Catechol-O-Methyltransferase Genotype Modulates Cancer Treatment-Related Cognitive Deficits in Breast Cancer Survivors

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BACKGROUND: Recent attention has focused on the negative effects of chemotherapy on the cognitive performance of cancer survivors. The current study examined modification of this risk by catechol-O-methyltransferase (COMT) genotype based on evidence in adult populations that the presence of a Val allele is associated with poorer cognitive performance. METHODS: Breast cancer survivors treated with radiotherapy (n = 58), and/or chemotherapy (n = 72), and 204 healthy controls (HCs) completed tests of cognitive performance and provided saliva for COMT genotyping. COMT genotype was divided into Val carriers (Val+; Val/Val, Val/Met) or COMT-Met homozygote carriers (Met; Met/Met). RESULTS: COMT-Val+ carriers performed more poorly on tests of attention, verbal fluency, and motor speed relative to COMT-Met homozygotes. Moreover, COMT-Val+ carriers treated with chemotherapy performed more poorly on tests of attention relative to HC group members who were also Val+ carriers. CONCLUSIONS: The results suggest that persons treated with chemotherapy for breast cancer who also possess the COMT-Val gene are susceptible to negative effects on their cognitive health. This research is important because it strives to understand the factors that predispose some cancer survivors to more negative quality-of-life outcomes. Cancer 2011;117:1369–76. © 2010 American Cancer Society.

KEYWORDS: cancer survivor, cognitive performance, genetics, research methods.

In recent years there has been considerable interest in quality-of-life outcomes among adult cancer survivors.1 For example, attention has been directed at the topic of “chemobrain,” or the presence of deficits in cognitive performance associated with treatment for cancer.2–4 Statistically significant differences5,6 on multiple domains of cognitive performance have been observed between cancer survivors and controls with no history of cancer, as well as among cancer survivors as a function of treatment modality. More recently, investigators have sought to elucidate factors that may influence cognitive functioning among cancer patients including psychological, physiological, demographic, and genetic determinants.7–9 The potential for genetic variation to affect cognitive quality-of-life outcomes among cancer survivors has been examined only once before, by Ahles et al.10 They reported that the presence of an ε4 polymorphism of apolipoprotein E (APOE), a known genetic risk factor for Alzheimer disease (AD)11 and poorer cognitive performance among persons without dementia,12,13 was associated with poorer performance on tests of verbal memory and spatial ability among breast cancer and lymphoma survivors treated with chemotherapy. However, this study was characterized by small sample sizes, lack of a control group with no history of cancer, as well as an inability to examine treatment effects because all patients were treated with the standard dose of chemotherapy.

The current article focuses on the moderating role of the catechol-O-methyltransferase (COMT) genotype on cognitive performance following treatment for breast cancer. The COMT genotype is associated with levels of dopamine (DA)
The COMT Val158Met single-nucleotide polymorphism leads to a substitution of valine (Val) with methionine (Met) at codon 158 on chromosome 22q11. The presence of the Val allele of COMT (Val+, Met/Val, Val/Val) is related to 3 to 4 times higher enzymatic activity, compared with that in COMT-Met (Met/Met) homozygote carriers. As a result, COMT-Val+ carriers have greater degradation of DA and less availability of this neurotransmitter at synaptic receptors. Several studies have reported that COMT-Val+ carriers perform more poorly on tests of attention and executive function, abilities heavily influenced by the integrity of the frontal lobes, than do COMT-Met carriers. The potential for the COMT genotype to influence cognitive functioning in cancer survivors is suggested by recent work examining neuroimaging correlates of chemotherapy treatment for cancer. Two studies reported that persons treated with chemotherapy had greater activation in the frontal lobes, as shown with functional magnetic resonance imaging (fMRI) or positron emission tomography imaging, compared with persons who did not receive this treatment. This pattern of increased activation was interpreted as a compensatory mechanism so that persons treated with chemotherapy had to recruit additional brain structures to perform the same cognitive task. To the extent that the greater activation is limited by DA losses in the frontal lobes associated with the COMT genotype, this may affect the cognitive functioning of persons treated with chemotherapy.

In the current study, we examined the influence of the COMT genotype on cognitive performance among women with no history of cancer, women treated for breast cancer with chemotherapy with or without radiotherapy, and women treated for breast cancer with radiotherapy only. We predicted that 1) women treated with chemotherapy would perform more poorly than women treated with radiotherapy only and women without a history of cancer, 2) COMT-Val+ carriers would perform more poorly relative to COMT-Met carriers, especially on tests that are heavily dependent on frontal lobe integrity, and 3) women who are COMT-Met carriers treated with chemotherapy would be most impaired on tests of cognitive performance. The current study builds on our previous work, which reported small but statistically significant treatment group differences in tests of attention and complex cognition. In the current study, we examined a subset of these participants, who provided a DNA sample for COMT genotyping.

MATERIALS AND METHODS

Participants

Breast cancer survivors

As part of a larger study examining quality of life during and after breast cancer treatment, women diagnosed with stages 0 to II breast cancer were recruited at the H. Lee Moffitt Cancer Center (HLMCC) at the University of South Florida and the Markey Cancer Center (MCC) at the University of Kentucky (a detailed description of inclusion and exclusion criteria was reported previously). Groups were categorized as those who received only chest wall radiotherapy as part of treatment (radiotherapy [RT]) and those who received chest wall radiotherapy plus a minimum of 4 cycles of standard-dose chemotherapy or a minimum of 4 cycles of standard-dose chemotherapy alone (CT; mean number of cycles of chemotherapy, 5.61; standard deviation [SD], 1.84). The chemotherapy regimens (with percentage of the sample in parentheses) were: anthracycline and cyclophosphamide (51.52%); anthracycline, cyclophosphamide, and taxane (31.82%); cyclophosphamide, methotrexate, and 5-fluorouracil (9.09%); anthracycline and taxane (1.52%); anthracycline, cyclophosphamide, and 5-fluorouracil (3.03%); and anthracycline, cyclophosphamide, 5-fluorouracil, and taxane (3.03%).

Noncancer controls

Potential healthy control participants (HCs) were identified using a database maintained by Marketing Systems Group, Inc. (Fort Washington, PA) that draws from all listed telephone households in the United States and is estimated to include demographic and contact information for approximately two-thirds of the US population.

Measures

Demographic and clinical data

Demographic data were obtained from all participants via a self-report measure. Survivor disease and treatment information was collected via medical chart review.

Cognitive performance

Cognitive performance was assessed using a battery of neuropsychological tests to evaluate overall intellectual ability as well as 5 major domains of cognitive functioning, which were based on our previous research.

Overall intellectual ability

The National Adult Reading Test (NART) was administered to estimate overall intellectual ability, and
the results are expressed as Wechsler Adult Intelligence Scale (WAIS)-R full-scale intelligence scores.

Episodic memory
The composite variable for this domain was constructed with 3 items (free recall–short delay, free recall–long delay, and discrimination) from the California Verbal Learning Test (CVLT)\(^{22}\) and 3 items (immediate recall, delayed recall, and delayed recognition) from the Visual Reproduction subtest of the Wechsler Memory Scales-III (WMS-III).\(^{23}\)

Attention
The Digit Span and the Spatial Span subtests of the WAIS-III\(^{24}\) and trial 1 from the Color Trails Test\(^{25}\) were administered to assess attention.

Complex cognition
The Digit Symbol subtest of the WAIS-III\(^{24}\) and trial 2 of the Color Trails Test\(^{25}\) were administered to assess complex cognition.

Verbal fluency
The Controlled Oral Word Association (COWA) test\(^{26}\) was administered to assess verbal fluency.

Motor speed
The Finger Oscillation Test\(^{27}\) (dominant and non-dominant hands) was used to assess motor speed.

DNA Collection and COMT Genotyping
DNA was extracted from saliva collected using DNA Genotek Oragene saliva collection kits (Ottawa, ON, Canada). Saliva samples were divided into 500-mL aliquots and sent to a core facility at the HLMCC for DNA extraction using a Qiagen Universal Biorobot system (Valencia, CA) with an RNA carrier. The COMT (Val158Met) genotype was determined using Taqman gene expression assays from Applied Biosystems (Foster City, CA) for rs4680.

Procedures
All procedures were approved by the institutional review boards at both study sites, and participants provided written informed consent. Potential participants were contacted by telephone or mail, informed of the current study, and invited to participate. Study materials were mailed and participants returned a signed copy of the consent form, saliva sample, and completed study questionnaires via mail. Cognitive performance was measured in person at HLMCC or MCC for all participants as part of the larger study on breast cancer and quality of life. For cancer survivors, cognitive performance was assessed approximately 6 months following the completion of treatment (mean (M)\(_{\text{RT}}\), 6.16 months; SD\(_{\text{RT}}\), 1.24 months; M\(_{\text{CT}}\), 6.64 months; SD\(_{\text{CT}}\), 2.07 months; \(P > .10\)).

Statistical Analyses
Consistent with the administration manuals, raw scores from the CVLT,\(^{22}\) WMS-III,\(^{23}\) and WAIS-III\(^{24}\) subtests were converted to age-corrected \(t\) scores. Raw scores from the COWA were converted to education-corrected \(t\) scores.\(^{26}\) Raw scores from the Color Trails Test\(^{25}\) and the Finger Oscillation Test\(^{27}\) were converted to age-corrected and education-corrected \(t\) scores. A composite overall cognition score was also created by average performance across the 5 individual domains. In all cases, higher scores indicate better performance.

Differences in age, education, and NART were examined using 3 (group: HC, RT, CT) \(\times\) 2 (COMT: Met, Val+) analyses of variance (ANOVAs). Variables that differed significantly between groups \((P < .05)\) were entered as covariates in later analyses. To examine mean-level differences in cognitive functioning, a series of 3 (group: HC, RT, CT) \(\times\) 2 (COMT: Met, Val+) ANOVAs were applied to data from each cognitive outcome, as well as for the composite measure of overall cognitive performance. COMT genotype was classified as COMT-Val+ carriers (Val+; Met/Val, Val/Val) or COMT-Met homozygote carriers. The data met assumptions for distributional normality and homogeneity of variances. To examine differences in rates of cognitive impairment, participants were categorized as impaired or unimpaired on individual domains based on being 1.5 SD below normative values.\(^{28-31}\) Logistic regression analyses were conducted to determine whether group, COMT genotype, and their interaction were related to rates of impairment. In addition, the number of impaired domains was compared using a 3 (group) \(\times\) 2 (COMT) ANOVA.

RESULTS
Sample Characteristics
Demographic characteristics are presented in Table 1. Three (group) \(\times\) 2 (COMT) ANOVAs on age, years of education, and NART scores indicated that the groups were significantly different in age, with the CT group being younger.
being younger than the other 2 groups ($P < .001$), who did not differ from one another. Consequently, age was used as a covariate in the analyses that follow. The 3 groups were similar in years of education and NART score. There was no main effect of COMT genotype or an interaction between group and genotype for age, years of education, or NART score. There were no statistically significant differences in the distribution of COMT genotype across the 3 groups ($\chi^2 [2] = 1.75; P > .05$). COMT genotype was in Hardy-Weinberg equilibrium for the groups as a whole ($\chi^2 [2] = 0.17$, as well as within the HC, RT, and CT groups ($\chi^2 [2] = 0.46, 1.04$, and 1.94, respectively). Clinically, persons treated with chemotherapy were more likely to have a more advanced stage of cancer at diagnosis ($\chi^2 [2] = 56.47; P < .001$) and were more likely to receive a mastectomy as the surgical option ($\chi^2 [1] = 11.35; P < .001$). There were no treatment group differences in current hormone therapy or postmenopausal status.

### Mean-Level Cognitive Performance

Means and standard deviations for the cognitive outcomes are shown in Table 2. Only COMT genotype was significantly related to composite cognitive performance, with COMT-Met carriers (mean, 52.01; standard error [SE], 0.65) outperforming COMT-Val carriers (mean, 49.72; SE, 0.37; $P = .002; d = 0.39$). The main effects of group and group $\times$ COMT genotype interaction were not statistically significant for the composite measure of cognitive performance.

The results of the mean-level comparisons for the individual domains of performance revealed that the effect of group was statistically significant for motor speed. Post hoc comparisons with Holm-Bonferroni correction indicated that the HC group (mean, 44.71; SE, 0.86) performed more poorly than the RT group (mean, 49.65; SE, 1.54; $P = .007; d = 0.41$) and the CT group (mean, 49.83; SE, 1.61; $P = .005; d = 0.41$), who did not differ from one another. For the main effect of COMT

### Table 1. Background Characteristics by Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>HC</th>
<th>RT</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>204</td>
<td>58</td>
<td>72</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>57.07</td>
<td>56.93</td>
<td>51.22</td>
</tr>
<tr>
<td>SD</td>
<td>9.52</td>
<td>9.01</td>
<td>8.63</td>
</tr>
<tr>
<td>Y of education</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>14.71</td>
<td>15.09</td>
<td>14.33</td>
</tr>
<tr>
<td>SD</td>
<td>2.50</td>
<td>2.49</td>
<td>2.57</td>
</tr>
<tr>
<td>NART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>110.77</td>
<td>112.98</td>
<td>111.65</td>
</tr>
<tr>
<td>SD</td>
<td>6.92</td>
<td>6.54</td>
<td>6.94</td>
</tr>
<tr>
<td>COMT genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Met/Met, no. (%)</td>
<td>51 (25.00)</td>
<td>17 (29.31)</td>
<td>14 (19.44)</td>
</tr>
<tr>
<td>Met/Val, no. (%)</td>
<td>103 (50.49)</td>
<td>27 (46.55)</td>
<td>34 (47.22)</td>
</tr>
<tr>
<td>Val/Val, no. (%)</td>
<td>50 (24.51)</td>
<td>14 (24.14)</td>
<td>24 (33.33)</td>
</tr>
<tr>
<td>Study site</td>
<td></td>
<td></td>
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<tr>
<td>HLMCC, no. (% within group)</td>
<td>121 (59.31)</td>
<td>36 (62.07)</td>
<td>50 (69.44)</td>
</tr>
<tr>
<td>MCC, no. (% within group)</td>
<td>83 (40.69)</td>
<td>22 (37.93)</td>
<td>22 (30.56)</td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0, no. (%)</td>
<td></td>
<td>14 (24.13)</td>
<td>2 (2.78)</td>
</tr>
<tr>
<td>I, no. (%)</td>
<td></td>
<td>42 (72.41)</td>
<td>24 (33.33)</td>
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<tr>
<td>II, no. (%)</td>
<td></td>
<td>2 (3.45)</td>
<td>46 (63.89)</td>
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<tr>
<td>Surgery type</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy, no. (%)</td>
<td>2 (3.44)</td>
<td>17 (24.29)</td>
<td></td>
</tr>
<tr>
<td>Current hormone therapy, no.</td>
<td></td>
<td>40 (68.97)</td>
<td>34 (47.22)</td>
</tr>
<tr>
<td>Postmenopausal status, no. %</td>
<td></td>
<td>40 (68.97)</td>
<td>40 (55.56)</td>
</tr>
</tbody>
</table>

HC indicates healthy control; RT, radiotherapy; CT, chemotherapy; SD, standard deviation; NART, National Adult Reading Test; COMT, catechol-O-methyltransferase; HLMCC, H. Lee Moffitt Cancer Center; MCC, Markey Cancer Center.
genotype, statistically significant differences were observed for attention (M_Met, 54.43, SE_Met, 0.79; M_Val+, 52.19, SE_Val+, 0.45; \( P = .015; d = 0.31 \)), verbal fluency (M_Met, 51.45, SE_Met, 1.35; M_Val+, 47.35, SE_Val+, 0.77; \( P = .009; d = 0.34 \)), and motor speed (M_Met, 49.76, SE_Met, 1.38; M_Val+, 46.37, SE_Val+, 0.78; \( P = .015; d = 0.27 \)), the latter effect was not statistically significant after correcting for multiple comparisons. In all cases, the COMT-Val+ carriers performed more poorly than did the COMT-Met homozygote carriers.

Finally, a statistically significant group \( \times \) COMT genotype interaction was seen for attention (\( P = .019 \)). Comparisons between the COMT alleles within each group revealed statistically significant genotype differences in favor of the COMT-Met carriers within the CT group (\( P < .001; d = 0.96 \)), but not in the HC or RT groups. Among COMT-Met carriers, the CT group outperformed the RT group (\( P = .029; d = 0.81 \)), and among COMT-Val carriers, the HC group outperformed the CT group (\( P = .049; d = 0.27 \)), although neither effect was significant after correcting for multiple comparisons. Across the 5 cognitive domains, the mean difference between COMT genotype groups was not statistically significant for the HC and RT groups (\( d = 0.14 \); 95% confidence interval \( [95\% \text{ CI}], -0.01 \) to 0.28 \( [d = 0.14] \); 95% CI, -0.12 to 0.39, respectively). However, the mean difference between genotypes across cognitive domains in the CT group was almost half a standard deviation (\( d = 0.46 \); 95% CI, 0.20-0.73), in favor of the COMT-Met carriers.

### Prevalence of Cognitive Impairment

The rates of impairment in the cognitive domains are shown in Table 3. What is clear from the table is that the impairment rates were very low. Mean-level comparisons of number of impaired domains did not reveal any statistically significant effects of group or COMT genotype. Similarly, despite the finding that the COMT-Val carriers who received chemotherapy appeared to have higher rates of impairment, none of the group \( \times \) COMT genotype interaction effects were statistically significant.

### DISCUSSION

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### DISCUSSION

The results of the present study indicated that 1) breast cancer survivors treated with radiation and/or
chemotherapy performed similarly on most tests of cognitive performance compared with women with no history of cancer; 2) COMT-Val carriers performed more poorly than COMT-Met homozygote carriers on tests of attention, verbal fluency, and motor speed; and 3) COMT-Val carriers treated with chemotherapy performed more poorly than women with no history of breast cancer on tests of attention. The results of this study are innovative in that they represent the first demonstration of a link between a risk factor for poorer cognitive performance, COMT genotype, and cognitive deficits associated with chemotherapy treatment for breast cancer.

The lack of statistically significant differences between the breast cancer survivors and healthy controls irrespective of genotype is surprising given that previous research has demonstrated cognitive deficits associated with breast cancer treatment. Moreover, the only group difference that was statistically significant was in favor of the RT and CT groups for motor speed. This finding was unexpected and should be treated with caution because chemotherapy treatment for cancer, especially with taxane-based therapies, is often associated with peripheral neuropathy. The relatively short interval in the present study between the end of treatment and the assessment of cognitive performance in the cancer survivors may have worked against observing substantial deficits in cognitive functioning among this group. The majority of studies that have reported statistically significant differences between cancer survivors and healthy controls have tested cognitive performance many years after the end of treatment.

The results indicating statistically significant differences in favor of the COMT-Met homozygote carriers in tests of attention, verbal fluency, and motor speed are in line with previous reports. Moreover, the specificity of these effects is consistent with the importance of the frontal lobes for attentional and executive functioning cognitive abilities, as well as the mechanism of action of COMT genotype on DA in the frontal lobes. However, a recent meta-analysis reported equivocal evidence for a relationship between the COMT polymorphism and cognitive performance. Specifically, they failed to observe significant effects of COMT genotype on measures of verbal fluency and Trailmaking, one of the components of the attention domain score. However, the meta-analytic results were from a variety of subject populations, including many individuals with schizophrenia.

The results of the present study also indicated that COMT genotype modified the presence of cognitive differences as a function of cancer treatment. The poorer performance on the domain of attention among COMT-Val carriers treated with chemotherapy, compared with healthy controls, is consistent with predictions based on the impact of chemotherapy on the frontal lobes of cancer survivors, as well as the role of DA in the functioning of these brain structures. However, this is not to say that cognitive deficits after treatment for cancer are necessarily a frontal lobe syndrome, because the existing meta-analyses have failed to observe any dominant pattern of deficits that could be associated with a particular brain region, and the neuroimaging evidence was based on 2 studies with small sample sizes. The tests used to assess the domain of complex cognition in the current study also appear to be heavily dependent on frontal lobe functioning; they did not produce a statistically significant interaction between COMT genotype and group status. However, the main effect of COMT genotype on this cognitive domain also was not statistically significant, and this may have mitigated against observing statistically significant variation as a function of group status.

Finally, results indicated that COMT-Met carriers treated with chemotherapy exhibited superior performance on tests of attention relative to COMT-Val carriers in the CT group and to COMT-Met carriers treated with radiation. The reason for this pattern of results is unclear. It does not appear to simply reflect the cognitive superiority of this group. For example, episodic memory performance, a domain largely unaffected by COMT genotype, did not differ between COMT-Met carriers treated with chemotherapy and the other groups. Perhaps the greater brain activation required for breast cancer survivors treated with chemotherapy to maintain cognitive abilities and the higher levels of DA associated with the COMT-Met genotype are the source of this superior performance. Further research, using larger samples of COMT-Met carriers, is necessary to replicate and extend the results observed here.

The results of the present study can be placed in the context of “personalized medicine,” whereby treatments for various diseases are tailored to the genetic characteristics of individuals. Our results suggest that persons who are COMT-Val carriers and have received chemotherapy as part of their treatment for breast cancer are more likely to exhibit poorer performance on attentional tasks relative to women not treated for cancer. Together with evidence from Ahles et al on poorer cognitive performance among cancer survivors with the ε4 allele of APOE, these results suggest that the presence of poorer
cognitive quality of life outcomes among cancer survivors may be related to genetic variation among individuals. The lack of overlap in the genotype/cognitive domain interactions seen here (ie, attention) and the impact on tests of memory and spatial ability reported by Ahles et al. The results suggest that multiple genetic polymorphisms may impact different cognitive abilities among cancer survivors.

Do the results observed here for COMT-Val carriers, as well as those reported for APOE-ε4 carriers, mean that these persons should not receive chemotherapy as part of their treatment for breast cancer for fear of negative repercussions on their long-term cognitive health? Among persons treated with chemotherapy, the average difference between the COMT-Met and Val carriers was almost half a standard deviation. The differences as a function of APOE genotype observed by Ahles et al were slightly smaller but still greater than 0.25 SD. It is unlikely that differences such as these will alter clinical practice for COMT-Val or APOE-ε4 carriers, but attention should be paid to the interaction of treatment and genetic predisposition in terms of long-term quality-of-life outcomes among cancer survivors.

Although the results of the present study are informative, a number of limitations should be acknowledged. First, the sample was composed primarily of white women. Thus, the extent to which the results observed here can be generalized to more diverse populations is unclear. Second, the sample sizes examined here, especially for some of the group by genotype pairs were small, and this limited statistical power to detect effects; also, several effects were no longer statistically significant after correcting for multiple comparisons. Moreover, the small sample sizes did not permit us to examine dose-response relationships among persons who were COMT-Val carriers in terms of the presence of 1 or 2 copies of the Val allele. The decision to compare COMT-Val carriers with COMT-Met homozygote carriers was made to ensure sufficiently powerful statistical comparisons. With that said, the sample sizes examined here were substantially larger than those reported by Ahles et al, the only other study to examine the relationship between genetic polymorphisms and cognitive performance among cancer survivors. Moreover, the current study also included a control group with no history of cancer, which represents another methodologic advantage over previous research. Third, there was no pretreatment assessment of cognitive performance for the breast cancer survivors; therefore, we were unable to determine whether the functioning observed in the current study differed from that prior to cancer treatment. Future studies that incorporate a pretreatment assessment of cognitive performance and follow participants longitudinally are necessary in order to understand the nature and course of cognitive deficits among persons treated for cancer. Finally, there was relatively low prevalence of cognitive impairment among individuals in the current study.

In summary, the data from the current study suggest that the COMT-Val allele conveys an added risk of poorer cognitive performance among women treated for breast cancer with chemotherapy. Research to identify not just the presence of cognitive deficits associated with treatment for cancer but also risk factors that modify the likelihood of observing these differences is necessary to be able to target the persons at greatest risk of impaired cognitive functioning. It is likely that genetic factors such as COMT and APOE genotype will continue to play an important role in our understanding of risk factors for poorer cognitive health among cancer survivors.

CONFLICT OF INTEREST DISCLOSURES
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REFERENCES


