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Vitamin D and Flavonoids Examined for Impact on Breast and Ovarian Cancers

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Field(s) of Research: Cellular and Molecular Biology, Prevention Research, Tumor Biology

WASHINGTON, D.C. - While risk factors for breast and ovarian cancers include menopause, obesity, family history and specific genetic mutations, researchers also are looking at the role of diet in the development, as well as the treatment and prevention of these tumors. At the 97th Annual Meeting of the American Association for Cancer Research, two groups of scientists using sophisticated statistical techniques report their findings of possible preventive properties of Vitamin D against breast cancer. Two other groups of scientists present their work analyzing the possibility that natural antioxidants found in plants, substances called flavonoids, could play a powerful role in preventing both breast and ovarian cancer.

Potential Reduction in Breast Cancer Risk Associated with Vitamin D: Abstract No. 4009

Though scientists have suspected that Vitamin D helps to prevent and possibly even treat breast cancer, population-based studies on the possible link have been few and of limited scope.

Now, new studies by researchers at the Samuel Lunenfeld Research Institute at Mount Sinai Hospital in Toronto suggest the "sunshine" vitamin may play a significant role in reducing breast cancer risk. The results, based on population data, found the reduction was most apparent among subjects exposed to the highest levels of vitamin D when they were young.

By interviewing about 576 patients who had been diagnosed with breast cancer and 1,135 people who had no cancer, the scientists discovered that significant reductions in breast cancer were found in those who had either worked in an outdoor job, had taken part in outdoor activities when young, or consumed cod liver oil or milk.

Working an outdoor job between ages 10 to 19 resulted in an estimated 40 percent reduced risk of breast cancer, while frequent outdoor activities between ages 10 to 29 lowered breast cancer risk by an estimated 35 percent.

"These outdoor activities included those that didn't involve physical activity," said Julie Knight, who headed the Mount Sinai research team. "And so we believe that this is evidence of a reduction of breast cancer risk, associated with earlier exposure to the sun."

For dietary influences on cancer development, taking cod liver oil between ages 10 to 19 reduced breast cancer risk by about 25 percent, and consuming at least nine glasses of milk every week between the ages of 10 to 29 reduced the risk by 35 percent. The dietary and lifestyle reductions were significant, even when adjusted for other risk factors for breast cancer such as age, ethnicity, close relatives with breast cancer, age at menarche and age at a woman's first birth.

"What you are exposed to during breast development may be particularly important in determining future breast cancer risk," Knight said. "Current thinking is that exposures during adolescence or before a full-term pregnancy may have a greater effect, as that is when breast tissue is going through the most rapid

development."

Knight emphasizes that these findings are preliminary estimates of the risk reduction of breast cancer brought about by Vitamin D. The researchers are now looking to solidify these findings, and determine whether physical exercise while outdoors is in any way associated with breast cancer.

Evidence of Need for Increased Vitamin D Fortification of Food Based on Pooled Analysis of Studies of Serum 25-hydroxyvitamin D and Breast cancer: Abstract No. 4008

Increasing doses of dietary Vitamin D may help prevent breast cancer, with the optimal level of intake of Vitamin D more than three times the current average for Americans, according to a study conducted at the University of California, San Diego.

Previous studies have suggested a link between Vitamin D deficiency and higher incidence of breast cancer. Cedric Garland, Dr. P.H., and Edward Gorham, Ph.D., of UCSD, and their colleagues examined existing cancer studies to determine if higher Vitamin D levels in the blood could reduce the risk of cancer.

"There is a strong inverse dose-response relationship between the serum concentration of 25-hydroxyvitamin D and the risk of breast cancer," Garland said. "It's a close fit to a linear model," meaning that higher amounts of 25-hydroxyvitamin D in the serum resulted in decreased risk of breast cancer. The evidence further pointed to a level of Vitamin D measured in blood that correlated with a 50 percent reduction in the incidence of breast cancer.

Garland, Gorham and their colleagues studied a serum Vitamin D metabolite known as 25-hydroxyvitamin D and its association with breast cancer occurrence in a pooled study that included 1,760 women. The studies that provided the data for the pooled analysis were conducted by Elizabeth R. Bertone-Johnson and colleagues at Harvard, and L.C. Lowe and associates at Saint George's Hospital Medical School in London.

According to the pooled analysis, Vitamin D in blood serum equal to 52 nanograms per milliliter was associated with a 50 percent reduced risk of breast cancer. To move closer to a serum concentration of 52 nanograms/milliliter, a typical individual would have to consume no less than 1,000 International Units (IU) of Vitamin D every day, through supplements or vitamin D-fortified foods. Currently, a typical American consumes only 320 International Units of Vitamin D a day. The upper limit for vitamin D intake established by the National Academy of Sciences is 2,400 IU/day, but no toxic effects of vitamin D intake have been reported for intakes below 3,800 IU per day.

"There is no substantial downside to a serum level of 52 nanograms per milliliter of Vitamin D," said Gorham. "Such levels are common in sunny climates. There is no known adverse effect of serum levels below 160 nanograms per milliliter."

However, since many people use sunscreens and are involved in indoor occupations or shift work, dietary supplements and vitamin D fortified foods are necessary to maintain optimal levels of Vitamin D, the scientists noted.

High intakes of calcium, which could occur with intake of Vitamin D supplements containing calcium, could increase the risk of kidney stones, they warn. However, the dosage level of vitamin D associated with kidney stones in patients far exceeded 3,800 IU/day. Until more studies are completed, the scientists recommended that everyone consume at least 1,000 IU/day of vitamin D3.

Dietary Flavonoid Intake and Breast Cancer Risk among Women in the Long Island Breast Cancer Study Project: Abstract No. 4014

Flavonoids, a class of antioxidants found in plants, is associated with a reduced risk of breast cancer among post-menopausal women, according to results of the Long Island breast cancer study project. The results are one of the first epidemiologic studies to suggest that these compounds could have a chemoprotective effect among women.

Brian Fink, Susan Steck and Marilie Gammon of the University of North Carolina, Chapel Hill, and other colleagues studied data from a large study of breast cancer incidence and risk factors conducted among women living during the mid-1990s on Long Island, N.Y.

Breast cancer risk was reduced for the highest percentages of total flavonoid intake, compared to the lowest intake of the plant antioxidants. The decreased risk was about 45 percent among post-menopausal women. Risk decreases were not seen in pre-menopausal women. Specific flavonoids -- including flavones, flavan-3-ols and lignans -- were associated with reduced cancer risks ranging from 26 to 39 percent; other

flavonoids, such as flavanones, isoflavones and anthocyanidins, showed no relationship with reduced cancer risk.

"These results are consistent with other studies conducted among Mediterranean women," said Fink. "Few epidemiologic studies have examined whether there is a relationship between breast cancer and dietary flavonoids. Our study proposes that dietary flavonoids can help American post-menopausal women reduce their risk of breast cancer."

The researchers examined data from the Long Island study, which was conducted by Dr. Gammon and colleagues between August 1996 and July 1997. The team compared data from 1,434 women with breast cancer to data from 1,440 women who were not diagnosed with the disease.

Flavonols, flavones, lignans and anthocyanidins are all flavonoids, molecules that give plants protection from oxidative damage due to disease and environmental stresses. Flavonoids are classified according to chemical structure, and have been studied for their varying degrees of effectiveness against human diseases, both in treatment and prevention. They are found in green tea, red wine, soybeans, fruit and vegetables.

"There are no recommended dietary standards for ingestion of flavonoids, and we do not know exactly how these chemicals may work on a cellular level," said Fink, whose work was supported with funding from the National Institutes of Health and the Lance Armstrong Foundation. "Minute differences in chemical structure could determine how a certain natural antioxidant may work to prevent disease, including cancer. More study is needed to determine why certain flavonoids appear to be effective at reducing cancer risk, and others do not appear to have these properties."

A Prospective Analysis of Dietary Flavonoid Intake and Epithelial Ovarian Cancer Incidence: Abstract No. 4013

The incidence of ovarian cancer may be reduced with increased consumption of dietary flavonoids, plant chemicals that are found in tea, red wine, fruits and vegetables, according to researchers from Brigham and Women's Hospital and the Harvard School of Public Health.

The study, conducted by Margaret Gates, a doctoral candidate at the Harvard School of Public Health, looked at food intake surveys and ovarian cancer data from 66,384 participants in the Harvard Nurses' Health Study, which collected health data from 121,700 women over a period of 30 years. "This is the first prospective analysis of flavonoid intake and ovarian cancer incidence," Gates said.

Gates studied the association between flavonoid intake from food frequency questionnaires completed by the women in 1984, 1990, 1994 and 1998; and 344 confirmed cases of ovarian cancer diagnosed between 1984 and 2002. While there was a significant trend toward decreasing incidence of ovarian cancer with increasing total flavonoid intake, Gates warned that "because this is one of the first studies of the topic, this association needs to be evaluated in another prospective study population before conclusions can be made."

Gates also analyzed individual flavonoids to evaluate their impact on ovarian cancer incidence. The flavonoid kaempferol, which the nurses consumed primarily from caffeinated tea, broccoli and kale, was associated with decreased ovarian cancer risk. Women with the highest levels of kaempferol intake had a significant 38 percent decrease in ovarian cancer incidence, compared to women with the lowest levels of intake. Two other flavonoids, myricetin and quercetin, showed a possible inverse association with ovarian cancer risk, although the results were largely non-significant.

"The associations were stronger when exposure was defined as cumulative average flavonoid intake over a period of 14 years, which suggests that long-term intake of flavonoids may be important," Gates said.

But she cautioned that "these findings need to be confirmed by others before any public health recommendations can be made. However, if confirmed, consumption of flavonoids would provide another means for women to decrease their risk of ovarian cancer."

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The mission of the American Association for Cancer Research is to prevent and cure cancer. Founded in 1907, AACR is the world's oldest and largest professional organization dedicated to advancing cancer research. The membership includes more than 24,000 basic, translational, and clinical researchers; health care professionals; and cancer survivors and advocates in the United States and more than 60 other countries. AACR marshals the full spectrum of expertise from the cancer community to accelerate progress in the prevention, diagnosis and treatment of cancer through high-quality scientific and educational programs. It funds innovative, meritorious research grants. The AACR Annual Meeting attracts over 16,000 participants

who share the latest discoveries and developments in the field. Special Conferences throughout the year present novel data across a wide variety of topics in cancer research, treatment, and patient care. AACR publishes five major peer-reviewed journals: *Cancer Research*; *Clinical Cancer Research*; *Molecular Cancer Therapeutics*; *Molecular Cancer Research*; and *Cancer Epidemiology, Biomarkers & Prevention*. Its most recent publication, *CR*, is a magazine for cancer survivors, patient advocates, their families, physicians, and scientists. It provides a forum for sharing essential, evidence-based information and perspectives on progress in cancer research, survivorship, and advocacy.

Contact:

Warren R. Froelich
215/440-9300, Ext. 198
froelich@aacr.org
In Washington, DC (4/1-4/5)
202/249-4004
202/249-4005 fax

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