Fallopian Tube Removal May Reduce Ovarian Cancer Risk

Alternative approach to prophylactic surgery for women with BRCA mutations averts early menopause

By Jill Delsigne-Russell

A new understanding of the origins of ovarian cancer is driving efforts to determine whether the removal of the fallopian tubes alone can enable women who have BRCA1 or BRCA2 mutations to reduce their cancer risk while avoiding early menopause and maintaining their quality of life.

“We’ve come to understand that many genetic ovarian cancers appear to start in the fallopian tubes. So removing these tubes may greatly reduce risk,” said Denise Nebgen, M.D., Ph.D., an associate professor in the Department of Gynecologic Oncology and Reproductive Medicine at The University of Texas MD Anderson Cancer Center.

Removing only the fallopian tubes and leaving the ovaries to be removed at a later date may avoid the side effects stemming from early menopause in women who have BRCA1/2 mutations and desire prophylactic surgery to reduce their risk of ovarian cancer, a recent clinical trial by physicians at The University of Texas MD Anderson Cancer Center has demonstrated.

Imperfect risk management options

More than 60% of ovarian cancers are not diagnosed until the disease has metastasized, and the 5-year overall survival rate of patients with metastatic ovarian cancer is less than 50%. Although women in the general population have only a 1.4% risk of ovarian cancer, BRCA1 and BRCA2 mutations increase the risk to 46% and 27%, respectively.
Strategies to mitigate the risk of ovarian cancer for women with BRCA1/2 mutations include regular screening, oral contraceptives, and bilateral salpingo-oophorectomy. Unfortunately, none of these strategies is ideal.

Oral contraceptives decrease the risk of ovarian cancer in women with BRCA1/2 mutations by only $50\%$. And the screening methods for ovarian cancer—transvaginal ultrasonography and the CA-125 (carbohydrate antigen 125) blood test—lack the sensitivity and specificity to reliably detect early-stage disease. For this reason, screening guidelines vary for women with increased risk of the disease.

Bilateral salpingo-oophorectomy between the ages of 40 and 45 years in women with BRCA1/2 mutations reduces the risk of ovarian cancer by $80\%–90\%$ and may reduce the risk of breast cancer by $50\%$. However, removing the ovaries causes premature menopause, which can increase the risk of cardiovascular disease, osteoporosis, and symptoms that can reduce quality of life (including hot flashes and sexual and cognitive dysfunction). Moreover, hormone replacement therapy to ameliorate these symptoms is controversial in this group of patients because such therapy may increase the risk of breast cancer.

**Alternative approach**

The understanding of the origins of ovarian cancer has changed substantially in the past 5 years. Previously, ovarian cancer was thought to originate exclusively in the ovarian surface epithelium, but recent research indicates that many ovarian cancers originate in the fallopian tubes. The origin of ovarian cancer in the fallopian tubes is further supported by the fact that bilateral tubal ligation, a procedure often used for permanent birth control, reduces ovarian cancer risk by $50\%$. In addition, researchers have identified serous tubal intraepithelial carcinomas and occult invasive serous carcinomas of the fallopian tubes, but no ovarian lesions, in women with BRCA1/2 mutations who undergo prophylactic salpingo-oophorectomies.

The refined understanding of the origins of ovarian cancer has led to the emergence of bilateral salpingectomy, or removal of just the fallopian tubes, as an alternative to salpingo-oophorectomy for women 30–40 years old who have BRCA1/2 mutations. Salpingectomy enables women to reduce their risk of ovarian cancer while retaining their ovaries for several years. Sparing the ovaries helps patients maintain their quality of life and avoid the health risks posed by premature menopause. “We do not know, however, to what extent the risk of ovarian cancer is reduced by salpingectomy,” Dr. Nebgen said.

The disadvantage of salpingectomy is that patients later must undergo a second surgery—an oophorectomy—to further reduce their risk of ovarian and breast cancers. In accordance with national guidelines, the oophorectomy is performed at ages 40 and 45 years, respectively, for women with BRCA1 and BRCA2 mutations.

“I tell women that salpingectomy is an interim measure we can take,” Dr. Nebgen said. “Eventually these women will also want their ovaries removed to decrease not only ovarian cancer risk but also breast cancer risk. But having the tubes out early, and then the ovaries out later, can be a stop-gap that reduces risk in this window without initiating menopause.”

Beginning in 2014, Dr. Nebgen was the principal investigator for the first clinical trial (No. 2013-0340) in the United States to offer salpingectomy to women with BRCA1/2 mutations to see if this group would be interested in the option. Forty-four patients participated in the trial. The participants were allowed to choose their interventions: 20 patients chose salpingectomy, 12 chose screening at 6-month intervals, and 12 chose salpingo-oophorectomy. The trial closed in 2016, but it will take many years to determine the long-term effects of salpingectomy and whether the patients who chose this option will follow up and have their ovaries removed at a later time. So far, one patient has.

After the success of the first study, Karen Lu, M.D., a professor in and chair of the Department of Gynecologic Oncology and Reproductive Medicine, designed a phase II trial, the Women Choosing Surgical Prevention (WISP) trial (No. 2015-0814). “Dr. Nebgen’s proof-of-concept study confirmed that women are interested in salpingectomy to reduce cancer risk and stave off menopause,” Dr. Lu said. “Now we’re ready to build on that initial research with larger studies that give us data on salpingectomy’s safety and effectiveness.”

The WISP trial opened in May 2016 at six United States sites and will enroll 270 women who have mutations in BRCA1, BRCA2, or other genes linked to increased ovarian cancer risk. So far, 13 patients have enrolled. These patients will choose between salpingo-
oophorectomy and salpingectomy followed by delayed oophorectomy.

The primary objective of the WISP trial is to compare sexual function and quality of life between the two treatment groups. Other objectives include comparing the incidence of ovarian cancer in the two groups and determining whether patients who undergo salpingectomy later undergo oophorectomy. Dr. Nebgen is confident that the study will show that salpingectomy, like tubal ligation, reduces ovarian cancer risk by at least 50%.

**Recommendations for patients at risk**

Dr. Nebgen urges women who have a family history of breast or ovarian cancer at a young age in first- or second-degree relatives (i.e., sisters, mothers, aunts, or grandmothers) to participate in genetic counseling and screening. Women who have confirmed BRCA1/2 mutations or Lynch syndrome are advised to consider undergoing recommended cancer screening at a clinic with experience in screening high-risk patients and to consider surgical prophylaxis.

“We women and their doctors should be aware that there are several preventive methods for ovarian cancer, but the timing of these procedures is crucial,” Dr. Nebgen said. “Sometimes risk-reducing salpingo-oophorectomy can be performed too soon, leading to other health problems. Salpingectomy allows women to reduce their risk while postponing menopause.” She added that patients who choose to undergo salpingectomy should be encouraged to follow up with cancer screening and eventual ovary removal.

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**FOR MORE INFORMATION**

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To learn more about the WISP trial, visit www.clinicaltrials.org.

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**Highlights from the 2016 San Antonio Breast Cancer Symposium**

**MD Anderson researchers present findings regarding diagnosis, staging, treatment**

**By Christina Bennett**

Researchers, clinicians, and other professionals from around the world convened in San Antonio, Texas, in December to present and discuss the latest breast cancer research. Among the findings presented were those from several studies conducted at The University of Texas MD Anderson Cancer Center involving the aggressive HER2-positive, inflammatory, and triple-negative subtypes. A few of these studies are highlighted below.

**Lapatinib may be effective for trastuzumab-resistant HER2-positive metastatic breast cancer**

Lapatinib has a clinically relevant benefit for patients with HER2-positive metastatic breast cancer previously treated with pertuzumab and ado-trastuzumab emtansine (T-DM1), according to findings from a retrospective study (Abstract P4-21-20). The study compared responses to lapatinib, which is approved in combination with capecitabine for trastuzumab-resistant HER2-positive metastatic breast cancer, in patients previously treated with pertuzumab and T-DM1 and patients who had received other trastuzumab-based regimens.

Looking at medical records in an MD Anderson database, researchers identified patients who had trastuzumab-resistant HER2-positive metastatic breast cancer and were treated with lapatinib. The target cohort included 29 patients who received lapatinib after pertuzumab and T-DM1, and the comparison cohort included 445 patients who received lapatinib after trastuzumab-based regimens that did not include pertuzumab and T-DM1.

In the target cohort, 58% of patients had a clinical benefit—defined as a complete response, partial response, or stable disease for at least 6 months—compared with 78% in the comparison cohort. The median overall survival was 23.9 months for patients in the target cohort and 25.8 months for those in the comparison cohort. The median time to progression was 4.9 months for the target cohort and 5.7 months in the comparison cohort. In both cohorts, patients with de novo disease had longer overall survival and time to progression than did those with recurrent disease.

“We found that over half the patients who were previously treated with per-

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“**We believe surgery may be redundant for many patients—at least among patients with these two subtypes of breast cancer.**”

– Dr. Henry Kuerer

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tuzumab and T-DM1 received a clinical benefit from lapatinib for more than 6 months and had no significant increase in toxicity,” said Luis Báez-Vallecillo, M.D., a fellow in the Division of Cancer Medicine and the report’s lead author. “Thus, there is a partial lack of cross-resistance among these HER2-targeted therapies.”

The differences in the clinical benefit rate, overall survival, and time to progression between cohorts could be attributed to the fact that patients in the target cohort had received more previous therapies than those in the comparison cohort. About 25% of patients in the target cohort had received three or more lines of therapy compared with only 10% in the comparison cohort.

The researchers plan to validate their findings in a larger cohort in a collaborative retrospective study at MD Anderson and four other institutions.

Dr. Báez-Vallecillo said, “Our data suggest that lapatinib can be used after trastuzumab, pertuzumab, and T-DM1 because patients showed a clinical benefit, and some may have a very long time to progression despite prior exposure to HER2-targeted therapies.”

Researchers propose new breast cancer staging system

A new breast cancer staging system that would incorporate clinical and biological factors is being recommended on the basis of recent findings (Abstract P6-09-35). The current American Joint Committee on Cancer staging system focuses on tumor size and disease spread and does not include other clinical and biological factors that affect the prognosis of breast cancer patients.

“Staging has historically been based on describing the anatomical extent of disease,” said Rashmi Murthy, M.D., an assistant professor in the Department of Breast Medical Oncology and lead researcher of the study. “However, in this era of personalized medicine, other factors should be incorporated into the staging system.”

Using an MD Anderson database, the researchers identified 21,691 patients with newly diagnosed stage I–III invasive breast cancer who received surgery as an initial treatment from 1997 to 2014. To determine factors associated with breast cancer–specific survival, the researchers retrospectively analyzed patients’ age at diagnosis; tumor pathological stage, grade, estrogen receptor status, progesterone receptor status, and HER2 status; adjuvant treatment history; and outcomes.

On multivariable Cox regression analysis, age, tumor grade, hormone receptor status, and HER2 status were associated with breast cancer–specific survival. On the basis of these findings, the researchers proposed that the current staging system be modified to include clinical and biological factors. Dr. Murthy said that such a system could provide more accurate prognostic information and reflect current standards of care.

Dr. Murthy and her colleagues plan to confirm their findings by analyzing patient data from a larger national database as well as an external validation set. “Hopefully, these analyses will add to the literature to help support including these other variables in the breast cancer staging system,” Dr. Murthy said.

Image-guided biopsy may predict which breast cancer patients do not need surgery

Image-guided biopsy can accurately identify which patients do not need surgery after neoadjuvant therapy, according to a recent clinical trial (Abstract P5-16-30). Currently, nearly 60% of patients who have early-stage triple-negative or HER2-positive breast cancer and receive neoadjuvant therapy experience a pathological complete response, a measure used to predict prognosis; but this response cannot be detected by imaging alone.

“The problem is that imaging can’t tell us with any accuracy that there’s no residual disease,” said Henry Kuerer, M.D., Ph.D., a professor in the Department of Breast Surgical Oncology and the study’s lead researcher. Thus, patients typically undergo surgery to remove the tumor even though surgery may not be necessary. Image-guided biopsy can accurately detect disease at diagnosis, but whether this technique could also detect disease after neoadjuvant therapy has not been studied until now.

To determine the predictive value of image-guided biopsy, Dr. Kuerer and his colleagues conducted an MD Anderson—only trial that enrolled 34 patients who had early-stage triple-negative or HER2-positive breast cancer—two subtypes for which neoadjuvant therapy is commonly used. The patients received standard neoadjuvant therapy is commonly used.

“Tucatinib is a specific HER2 inhibitor with much less toxicity than that reported for other drugs in its class.”

– Dr. Stacy Moulder
systemic therapy and underwent ultrasound- and/or mammography-guided vacuum-assisted core biopsy (VACB) and image-guided fine-needle aspiration (FNA) biopsy before surgery. For each individual biopsy technique and the two techniques combined, the researchers measured the accuracy, false-negative rate, and predictive value for determining whether residual disease was present after neoadjuvant systemic therapy.

VACB and FNA together had 100% accuracy, sensitivity, and specificity; a 0% false-negative rate; and 100% negative and positive predictive values for determining whether residual disease was present. These results suggest that image-guided biopsy can accurately identify which patients do not have residual disease and therefore do not need surgery.

“We believe surgery may be redundant for many patients—at least among patients with these two subtypes of breast cancer,” Dr. Kuerer said. However, he cautioned, “This is not at all standard practice. It is just the beginning of these studies.”

Dr. Kuerer recently opened a phase II trial (No. 2016-0046) to determine the safety of forgoing surgery for patients with stage I or II HER2-positive or triple-negative breast cancer who experience a complete pathological response to neoadjuvant therapy.

**Biomarker assay may detect breast cancer, distinguish inflammatory breast cancer**

Using a protein biomarker assay to analyze plasma samples, researchers distinguished between patients with breast cancer and healthy participants and between patients with inflammatory breast cancer (IBC) and those with non-IBC disease (Abstract P1-02-07). The main objective of the study was to develop a noninvasive clinical tool to identify cancer.

For IBC, several large-scale, multi-institutional studies have been conducted for gene expression profiling but not protein expression. “Studies have shown that gene expression does not translate into anything meaningful because the ultimate product of the functional unit is a protein,” said Gitanjali Jayachandran, Ph.D., a senior research scientist in the laboratory of James Reuben, Ph.D., a professor in the Department of Hematopathology. “So we need to pay attention to the protein.”

Previous multi-protein biomarker panels lacked the necessary specificity, sensitivity, scalability, and dynamic range to distinguish cancer. But recently, Olink Proteomics developed a proximity extension assay with several biomarker panels that measure 92 proteins simultaneously. This technology overcomes the inherent shortcomings of traditional protein quantification methods and requires only 1 μL of a biological sample.

The researchers obtained plasma samples from 25 patients with IBC, non-IBC, metastatic breast cancer, and non-metastatic breast cancer and samples from seven healthy participants. The samples were then analyzed using the 92-protein biomarker assay.

The analysis revealed several plasma protein signatures that could distinguish between all the sample types. Dr. Jayachandran, the study’s lead researcher, said, “At this point, we don’t know enough to say if this panel can be used as a diagnostic tool, but we are hopeful.”

**Tucatinib plus capecitabine and trastuzumab shows efficacy against HER2-positive disease**

The HER2 inhibitor tucatinib, in combination with capecitabine and trastuzumab, has a clinical benefit in patients with HER2-positive metastatic breast cancer, according to the preliminary results of an ongoing clinical trial (Abstract P4-21-01).

The multicenter phase IB dose-escalation trial enrolled patients with HER2-positive metastatic disease who had previously been treated with one or more lines of trastuzumab, a taxane, and T-DM1. The patients received tucatinib (also called ONT-380) as monotherapy, with trastuzumab, with capecitabine, or with capecitabine and trastuzumab. Updated preliminary results for the tucatinib, capecitabine, and trastuzumab combination were presented at the symposium by Dr. Murthy, a co–principal investigator on the trial.

Patients treated with tucatinib, capecitabine, and trastuzumab had a median progression-free survival of 7.8 months, a clinical benefit rate of 74%, an overall response rate of 61%, and a median response duration of 10 months. Most toxic effects were grade 1 effects; grade 3 effects included palmar-plantar erythrodysesthesia, diarrhea, fatigue, and reversible increases in liver enzyme levels.

Stacy Moulder, M.D., an associate professor in the Department of Breast Medical Oncology and a co–principal investigator on the trial, said the preliminary results are encouraging, especially the toxicity profile. “Although
In women with newly diagnosed breast cancer, locoregional restaging with mammography and ultrasonography of the whole breast and regional nodes led to incremental cancer detection (i.e., discovery of additional lesions in the breasts) and improved the accuracy of clinical staging, according to a retrospective study conducted at The University of Texas MD Anderson Cancer Center. The value of repeating breast imaging studies in women who are referred to tertiary care centers for breast cancer treatment previously had not been validated.

A group led by Rosalind Candelaria, M.D., Monica Huang, M.D., and Beatriz Adrada, M.D., of the Section of Breast Imaging in the Department of Diagnostic Radiology reviewed the records of 1,000 women referred to MD Anderson’s breast imaging center in 2010. Four hundred one women with primary breast cancer were included in the final analysis. At the breast imaging center, all 401 women underwent bilateral full-field digital mammography followed by ultrasonography of the entire affected breast and regional lymph nodes. The restaging at MD Anderson changed the known extent of the disease in 68 of the 401 women, which represented an incremental cancer detection rate of 15.5% (62 women) in the ipsilateral breast and 3.9% (six women) in the contralateral breast. Furthermore, locoregional restaging at MD Anderson resulted in a higher disease stage in 100 (25%) of the 401 women, including a higher N stage in 94 (23%) and a higher T stage in 86 (21%).

The changes in known disease extent also led to changes in surgical management. Fifty women in whom restaging revealed extensive multifocal or multicentric disease underwent mastectomy rather than breast-conserving surgery. Radiation strategies and consideration for neoadjuvant chemotherapy were also affected by restaging.

“Our findings confirmed that in women with newly diagnosed breast cancer, locoregional restaging with mammography and ultrasonography led to incremental cancer detection, reduced underestimation of disease, and influenced treatment strategies,” said Dr. Candelaria, the lead author of the study’s report, which was published in Academic Radiology.
Stem Cell Transplant Terms

Helpful definitions for patients and families

Stem cell transplants are used to treat cancers such as leukemia, lymphoma, and myeloma, which affect the bone marrow where blood cells are made. Stem cell transplants are also used to treat certain immune system diseases and other conditions. If you or a loved one will have a stem cell transplant, here are some helpful terms to know.

**Types of stem cell transplants**

- **Allogeneic transplants** use stem cells from a donor whose tissue closely matches the patient's tissue. This type of transplant helps the patient form a new immune system.

- **Autologous transplants** use stem cells that come from a patient's own blood or bone marrow. The stem cells are collected before the patient begins treatment such as chemotherapy or radiation therapy that can destroy stem cells. The decision whether to use an allogeneic or autologous transplant is based on many factors, including the type of cancer and the patient's health.

- **Bone marrow transplant** is an outdated term for stem cell transplant. In the past, stem cells were primarily collected from the bone marrow, but now they are usually collected from the blood.

**Parts of the body**

- The **bone marrow** is a sponge-like tissue found in the center of some bones. Red blood cells, white blood cells, and platelets are made in the bone marrow.

- **Human leukocyte antigens (HLAs)** are proteins found on the surface of most cells. The immune system uses HLAs to tell which cells are the body's own normal cells and which are abnormal (such as cancer cells) or come from outside the body (such as donor stem cells). Doctors use HLA tests to find a stem cell donor with HLAs that closely match the patient's.

- The **immune system** helps the body to fight infection and includes organs, tissues, cells, and substances made by the body. For example, the tonsils, bone marrow, lymph nodes, and white blood cells are all part of the immune system.

  - **Platelets** are found in the blood. They help blood to clot.
  - **Red blood cells** carry oxygen to every part of the body.
  - **Stem cells** are cells from which other types of cells form. For example, **hematopoietic stem cells** are formed in the bone marrow and later develop into blood cells.

  - **Umbilical cord blood** from newborns can be used in allogeneic stem cell transplants for patients who do not have a related or matched unrelated donor (see below). This blood is taken from the cord and placenta after a baby is born. MD Anderson has a cord blood bank that accepts donations of umbilical cord blood (see box).

  - **White blood cells** help the body to fight infection. Neutrophils and lymphocytes—such as T cells, B cells, and natural killer cells—are among the types of white blood cells.

**Types of donors**

- A **first-degree relative** is a person's parent, child, brother, or sister. First-degree relatives are usually the best people to donate stem cells to a patient who is having an allogeneic transplant.

- A **matched unrelated donor** is not in a patient's family but has HLAs similar to the patient's.

**Transplant-related treatments and conditions**

- **Conditioning regimens** are courses of chemotherapy and/or radiation therapy often given before a stem cell transplant. These treatments kill cancer cells in the body and destroy existing bone marrow to make room for new marrow created by the new stem cells. In allogeneic transplants, these regimens may include immunosuppressive drugs (see next column).

- **Graft-versus-host disease (GVHD)** happens when stem cells from a donor harm the normal tissue of a patient who has received an allogeneic stem cell transplant. Doctors are careful to choose stem cell donors who have tissue similar to the tissue of the patient receiving a stem cell transplant so that GVHD will be less likely.

- **Immunosuppressive drugs** suppress the body's immune system. They may be given before or after an allogeneic transplant to prevent GVHD or after GVHD occurs.

  - **Myelosuppression**, which results from conditioning regimens, is a decrease in bone marrow activity that causes low levels of red blood cells, white blood cells, and platelets. Severe myelosuppression is called **myeloablation**.

Be sure to ask your medical team to explain any terms they use that aren’t familiar to you. Your team will be happy to help.

– L. Russell

FOR MORE INFORMATION

- Ask your physician
- Call askMDAnderson at 877-632-6789
- Visit www.mdanderson.org

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Algorithms for Managing Treatment-Related Conditions

Cancer treatments expose patients to numerous side effects, which vary in severity, duration, and predictability. To help health care professionals minimize these effects, The University of Texas MD Anderson Cancer Center offers clinical management algorithms that describe current best practices for the diagnosis and treatment of specific conditions that arise during the course of cancer treatment.

Topics covered in the clinical management algorithms include:

- Acute intracranial hemorrhage
- Acute ischemic stroke
- Anemia
- Atrial fibrillation
- Cancer pain
- Chimeric antigen receptor cell therapy–related toxicity
- Contrast media reactions
- Distress screening and psychosocial management
- Early intervention for suspected sepsis
- Fertility options
- Heparin-induced thrombocytopenia
- Hepatitis B and C
- Hyperglycemic emergencies
- Hypersensitivity/allergic reactions
- Hypoglycemia
- Malignant hyperthermia
- Nausea and vomiting
- Neutropenic fever
- Pleural effusion
- Pneumonia
- Post–cardiac arrest targeted temperature management
- Postoperative pain
- Spinal cord compression
- Suicide risk assessment
- Surgical antibiotic prophylaxis
- Thyroid nodule evaluation
- Tumor lysis
- Vascular access devices—selection and management
- Venous thromboembolism

The clinical management algorithms, developed by MD Anderson clinicians and researchers, are not a replacement for physicians’ clinical judgment but are intended to help physicians make evidence-based recommendations to their patients. The algorithms are available at http://bit.ly/2f8WS55.

“Useful Resources” introduces tools for community physicians and other medical professionals available free of charge on MD Anderson’s Web site.