drug at the Gabrail Cancer Center in Ohio, said in a news release from the manufacturer, Archimedes Pharma.

"If reported, the pain is typically managed by either increasing the dose of background opioids or giving an additional dose of a short-acting oral opioid – neither of which is optimal therapy. Lazanda, with its rapid and controlled availability, can provide pain relief with an onset of action and duration of effect that addresses the time course of a typical breakthrough pain episode."

Lazanda uses the company's patented "PecSys" drug-delivery system, which allows the active ingredient to be rapidly absorbed across the nasal membrane and directly into the blood stream. The drug is marketed as PecFent (fentanyl pectin nasal spray) in Europe, where it is available in six countries.

Fentanyl is a Schedule II controlled substance. Lazanda will be available through a Risk Evaluation and Mitigation Strategy (REMS) program, which is intended to minimize the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors. Under the Lazanda REMS program, pharmacies, distributors, and health care professionals who prescribe to outpatients are required to enroll in the program to dispense, distribute, and prescribe Lazanda.

The efficacy of the drug for the management of breakthrough pain in adult cancer patients was established in a double-blind, placebo-controlled clinical study in patients receiving opioid therapy for background pain, in which Lazanda showed a statistically significant improvement compared with placebo on the primary endpoint, the sum of the pain intensity difference at 30 minutes (SPID30).

More than 500 patients were evaluated in the clinical trial program, which included three Phase III trials. The most common adverse events associated with Lazanda, consistent with opioid treatment treatment, were vomiting, nausea, fever, and constipation.

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Michigan scientific collaboration with Ghana. She noted that women in Ghana tend to develop breast cancer at a younger age, and they have a very high incidence of triple-negative breast cancer.

In Ghana, reproductive history (such as multiple births) does not seem to correlate with TNBC, Dr. Newman said, adding, "We really don't know a lot about what drives these triple-negative tumors."

An earlier study published in *Cancer Epidemiology, Biomarkers & Prevention,* found that two or more full-term births put African American women at higher risk of hormone receptor-negative breast cancer. However, the increased risk occurred only in women who did not breast-feed. Data came from the Black Women's Health Study, which has followed 59,000 African American women since 1995.