

## Study finds increased cancer risk with bone growth product

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Spine surgery patients who got a bone growth stimulating agent as part of a clinical trial were three to five times more likely to develop cancer two to three years after being implanted with the product, according to a new analysis.

The report is the latest cautionary note involving Medtronic's controversial bone morphogenetic protein-2, or BMP-2, a popular genetically engineered product used in [spinal fusion surgery](#) as an alternative to using a small amount of a patient's own bone.

The analysis led by Eugene Carragee, a Stanford University orthopedic surgeon, echoes findings in a recent Milwaukee Journal Sentinel/MedPage Today investigation. That story showed an elevated cancer risk in the clinical trial of the [Medtronic](#) product containing BMP-2 that is known as Amplify.

The story noted that doctors who have received millions of dollars in royalties from Medtronic had authored a 2009 paper about Amplify that failed to identify a significant cancer risk though they and the company were aware of data linking it to cancer. The royalties paid were not for BMP-2.

Doctors say Carragee's new analysis raises serious concerns about a [cancer risk](#) posed by BMP-2, which has been used in hundreds of thousands of patients since it came on the market in 2002.

"This is a provocative study that should make surgeons most concerned," said Dan Spengler, a professor of [orthopedic surgery](#) at Vanderbilt University Medical School. "I can't see a justification for its use except in extreme cases."

In response to questions on the earlier story, Medtronic and one of the authors of the paper said the cancer cases were not statistically significant. Two of the authors of the study did not respond to an email Thursday.

Medtronic spokeswoman Marybeth Thorsgaard did not address the cancer issue.

Instead she said the company was waiting for results of independent reviews being managed by doctors at Yale University. In August, Medtronic said it would spend \$2.5 million to hire the Yale researchers to do an independent review of the safety and effectiveness of the product.

That followed news in June that a U.S. Senate committee had launched an investigation into reports that doctors with financial ties to Medtronic were aware of serious complications with BMP-2 yet failed to reveal those problems in medical journal articles. The Senate Finance Committee said it opened the probe after reports in the Journal Sentinel.

The new BMP-2/cancer analysis was presented Thursday at the North American Spine Society's annual meeting in Chicago.

The clinical trial it focused on involved 239 patients who got the high-dose Amplify product and 224 who got a conventional graft of their own hip bone.

Among those who underwent follow-up about three years after the

surgery, 5 percent of those who got Amplify, or 12 patients, were diagnosed with a new cancer, compared with 1.3 percent, or three patients, who got a graft of their own hip bone. The difference was statistically significant.

After two to three years of follow-up, Amplify patients were four to five times more likely to develop at least one new malignancy, the analysis found. Viewed another way, one extra patient would be expected to develop cancer out of every 20 to 25 treated with Amplify.

The cancer numbers and ethical questions raised about conflicts of interest drew criticism from surgeons attending the presentation:

"Who do we believe?" asked John Jacquemin, an orthopedic surgeon from Cincinnati. "When the literature comes out, what's real and what is not?"

Jacquemin said he was especially troubled by allegations of bias in papers written by doctors with financial conflicts.

"That scares me and troubles me," he said.

Jerry Knirk, an [orthopedic surgeon](#) from New Hampshire, said he was concerned that most funding for medical devices comes from corporations.

"Money corrupts," he said.

The authors of the 2009 paper mentioned the cancer link only in a table accompanying the paper. The text itself never addressed the concern of whether BMP-2 might fuel cancer.

It was written by six physician authors. The first three authors of the

paper - or entities they are associated with - received about \$10 million from Medtronic, mostly in royalties, in 2010 alone. The royalties were for other products, not for BMP-2.

While the authors failed to warn of the cancer concern, the Journal Sentinel found a full airing of the cancer question in more than 1,000 pages of U.S. Food and Drug Administration records. That information included FDA reports and information filed with the agency by Medtronic as part of its application to win approval for Amplify.

At a 2010 Amplify hearing, for example, an FDA staffer said "the primary statistical concern is an apparent association with malignancy."

Since coming on the market in 2002, BMP-2 has become popular in spinal surgery. By stimulating [bone growth](#), it can eliminate the need to harvest a small amount of a patient's own bone for use in a spinal fusion surgery.

The product was approved for a narrow use after an earlier clinical trial showed it worked about as well as a standard hip bone graft in a specific kind of spinal fusion surgery. But doctors quickly began using BMP-2 in other, unapproved ways, known as "off-label" use. That helped fuel annual sales of \$700 million.

With the Amplify trial, Medtronic was seeking additional FDA approval for a different BMP-2 spinal fusion product. The FDA has refused to grant approval, a decision Medtronic is appealing. Doses of BMP-2 similar to what was used in the Amplify trial are commercially available.

Carragee said only a small portion of BMP-2 use follows the protocols of how the product originally was approved by the FDA. Most of its use is in so-called off-label applications.

He noted the doses of BMP-2 as well as the carrier used in the Amplify clinical trial are commercially available and as such are used off-label by surgeons.

Carragee said he thinks BMP-2 may fuel existing cancers.

He said the theory is that as people get older they have more cancer cells in their body, which the immune system tries to keep in check.

The addition of BMP-2, especially in higher doses, may disturb that balance and allow a cancer to grow, he said.

"At higher doses in people who are older and who have less resiliency to [cancer](#), it's more worrisome," he said. "I would say, why risk it?"

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