The results came as a surprise, even though the researchers had a sense that women on the experimental regimen had done well.

“After publication of the other high-dose trials, we did not expect to see such a large survival difference,” Nitz said. “As survival rates for this subgroup of patients with standard regimens have not been improved substantially over the last 20 years, we think that the rapidly cycled tandem high-dose regimen is a very good option for these patients and should be investigated further.”

One important point that is sure to generate discussion is the composition of the chemotherapy regimes the researchers used, said Larry Norton, MD, Deputy Physician-in-Chief for Breast Cancer Programs at Memorial Sloan-Kettering Cancer Center in New York. Neither the control arm nor the high-dose arm used a taxane.

“This may be an issue of an inferior control arm rather than a superior trial arm,” said Norton, who was not involved in the German study. “The single most active class of agents in breast cancer is absent in both treatments.”

Nitz and colleagues acknowledge, and dismiss, that concern in their paper.

“Another issue not raised in 1995 [the year the trial began] but unequivocally important today is the role of taxanes in the control group,” they write.

They go on to note that taxanes have been shown to be most effective in women with one to three involved lymph nodes, and less effective in women with more than four involved nodes. They also cite findings from the Breast Cancer International Research Group that taxanes may even be inferior in patients with 10 or more positive nodes.

“We therefore conclude that our dose-dense anthracycline-based regimen is up to date and appropriate,” they write. “Superiority of high-dose chemotherapy in this trial cannot be attributed to a weakness of the control regimen.”

Nevertheless, Norton said the new study is unlikely to change practice in the United States.

“Essentially, all the well-done, well-controlled, and audited clinical trials showed high-dose chemotherapy didn’t add anything except toxicity, and if it did add anything it was at enormous cost, so it did fall out of favor,” he said. “I think cytotoxic therapy has accomplished all it can.

“The real future is going to come from targeted biological agents combined with cytotoxic drugs,” he continued. “There are dozens of exciting compounds, and integrating those into the treatment regimens is something we should be focusing on.”

**MODIFIABLE RISK FACTORS STILL MAJOR CAUSE OF CANCER DEATHS WORLDWIDE**

Nine modifiable risk factors are responsible for more than one-third of cancer deaths worldwide, according to a recent estimate from researchers at the Harvard School of Public Health and other institutions. Of these, smoking and alcohol consumption are the most damaging, they reported in *The Lancet* (2005; 366:1784–1793).

The other risk factors assessed include: overweight/obesity, physical inactivity, low fruit and vegetable consumption, unsafe sex, urban air pollution, indoor smoke from household fuels, and contaminated injections in health care settings. The researchers looked at each factor’s impact on 12 different types of cancer based on age, sex, and region of the world. The data came from several sources, including the World Health Organization’s Comparative Risk Assessment project, an initiative to determine which risk factors play a role in the global burden of disease.

Of the 7 million global cancer deaths in 2001, the team estimated that 2.43 million (35%) were attributable to the cumulative effect of these nine risk factors. Smoking was by far the biggest contributor to mortality, causing
21% of those deaths overall (29% of cancer deaths in high-income countries and 18% in low/middle-income regions). Alcohol use caused about 5% of global cancer deaths, as did low fruit and vegetable intake.

“These results clearly show that many globally important types of cancer are preventable by changes in lifestyle behaviors and environmental interventions,” said senior study author Majid Ezzati, Assistant Professor of International Health at the Harvard School of Public Health.

Other experts agree. “What’s interesting is that even without the potential benefits of early detection and treatment, at least one-third of cancer deaths are preventable,” said Michael Thun, MD, MS, Vice President of Epidemiology and Surveillance Research at the American Cancer Society.

The findings highlight areas where the United States has made considerable progress in reducing the cancer burden. For instance, the impact of unsafe sex on cancer deaths (through transmission of human papilloma virus [HPV], which can cause cervical cancer) is higher in low- and middle-income regions of the world than it is in high-income regions like the United States, where screening for cervical cancer through Pap tests is widespread. Likewise, the risks from contaminated injections remain a problem in low-income nations that have poor sanitation and few resources for vaccinations against infectious agents like hepatitis that can cause cancer.

But the report also shows the tremendous toll that lifestyle factors like overweight and physical inactivity are taking in the United States. After smoking and alcohol use, overweight/obesity was the third most important cause of cancer death in high-income nations, the researchers found. (In low- and middle-income nations, low fruit and vegetable intake was the third most common risk factor for cancer deaths.) It was an especially important factor in colorectal cancer, breast cancer, and uterine cancer. Thun noted that the impact of excess weight on cancer may be even greater than reflected in the 

Lancet report because the rate of overweight and obesity is increasing so rapidly, particularly in the United States and other developed nations.

The study illuminates opportunities for public health policy and clinical interventions to reduce the global cancer burden, Thun said. For instance, promoting greater tobacco control, through the Framework Convention on Tobacco Control and other means, could greatly reduce the deadly impact of smoking. The development of vaccines for HPV holds great promise for reducing the number of cervical cancer cases and deaths, especially in regions of the world where screening is not widely available.

These types of measures are crucial in regions of the world where advanced medical facilities are not readily accessible, Ezzati said. “To win the war against cancer we must focus not just on advances in biomedical technologies, but also on technologies and policies that change the behaviors and environments that cause those cancers,” he said.

CANCER SURVIVORS NEED BETTER LONG-TERM FOLLOW UP

A report from the National Cancer Policy Board, the Institute of Medicine, and the National Research Council is calling on health professionals, insurers, advocates, and the government to work together to improve follow-up care for the 10 million cancer survivors in the United States. The report, From Cancer Patient to Cancer Survivor: Lost in Transition, makes 10 specific recommendations for changing the way the United States addresses the long-term consequences of cancer and its treatments.

“This is very practical information intended to shift our thinking of what we need to do for cancer survivors,” said Bonnie Teschendorf,