The purpose of this paper is to discuss issues involved in the effects of chemotherapy on everyday cognitive functioning in older and younger women recovering from breast cancer. We will examine the possibility that chemotherapy may affect cognitive processes that are necessary for driving, and how these might exacerbate normal age-related changes in cognition. This may be an especially important issue for older women, who are likely to live alone, and may not have other people that they can rely on to help with transportation. Older women are disproportionately affected by breast cancer: In the United States, two-thirds of new breast cancer patients are over the age of 55, and women ages 75-79 have the highest incidence of breast cancer. Many of these women are treated with chemotherapy; however, little is known about the effects of chemotherapy on the everyday lives and mobility of younger and older women.

It has been suggested by previous research that adjuvant chemotherapy given as a treatment for breast cancer produces general cognitive deficits in some patients, as measured by standard neuropsychological tests. What is not known is whether or not all breast cancer patients suffer from declines in cognition, or if only a subset of breast cancer patients do. Are cognitive deficits apparent in women who were high functioning before chemotherapy, as well as those who were low functioning? Are older or younger women more likely to experience cognitive deficits? In addition, little is known about the effects of chemotherapy on everyday activities that depend on cognition. Studies are needed to determine the effects of chemotherapy on specific cognitive tasks known to be highly predictive of performance on everyday activities, such as driving, that are critical to daily living and that may become problematic with increasing age. If chemotherapy affects the cognitive processes that underlie performance on critical daily activities, would chemotherapy be more likely to exacerbate performance problems of older as compared to younger chemotherapy breast cancer patients?

Chemotherapy and Cognition

Let us discuss for a few minutes the known effects of chemotherapy on cognition. Previous research has suggested that adjuvant chemotherapy given as a treatment for breast cancer produces general cognitive deficits in some patients, as measured by a wide variety of standard neuropsychological tests. The cognitive deficits found so far are subtle; however, these deficits have been reported as long as two years to ten years after completion of chemotherapy.

Using several research databases, we identified five studies that examined the long-term effects of chemotherapy on cognition using neuropsychological tests. Ideally, it would be preferable for studies to measure cognition before and after chemotherapy. However, four of the five studies used a post hoc design where a group receiving
chemotherapy was compared to controls not treated with chemotherapy—either healthy controls\(^6\) or early stage breast cancer survivors not treated with chemotherapy\(^3\, 5\, 2\). In one study\(^4\), researchers used vocabulary scores to estimate pre-morbid IQ and compared scores of chemotherapy-treated breast cancer patients to age and IQ adjusted norms. Four of the five studies were of women who had completed chemotherapy more than one year previously, suggesting that chemotherapy has long-term effects on women. According to a previous review of the five studies, deficits have been reported in areas such as attention, visuospatial ability, memory, language, and psychomotor functioning, although researchers do not necessarily agree about the relationship between specific tests and specific domains of functioning\(^7\).

A few tests were used in several of these five key studies. For three consistently used tests, Digit Symbol, Trailmaking (TMT) A and Trailmaking B (used in all but the Brezden et al., 2000, study), the effect sizes in four studies suggested poorer performance by chemotherapy subjects. In the two studies that directly tested the significance of chemotherapy/control differences on specific tests\(^3\, 5\), the average performance differences on Digit Symbol and TMT-B between controls and chemotherapy groups were significant.

Our research group\(^8\) in our first joint effort with North Mississippi Medical Center tested 18 breast cancer survivors (mean age = 57.2), 16 of whom had received adjuvant chemotherapy. Ten participants (mean age 54.7) completed an entire battery of instruments including the Trailmaking Tests (TMT), the Kaufman Brief Intelligence Test, the Rivermead Behavioural Memory Test (RBMT), and the Everyday Cognition Battery (ECB), which assesses daily living tasks such as reading menus. The chemotherapy participants scored within the normal range on most instruments with the exception of the TMT-B (with three below average) and the Rivermead Behavioural Memory Test (with two below average), which also measures everyday memory. However, only one chemotherapy participant had borderline performance on multiple instruments. Our results are consistent with the aforementioned studies: even though chemotherapy subjects performed more poorly than did controls on the average, the poorer performance suggested only mild impairment\(^4\, 2\). The implication of such subtle impairments for everyday functioning is not known, so it would be difficult for women to use the information derived from these studies to make informed decisions on whether or not to have chemotherapy treatment.

We are currently conducting a study to correct two weaknesses of existing studies on the chemotherapy effects on cognition. The first weakness is that researchers have not examined the relationship between cognitive deficits and the age of the woman receiving chemotherapy. Breast cancer patients treated with chemotherapy vary tremendously in age, from thirties to eighties\(^1\). Some researchers suggest that younger cancer patients should have greater declines in cognition than older women because chemotherapy induces premature menopause\(^7\), leading to a dramatic reduction in estrogen, such as women experience when they have hysterectomies. Women who have hysterectomies frequently experience mild cognitive deficits, which are lessened if they take hormone replacement therapy (HRT)\(^7\). By extension, women who experience chemotherapy-induced hysterectomies may show cognitive deficits in comparison to women of similar age who have not experienced menopause. Since hormone replacement therapy is not an option for women who have had breast cancer, cognitive deficits may possibly be more likely.

There are reasons to doubt that cognitive deficits from breast cancer are mostly due to drops of estrogen. According to Verstapen and associates\(^9\), the chemicals used in
chemotherapy itself are neurotoxins, which may directly affect cognition. Chemotherapy affects the cognitive processes of persons with cancers other than breast cancer, including individuals who do not experience great declines in estrogen, such as men, children, and postmenopausal women. Another clue is the dosage effect—higher dosages of chemotherapy produce greater cognitive deficits than low dosages; however, both high and low dosages tend to bring on early menopause. To the extent that both low and high levels of chemotherapy shut down the reproductive system, there should be no relationship between levels of chemotherapy and levels of estrogen. Thus, the relationship between dosage and cognition suggests that the effects of chemotherapy are not limited to its effects on estrogen.

Older women may be more affected by chemotherapy than younger women. Older women tend to perform more poorly than younger women on most cognitive tests, due to health problems or cognitive slowing. According to Baltes' reserve capacity hypothesis, most adults have “cognitive reserves” which allow them to improve their cognitive performance with practice or effort. These cognitive reserves tend to decline in advanced old age. There is evidence that older adults suffering from specific diseases such as hypertension and stroke are more likely than younger adults who suffer from the same diseases to experience disease-related cognitive deficits due to reserve capacity differences. Thus it would be expected that, if chemotherapy is associated with cognitive deficits, older breast cancer patients given chemotherapy would be more negatively affected in terms of cognitive performance than would younger breast cancer patients given chemotherapy, due to reduced cognitive reserves. This seems especially likely since the tests that have been shown so far to be affected by chemotherapy (i.e., Trailmaking B and Digit Symbol) tend to decline with age.

The second question we wanted to address today was the relationship between chemotherapy and everyday activities, such as driving. Typically, mild deficits on neuropsychological tests do not correlate with problems in everyday life, such as everyday memory or activities of daily living. However, one extremely important everyday task does seem to correlate with performance on several neuropsychological tests, and that is driving. For example, driving ability and crash risk correlate moderately with some of the tests that tend to be affected by chemotherapy, especially Trailmaking Tests, which measures executive functioning and the ability to switch attention.

Driving as Everyday Cognition
Driving is an important everyday activity that has implications both for safety and independent living. Older adults who do not drive engage in fewer social activities than those who do drive. Older adults who stop driving or who are forced to greatly restrict their driving report feelings of depression and isolation directly related to giving up driving. Yet many older adults drive who probably should not—individuals over the age of 85 have the highest crash rate and the highest driving mortality rate per mile driven of any age group, except for 16-24 year-olds. Very old women have particularly poor driving skills. To the extent that chemotherapy worsens cognitive processes in older female cancer patients, it may also impair their ability to drive. In our current research, we are examining the effects of chemotherapy on specific cognitive tests that predict driving.

Further investigation of cognitive deficits that could affect driving—a task for which performance may decline with age and also be affected by chemotherapy for age-related cancers—is important. Understanding the interrelationships between age, chemotherapy, and cognitive performance that are highly related to driving could lead to the development of training programs or other individually-focused interventions that may improve
performance when deficits are found or permit redesign of traffic or vehicle systems to minimize effects of specific deficits on crash risk. However, Trailmaking Tests are not the tests that are most closely and consistently linked to driving performance and crash risk\textsuperscript{12}. Therefore, it is important to explore the effects of chemotherapy on cognitive tests that show stronger relationships to everyday performance, such as driving ability, than do the traditional neuropsychological tests that have been used in prior studies.

Karlene Ball and associates have examined the relationship between a number of cognitive variables and driving, and they have found one cognitive test is more closely correlated with driving than others, useful field of view, or UFOV\textsuperscript{®}, which Ball developed\textsuperscript{18}. Useful field of view is defined as the amount of visual information that can be accessed at one time without turning one’s eyes or head. It is a measure of visual attention as much as measure of the visual field itself; the visual field does not actually shrink, but poor scores indicate less efficiency at extracting information from a crowded visual field\textsuperscript{21}. The UFOV\textsuperscript{®} yields scores for speed of processing and attention. UFOV\textsuperscript{®} declines with age, and has been found to be predictive of crash frequency in older adults\textsuperscript{20}. Training is thought to improve UFOV\textsuperscript{®} scores and lower accident risk in older adults\textsuperscript{22}. Recent research has found that medical illnesses that affect cognition, such as stroke and traumatic brain injury\textsuperscript{23} affect both UFOV\textsuperscript{®} and driving behavior.

The UFOV\textsuperscript{®} has been shown to be highly related to driving performance\textsuperscript{18} and to other important everyday activities\textsuperscript{24}. UFOV\textsuperscript{®} scores have been shown to decline with age\textsuperscript{25}, which would permit us to test not only the general effects of chemotherapy on an indicator of everyday performance but also to test for possible age by treatment interactions. Existing studies on cognitive deficits following breast cancer have not included the UFOV\textsuperscript{®}.

Ball suggests that the UFOV\textsuperscript{®}, which adjusts to the abilities of the users, is more sensitive to mild neuropsychological deficits than most standard neuropsychological tests\textsuperscript{24 11}. The UFOV\textsuperscript{®} is related to but separate from visual acuity. Approximately 50% of subjects who perform poorly on the UFOV\textsuperscript{®} have excellent vision\textsuperscript{25}. These individuals are at high risk for automobile crashes, but unlike individuals with vision problems, they may be unaware that they are at high risk, and thus, unlikely to alter their driving habits in accordance with their reduced skill\textsuperscript{11}. Since chemotherapy is likely to affect the cognitive components of UFOV\textsuperscript{®} more than visual acuity, chemotherapy patients may not be aware that their driving skills have been affected by their medication regime.

We are currently conducting a study to compare the performance of women who have had chemotherapy for breast cancer with similar aged women who have had general anesthesia. We are testing women with some of the cognitive instruments that have been used previously, including Trailmaking Tests A & B, and WAIS subtests such as digit symbol, vocabulary, and digit span. We have also included the UFOV\textsuperscript{®}. We expect that chemotherapy patients will display poorer performance on the UFOV than controls, and that older patients will be more likely than younger patients to show scores associated with high crash risk, due to age-related reductions in reserve capacity\textsuperscript{11}. Fortunately, recent studies have suggested that focused training may improve UFOV\textsuperscript{®} scores and lower accident risk in older adults\textsuperscript{21}.

**Implications for Future Research**

The impact of chemotherapy on cognition in women with breast cancer is far from definitive due to the very few available studies (i.e., the five studies discussed above), the problems with adequate controls, the choice and variety of types of instruments used to
assess cognition, and to the low numbers of participants in the studies. Although there appear to be some subtle deficits associated with the chemotherapy in breast cancer patients, the relationships of these deficits to everyday cognition is also uncertain. More definitive research with adequate experimental design is needed to examine how extensive the deficits are, and how they change with age and other cognitive conditions. Further, how such deficits affect everyday cognition should also be investigated. Since breast cancer is more likely to affect older women, it would be important to assess how any potential deficits affect everyday cognition, especially cognition involved in mobility within their immediate environments. Understanding the relationship between chemotherapy, attention, speed of processing, and driving behavior is one step in understanding how women are affected by cancer treatments. The impact of these factors on the independence and safety of older women who have experienced breast cancer and adjuvant chemotherapy is an important area for further study.

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