Medical Xpress

# Genetic differences may influence joint pain among women taking lifesaving breast cancer drugs

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Aromatase inhibitor-associated arthralgia (AIAA) is a major side effect in breast cancer survivors, producing joint pain so severe that as many as ten percent of women discontinue their therapy prematurely while undergoing treatment with these lifesaving drugs. New research presented by investigators from the University of Pennsylvania's Abramson Cancer Center at the 2010 meeting of the American Society of Clinical Oncology reveals a possible genetic basis for why these side effects occur and shows promise for treating these symptoms without interfering with the drugs' efficacy. Additional research will also be presented shedding light on the physical and psychological factors that influence women's decisions to stop taking the drugs.

Jun Mao, MD, MSCE, an assistant professor of Family Medicine and Community Health who heads the Abramson Cancer Center's integrative oncology program, led a team that studied individual genetic variations that could potentially influence both the onset and the severity of AIAA. ("Genetic variation in CYP19A1 and Interleukin-6 and aromatase inhibitor-associated arthralgia in breast cancer survivors," Abstract #526) His team studied 390 postmenopausal women with stage 0 to III breast cancer receiving adjuvant therapy with aromatase inhibitors who reported joint pain related to their drug therapy. They found that among this group, women carrying at least one copy of a "7-repeat" genetic variant in the aromatase enzyme (CYP19A1, the target of aromatase inhibitors) had a lower chance of developing AAIA than those with at

least one "8-repeat " allele of the same gene. Having at least one copy of a specific IL-6 haplotype was also correlated with increased pain severity, while the presence of a different variant of that gene was associated with decreased pain. Both these findings support previous research that indicates an important role for host estrogen metabolism and inflammation in causing AIAA.

"Due to genetic differences, women respond differently to aromatase inhibitors with regard to estrogen levels and inflammatory processes, and as a result, some women are more likely to have this pain or have more severe pain," says Angela DeMichele, MD, MSCE, an associate professor of Hematology/Oncology and Epidemiology and Biostatistics, and a co-author on all three of the studies. "There are millions of women receiving AIs, as many as 50 percent of them experience some level of arthralgia, and up to 10 percent discontinue their treatment prematurely, so this is a significant issue."

The investigators say that as more breast cancer patients become breast cancer survivors, clinicians must become more knowledgeable about the quality of life issues impacting women after they end active treatment for their cancers. The new findings are key to identifying which women may be at risk of problems like arthralgia - and then, Mao says, to developing more targeted interventions at both the physical and psychological levels.

The multidisciplinary team is also looking at issues related to clinician-patient communication, exercise, and co-factors such as arthritis or fibromyalgia that can increase pain and disability in order to keep more women on their treatment regimen. Mao, who is also a licensed physician acupuncturist, has begun a clinical trial examining the effectiveness of acupuncture for aromatase inhibitor associated arthralgia as part of conventional breast cancer survivorship care. These efforts are part of the Abramson Cancer Center's comprehensive

Wellness After Breast Cancer program.

"We believe that proactively informing women about the possibility that their breast cancer treatment may cause arthralgia and then intervening early is probably important to keeping them on these potentially life-saving cancer treatments," Mao says. "When they are not prepared, or become frustrated because they didn't know this could happen to them, they are far more likely to make the decision to stop treatment. Some studies have suggested that women with the most severe symptoms are those with the most complete blockage of aromatase. We want to do everything we can to assure that the women most likely to benefit from therapy don't end it too soon because they are experiencing pain related to their treatment."

In a related study, University of Pennsylvania researchers surveyed 300 breast cancer survivors to assess the impact of AIAA on upper and lower extremity functioning. (Functional disability and aromatase inhibitor-associated arthralgia in breast cancer survivors," Abstract #6073) They found that women with AIAA had greater impairment of both upper and lower extremities than those who did not experience these symptoms. As many as 29 percent of participants reported that the pain limited their ability to perform their normal activities.

In a third study, Carrie Stricker, PhD, RN, clinical assistant professor of Nursing and an oncology nurse practitioner, led the team of researchers in surveying 490 postmenopausal, non-metastatic breast cancer patients to assess the factors that influenced their stopping AI therapy prematurely. ("Understanding premature discontinuation of aromatase inhibitors (AI) therapy in postmenopausal breast cancer survivors," Abstract #9156) This is one of only a few studies to analyze the rates at which women discontinue AI therapy and the variables that predict their decision to do so, and the only designed to evaluate patient-reported reasons for ending AI treatment. The study found that 7 percent of the

patients studied had discontinued their AI treatment early, at a mean of 15.7 months from the beginning of treatment. The most significant predictors for stopping therapy were a previous history of taking tamoxifen, which can also cause arthralgia and other symptoms; having other inflammatory conditions such as arthritis; communication about difficulties with taking AIs, and being married. Patients who stopped AI treatment early cited side effects as the main reason, with arthralgia being the most common complaint. Effects on bone, hot flashes and cognitive effects were also named as reasons for cessation of therapy.

"These data suggest that we can develop a profile of the women who are most likely to make the decision to terminate their AI therapy prematurely, and if we can do that, we can design better supportive interventions for these women and incorporate them into our clinical practice," DeMichele says. "This information, derived directly from the patients themselves, reinforces our understanding that assessing and managing the side effects of cancer therapy, including joint pain, is critical to the overall success we can achieve in managing the disease itself."

Mao's study will be presented at a poster session on Breast Cancer from 2 p.m. to 6 p.m. on Monday, June 7. Stricker will present the premature discontinuation of AI findings at a poster session on Health Service Research from 1 p.m. to 5 p.m. on the 7th. Claire Friedman will present the functional disability findings at a poster session on Patient and Survivor Care from 1 p.m. to 5 p.m. on June 7.

Patients are available to discuss their experience with these treatments, upon request.

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