

Margaret Karagas has found intriguing connections between the use of certain painkillers and the risk of bladder cancer.



MARK WASHBURN

## Long-term NSAID use may reduce bladder cancer risk

As an epidemiologist interested in the causes and prevention of cancer, Margaret Karagas, Ph.D., was intrigued by early reports suggesting that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) might prevent the development of bladder cancer.

Bladder cancer is a very common urologic malignancy. While the prognosis is typically favorable, recurrences are common and progression in disease is possible. In northern New England, both the incidence and mortality rate of bladder cancer are higher than the national average.

Karagas wants to know why that is and to determine whether aspects of diet, lifestyle, or other environmental factors might increase or reduce the occurrence of bladder cancer.

Her interest in cancer began during childhood. An aptitude for math and an early fascination with biology led to an interest in the wonders of the human body. When the beloved priest—a nonsmoker—of her family's Greek Orthodox Church died from lung cancer, she became interested in how someone with healthy habits could develop a cancer that is clearly linked to smoking.

"This tragic event sparked my curiosity about why some people developed cancer and other apparently similar people didn't," Karagas recalls. "Discovering the causes of disease enables us to find ways of preventing it," she says. Additionally, her work can reveal markers of cancer's progression and inform the treatment of patients.

In 2007, she and her colleagues published a population-based study conducted in New Hampshire on the relationship between cancer and analgesic usage. Painkillers containing a now-discontinued drug—phenacetin—are a known carcinogen and suspected of being related to bladder cancer. Participants who had taken phenacetin before its withdrawal from

the market appeared to be at greater risk, but Karagas observed a reduced risk of bladder cancer among users of other NSAIDs, such as aspirin.

Based on these early findings, Karagas, a professor of community and family medicine at Geisel and co-director of the Cancer Epidemiology and Chemoprevention program at Norris Cotton Cancer Center,

and her colleague, Richard Waddell, D.Sc., a research assistant professor of medicine at Geisel, were approached by the Intramural Program at the National Cancer Institute to collaborate and expand the project regionally to include Maine and Vermont.

In 2012, they began looking further for connections between analgesics and bladder cancer. Karagas also studied 39 genes related to NSAID metabolism and a newer class of NSAIDs known as selective cyclooxygenase (COX-2) inhibitors.

Findings from this study suggest regular use—and particularly regular use over 10 years or more—of ibuprofen may reduce bladder cancer risk in individuals carrying a gene variant related to NSAID metabolism. Expecting a similar trend for selective COX-2 inhibitors, the researchers instead observed an increased risk of bladder cancer.

Noting that further investigation is needed, Karagas warns against leaping to conclusions or making recommendations.

"A growing body of literature suggests certain NSAIDs may reduce risk of bladder cancer, particularly in individuals with specific genetic traits," she says. "NSAIDs are a worthy area of pursuit—they may also reduce risk for other diseases and cancers."

The results were published in the *International Journal of Cancer*.

Susan Green

## SURVEY SAYS

Many doctors are skeptical that patients with CDI (an infection by the bacterium *Clostridium difficile*) would be willing to be treated with fecal microbiota transplantation (FMT). The treatment is both safe and effective, but it has an obvious drawback: the need to infuse a stool sample taken from a healthy donor into the patient. But Geisel researchers, led by several medical students, found in a survey that most people would be willing to consider FMT, despite the method of treatment. "Our data suggest that patients may be more ready and willing to accept FMT as a treatment alternative for CDI than previously assumed," the authors wrote in *Clinical Infectious Diseases*.

## ALIGNING INCENTIVES

From 2005 to 2006, Medicare lowered the reimbursement rate for chemotherapy given in the last 14 days of a patient's life in recognition of the fact that such treatments are often unnecessary. According to research led by Carrie Colla, Ph.D., an assistant professor of TDI, the change in payment led to a decrease in use of chemotherapy in the last two weeks of a patient's life at doctors' offices. By contrast, at hospitals, where the connection between a chemotherapy treatment and a doctor's salary is less direct, the chemotherapy rate remained unchanged. Colla noted in the *Journal of Oncology Practice* that "these results suggest that payment reform may be used to better align appropriate incentives with better quality of care."

## Improving immunity against multiple myeloma

For patients with a type of bone marrow cancer called multiple myeloma, an autologous stem cell transplant can significantly increase survival time. This procedure involves collecting bone marrow stem cells from a patient, storing the cells, and then reinjecting them after chemotherapy. To measure how effective the transplant is, physicians look at the number of lymphocytes that are present in the patient two weeks after the transplant, a marker that is closely correlated with overall survival. In most patients, however, the cancer eventually returns.

It's not clear which types of lymphocytes are most effective in fighting off the cancer—knowledge that might contribute to improving survival. In an attempt to find out, Kenneth Meehan, M.D., a professor of medicine at Geisel and the director of the bone marrow transplant program at DHMC, led a phase II clinical trial that manipulated the stem cells removed from patients to increase the number of a certain type of immune cell to see if that would improve the killing of cancer cells.



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**Kenneth Meehan, the director of DHMC's bone marrow transplant program, led a clinical trial to test a treatment that manipulates immune cells to improve their effectiveness against cancer.**

Based on research led by Charles Sentman, Ph.D., a Geisel professor of microbiology and immunology, Meehan suspected that T cells with a certain marker ( $NKG2D^+CD3^+CD8^+$  T cells) would be more effective than other lymphocytes in combating myeloma. Sentman had identified the marker that makes the T cells more effective in research with mice. Meehan and his colleagues manipulated the stored cells taken from the patients to increase the number of these T cells. They then reinjected the cells back into the patients, along with a standard immune-boosting molecule called interleukin-2.

The results were “striking,” Meehan says. All patients tolerated the therapy well, and compared to patients who received a standard transplant without immune therapy, those in the trial had a marked increase in the overall number of lymphocytes, more than double those who received standard treatment. There were too few patients in the trial to address the effect on longer-term survival, but Meehan says the results were encouraging.

In an unusual step, Meehan used the patients' own cancer cells to test the effectiveness of the T cells. When the stem cells were removed from the patients at diagnosis, half were set aside and saved. Meehan took some of the patients' blood post-transplant and mixed it with these original cancerous myeloma cells. “We saw a marked increase in killing effectiveness for patients who were in the trial compared to control,” Meehan says.

The next step, says Meehan, is to conduct a multicenter trial very similar to the one they just completed, but with many more patients in order to better determine just how much the altered T cells improve survival. So far, the numbers look good, but Meehan's team is eager to continue its work. “This is really an example of bench to bedside, back to bench and to bedside again,” says Meehan.

Lauren Ware

## CLEANLINESS IS NEXT TO HEALTHINESS

Despite evidence that consistent hand hygiene can reduce the rate of health-care-associated infections, hospitals across the country have struggled to get providers to wash their hands consistently. In recent years, DHMC undertook a large-scale effort to improve hand hygiene and reduce health-care-associated infections. Over the course of the project, the compliance rate increased from 41% to 91%. Over the same period, the rate of health-care-associated infections dropped from 4.8 to 3.3 per 1,000 inpatient days. The authors of a study on the effort noted that there is still room for improvement, especially among physicians, but, they added, “our study adds to the evidence that sustained and significant improvement in [hand hygiene] is achievable.”

## PAINFUL SPENDING INCREASES

A team of Geisel researchers recently examined changes in spending on back treatments and determined which types of treatment are responsible for much of the \$90 billion spent every year on lower back pain. From 1999 to 2008, the average expenditure (adjusted for inflation) for a patient with a back problem rose 95%, from \$487 to \$950, most of which was accounted for by spending on medical specialists. “There are important decisions on the horizon regarding the U.S. health-care system,” the authors noted in *Spine*. “Our findings imply that medical care, specifically specialty care, rather than primary care, chiropractic care, or physical therapy, is responsible for rising ambulatory care costs for spine conditions.”