Antihypertensives linked with increased breast cancer risk in postmenopausal women

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Older women who take certain types of medication to combat high blood pressure may be putting themselves at greater risk for developing breast cancer, according to a new study by a team of Fred Hutchinson Cancer Research Center scientists led by Christopher Li, M.D., Ph.D. The study is the first to observe that long-term use of a class of antihypertensive drugs known as calcium-channel blockers in particular are associated with breast cancer risk. The team's findings will be published online Aug. 5 in *JAMA Internal Medicine*.

Antihypertensive drugs are the most frequently prescribed type of medications in the United States, with more than 678 million prescriptions filled in 2010, nearly 98 million of which were for calcium-channel blockers.

Despite widespread and often long-term use of these drugs, studies and evidence linking antihypertensives to breast cancer have been sparse and inconsistent.

"Because hypertension is a chronic condition, most people with high blood pressure use antihypertensive drugs chronically and will often stay on the same regimen for long periods of time," said Li, head of the Translational Research Program and member of the Public Health Sciences Division at Fred Hutch. "Characterizing their potential associations with the most common cancer in women is an important clinical and public health issue, particularly with the increasing availability of alternative options to manage hypertension."

In addition to calcium-channel blockers, other classes of antihypertensive drugs include angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-receptor blockers, beta blockers and diuretics. Combinations of such drugs are also prescribed. "Each drug has different potential benefits as well as side effects," Li said. "Choice of which regimen a patient is given depends on their tolerance of medication, other conditions, and whether their hypertension can be managed by a single drug or requires a combination of drugs."

The purpose of the Hutch study was to assess the relationship between the major classes of antihypertensive drugs and risk of the two most common histological types of breast cancers in the United States: invasive ductal carcinomas, which represent approximately 70 percent of all breast cancers; and invasive lobular carcinomas, which represent an estimated 20 percent.

The study's key finding was that women currently taking calcium-channel blockers who have used them for 10 years or longer had an approximately two and a half times higher risk of both invasive ductal and invasive lobular cancers compared to those who never used such calcium-channel blockers and compared to users of other forms of antihypertensives. In contrast, the study found that use of other classes of antihypertensive drugs, including diuretics, beta blockers and angiotensin-receptor blockers, were not associated with an increased risk of breast cancer, even when used long term.

Li's team interviewed 1,763 study participants, all between the ages of 55-74 from the Puget Sound region, including 880 with invasive ductal cancer, 1,027 with invasive lobular cancer, and 856 cancer-free controls. Participants were interviewed in person to establish detailed histories of hypertension and heart disease, as well as risk factors for cancer, including family history, obesity, smoking and alcohol use. Through a series of structured questions, researchers also gathered detailed data

regarding use of antihypertensive drugs, including beginning and end dates of use, drug names, dose, route of administration, pattern of use and indication.

While calcium-channel blockers in particular appear to have an implication for increased cancer risk in cases of long-term use, the drugs have a broad spectrum of physiological effects, and more research will be required to understand the underlying biological mechanisms potentially responsible for the added risk. Calcium-channel blockers function by regulating the influx of calcium into muscle cells, decreasing arterial resistance and heart muscle oxygen demand. Some hypothesize that these drugs may increase cancer risk because they inhibit programmed cell death, or apoptosis, but supporting evidence is lacking.

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