Recent Research Highlights Importance of Trials Halted 10 Years Ago

Ten years ago, investigators from two large clinical trials ended their studies early—for entirely different reasons. For researchers heading the β-Carotene and Retinol Efficacy Trial (CARET), intervention stopped in January 1996 when scientists observed that current and former smokers taking β-carotene and vitamin A supplements—hypothesized to reduce cancer risk—were developing lung cancer at a higher rate than participants taking a placebo. A couple of months earlier, the National Surgical Adjuvant Breast and Bowel Project (NSABP) decided to halt its study of long-term use of tamoxifen for breast cancer treatment when scientists discovered that tamoxifen provided no additional benefit after 5 years of treatment.

β-Carotene: Beneficial or Harmful?

“We have no explanation for the possible adverse effects we observed to date,” Gilbert Omenn, M.D., Ph.D., of the Fred Hutchinson Cancer Research Center and University of Washington School of Public Health in Seattle, said to a reporter in the February 21, 1996, issue of JNCI. In 1996, no explanation was the best explanation scientists had for the 17% higher total mortality among participants taking β-carotene and vitamin A supplements.

Studies conducted since then have found that some nutrients, such as β-carotene, may increase the risk of cancers for smokers while at the same time decrease cancer risk for nonsmokers.

Last year, a study by Marie-Christine Boutron-Ruault, M.D., Ph.D., at INSERM in Villejuif, France, and colleagues also confirmed a higher risk of lung cancer among smokers with a high β-carotene intake, but they also found that high intake of the nutrient was associated with a lower risk of tobacco-related cancers among nonsmokers. Nonetheless, an accompanying editorial suggested that smokers should not take the evidence to mean they should exclude carotenoids from their diet.

A follow-up study of CARET by Gary E. Goodman, M.D., and colleagues in 2004 found that lung cancer risk among smokers decreased after they discontinued β-carotene supplementation—but it still remained slightly elevated for at least 4 years after the end of the trial. The authors suggested that the elevated risk may have been the result of the high doses of beta-carotene given to participants. Goodman and colleagues also put the trial results in the context of laboratory studies conducted in recent years that suggest that β-carotene interacts with agents in tobacco and may be responsible for the observed increase in risk of lung cancer.

Although the CARET study had to be shut down because of potential harm to its participants, researchers were able to get important information from it and learn the necessity of randomized trial testing before recommending a supplement to the general population, said Demetrious Albanes, M.D., of the National Cancer Institute, who led the Alpha-Tocopherol, β-Carotene Cancer Prevention (ATBC) Trial, which, like CARET, found an increased risk of lung cancer among male smokers who took β-carotene. “We learned how important it is to set up randomized controlled studies to test in a very precise way whether a micronutrient or dietary supplement has the hypothetical benefit that researchers have thought it may have, or may have been found to have based on other research,” he said. “It’s crucial to set up controlled studies that give a less ambiguous and very definitive answer.”

After Tamoxifen, What Next?

NSABP’s B-14 trial was originally launched to evaluate whether women with lymph node–negative, estrogen receptor–positive breast cancer benefit from tamoxifen treatment. Researchers also designed the trial to test the duration of tamoxifen therapy necessary to get the most benefit from the drug. In late 1995, an analysis of the study data revealed that the benefits of 5 years of tamoxifen therapy decreased a patient’s chances of breast cancer recurrence, but taking more than 5 years of tamoxifen conferred no additional benefit. For this reason, the B-14 trial was terminated in late November 1995.

Although 5 years is the generally accepted duration of tamoxifen therapy, there are more than 20,000 women enrolled in clinical trials that are attempting to confirm the optimal duration. The ATLAS (Adjuvant Tamoxifen Longer Against Shorter) trial of 15,000 women and the aTTom (Adjuvant Tamoxifen Treatment–Offer More?) trial of more than 8,000 women are both looking at 10 years versus 5 years of tamoxifen in women with breast cancer.

Despite the positive effect tamoxifen has for many breast cancer survivors, some tumors become resistant to tamoxifen, and some women need to stop taking the drug because the side effects, hot flashes being the most common, are intolerable. In the last few years, a newer class of drugs has come on the scene as treatment for breast cancer. Aromatase inhibitors, drugs whose method of attack was to inhibit enzymes that convert androgens into estrogen, started to be used in conjunction with, or
even in place of, 5 years of tamoxifen, particularly in postmenopausal women. Several clinical trials have been launched to study various combinations of tamoxifen and aromatase inhibitors to determine how to get the biggest decrease in risk of cancer recurrence. (See related story, p. 86.)

Eric Winer, M.D., director of the Breast Oncology Center at the Dana-Farber Cancer Institute in Boston, says the effect of the appearance of aromatase inhibitors “has been that they’ve further decreased a woman’s chance of having a recurrence of breast cancer.” He adds, “They have found their way into the standard treatment of most postmenopausal women with receptor-positive breast cancer.”

Winer and colleagues concluded in a 2004 technology assessment for the American Society of Clinical Oncology that “optimal adjuvant hormonal therapy for a postmenopausal woman with receptor-positive breast cancer includes an aromatase inhibitor as initial therapy or after treatment with tamoxifen. Women with breast cancer and their physicians must weigh the risks and benefits of all therapeutic options.”

But aromatase inhibitors can cause negative side effects—musculoskeletal problems, hot flashes, osteoporosis, and arthritis, among others—and scientists continue to search for better therapy. As for tamoxifen, Winer says they are still debating which treatment options work best for different categories of patients. “What we don’t know,” he said, “is whether a woman is best off receiving an aromatase inhibitor alone, or whether she’s better off using tamoxifen for some number of years followed by an aromatase inhibitor.”

Winer thinks that future research will focus on looking for alternate or adjunct therapies for breast cancer. “There’s a great deal of interest in looking at other targeted agents, other inhibitors of signal transduction pathways in combination with tamoxifen or aromatase inhibitors,” he said.

—Ariel Whitworth

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