Antioxidants May Make Cancer Worse

New animal studies explain why supposedly healthy supplements like beta-carotene could exacerbate a dread disease

By Melinda Wenner Moyer | October 7, 2015

Antioxidants are supposed to keep your cells healthy. That is why millions of people gobble supplements like vitamin E and beta-carotene each year. Today, however, a new study adds to a growing body of research suggesting these supplements actually have a harmful effect in one serious disease: cancer.

The work, conducted in mice, shows that antioxidants can change cells in ways that fuel the spread of malignant melanoma—the most serious skin cancer—to different parts of the body. The progression makes the disease even more deadly. Earlier studies of antioxidant supplement use by people have also hinted at a cancer-promoting effect. A large trial reported in 1994 (pdf) that daily megadoses of the antioxidant beta-carotene increased the risk of lung cancer in male smokers by 18 percent and a 1996 trial was stopped early after researchers discovered that high-dose beta-carotene and retinol, another form of vitamin A, increased lung cancer risk by 28 percent in smokers and workers exposed to asbestos. More recently, a 2011 trial involving more than 35,500 men over 50 found that large doses of vitamin E increased the risk of prostate cancer by 17 percent. These findings had puzzled researchers because the conventional wisdom is that antioxidants should lower cancer risk by neutralizing cell-damaging, cancer-causing free radicals.

But scientists now think that antioxidants, at high enough levels, also protect cancer cells from these same free radicals. “There now exists a sizable quantity of data suggesting that antioxidants can help cancer cells much like they help normal cells,” says Zachary Schafer, a biologist at the University of Notre Dame, who was not involved in the new study. Last year the scientists behind the melanoma study found that antioxidants fuel the growth of another type of malignancy, lung cancer.

For the new study, published in *Science Translational Medicine*, Martin Bergö, a cell biologist at the University of Gothenburg’s Sahlgrenska Cancer Center in Sweden, and his colleagues decided to look at melanoma because rates have been increasing and because the cancer is known to be sensitive to the effects of free radicals. They fed the antioxidant N-acetylcysteine (NAC) to mice that had been genetically engineered to be susceptible to melanoma. The per-weight dose they gave the mice was consistent with what people typically consume in supplements. Although the treated mice did not develop more skin tumors than similar mice that had not been fed the antioxidants, they developed twice as many tumors in their lymph nodes, a hallmark of the spread of cancer—a process called metastasis. When the researchers added NAC or a form of vitamin E to cultured human melanoma cells, they confirmed that the antioxidants improved the cells’ ability to move and invade a nearby membrane.

Antioxidants may bolster protection of these dangerous cells. Bergö and his colleagues found higher levels of glutathione, an antioxidant made by the body, inside metastatic tumor cells in treated mice compared with untreated mice. The treated mice also had a higher ratio of glutathione to glutathione disulfide, the molecule that glutathione becomes after it neutralizes free radicals. These findings suggest that when the body is given extra antioxidants, its tumor cells get to keep more of the antioxidants that they already make themselves. The cells can store

the surplus, improving their ability to survive damage. This idea is supported by work that shows some genes that drive cancer growth turn on other genes that make intrinsic antioxidants.

The substances may help cancer cells in other ways, too. Previous research has suggested that glutathione affects the activity of a protein called RhoA, which helps cells move to different parts of the body. “If you were to select one protein that is known to be involved in [cell] migration, RhoA is it,” Bergö explains. He and his colleagues confirmed that the extra glutathione in the treated mice caused levels of RhoA to increase in their metastatic tumors. In their 2014 lung cancer study they also found that antioxidant supplements caused lung tumor cells to turn off the activity of a well-known cancer-suppressing gene called *p53*; its inactivation is believed to drive metastasis. And Schafer’s work has shown that antioxidants help migrating breast cancer cells survive when they detach from the extracellular matrix, the network of proteins surrounding cells.

These molecular investigations shed light on the large human trials that have implicated antioxidants in cancer. It is possible that the supplements did not triggercancer but rather accelerated the progression of existing undiagnosed cancers, making later discovery of the disease likely.In other words, it “could be that while antioxidants might prevent DNA damage —and thus impede tumor initiation—once a tumor is established, antioxidants might facilitate the malignant behavior of cancer cells,” Schafer says.

The medical advice for people at this point is tentative. More studies need to be done to bolster this hypothesis and understand exactly how antioxidants affect cancer cells in humans. Bergö, who is not a medical doctor, does believe that people who are at an increased risk for lung cancer or melanoma or who have been diagnosed with either one should avoid antioxidant supplements. “There’s no conclusive evidence that it would be beneficial to them, and there’s mounting evidence that it could be harmful,” he says.

His results do have a silver lining. They suggest a potential new way to target the disease. If cancer is very sensitive to the damaging effects of free radicals, then it might be possible to develop drugs that target cancer cells specifically and prevent them from producing antioxidants or that ramp up free radical levels inside of the malignant cells, exploiting their newly discovered weakness.