# First study on long-term cognitive effects of breast cancer CMF chemotherapy finds subtle impairment

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Dutch investigators have reported that women who received CMF chemotherapy (a combination regimen including the drugs cyclophosphamide, methotrexate, and 5-fluorouracil) for breast cancer between 1976 and 1995 scored worse on cognitive tests than women who never had cancer. The differences in performance were subtle but statistically significant, and occurred mainly in word learning, memory and information processing speed. The findings – published February 27 in the *Journal of Clinical Oncology* – indicate that cognitive problems, which are known to occur shortly after treatment, may also be observed 20 years after treatment.

"To our knowledge, this is the first study to suggest that subtle cognitive deficits may be among the long-term effects of chemotherapy, especially of the earlier regimens," said one of the senior authors Sanne B. Schagen, PhD, a Group Leader at the Department of Psychosocial Research and Epidemiology at the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital in Amsterdam. "Our findings do not suggest that breast cancer survivors treated with CMF chemotherapy need to be monitored more closely for cognitive difficulties. But if breast cancer patients experience cognitive problems, information about the possible long-term effects of their breast cancer treatment may help to guide referral to appropriate support services."

Prior studies have shown that chemotherapy can have immediate effects

on cognitive function, such as causing forgetfulness or problems processing information, which can last five to ten years. Animal studies have also demonstrated that 5-fluorouracil, methotrexate and cyclophosphamide are associated with impaired learning and memory and changes in brain structure. Yet until the current study, the very long-term cognitive effects of such chemotherapy drugs have been unknown.

CMF chemotherapy was the standard of care for breast cancer worldwide from the 1970s through the 1990s and was received by thousands of women. Today it has been replaced by anthracycline-based adjuvant regimens but many women who received the regimen in the past are still alive. Moreover, cyclophosphamide and 5-fluorouracil are still commonly incorporated in modern chemotherapeutic regimens for breast cancer.

In this study, Dr. Schagen, Breteler, Koppelmans and colleagues, compared the results of neuropsychological tests among 196 women with breast cancer who had received CMF chemotherapy (six cycles following surgery) between 1976 and 1995 against those of women without cancer. Participants were assessed between November 2009 and June 2010. In addition to the neuropsychological examination, participants were also assessed for depression and self-perceived memory problems. The control group included 1,509 women who were enrolled in the Rotterdam Study (which is exploring risk factors for disease in the elderly) and who underwent the same neuropsychological tests and assessments. All women included in the current study were between the ages of 50 and 80 when they were first enrolled.

Adjusting for potential confounding factors such as age, education, and depression score, the investigators found that women who had CMF chemotherapy were more likely than the women without cancer in the control group to have lower scores on test of immediate and delayed verbal memory (the ability to recall words), information processing

speed, and psychomotor speed (coordination of thinking and hand movement, such as putting pegs in a board). The magnitude of the effects was comparable to approximately six years of age-related decline in cognitive function. The women who had received chemotherapy also had more memory complaints than the control women, but these complaints were not related to objective memory functioning.

Dr. Schagen noted that people with cognitive deficits can learn coping strategies to improve their daily life functioning, such as becoming more systematic in their daily routines, and preparing effectively for events such as travel or business meetings.

Researchers will continue to study the effects of chemotherapy on the brain and hope to determine which patients are most susceptible to cognitive problems.

"We don't know why some people are more vulnerable than others. We need more insights into the biological and psychological predictors of risk," said Dr. Schagen.

She added that she and co-investigator Dr. Breteler hope to compare cognitive function between breast cancer survivors who had chemotherapy and cancer survivors who did not have chemotherapy, to control for a possible influence of the cancer itself on cognitive functioning.

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