Published in final edited form as:
Menopause. 2013 September ; 20(9): 905–913. doi:10.1097/GME.0b013e3182843eff.

Does lifetime exposure to hormones predict pretreatment cognitive function in women before adjuvant therapy for breast cancer?

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Abstract

Objective—Women with breast cancer have been found to have poorer cognitive function before the initiation of systemic adjuvant therapy than their age- and education-matched counterparts. The basis for this may partly include hormone exposure during the course of a woman's life.

Methods—We compared cognitive function between postmenopausal women with breast cancer before the initiation of systemic adjuvant therapy and healthy age- and education-matched postmenopausal women and examined whether factors related to lifetime exposure to hormones predicted cognitive function before therapy.

Results—We found that, compared with healthy women, women with breast cancer had poorer memory ($P = 0.05$) and attention ($P = 0.006$). Controlling for the covariates age and estimated verbal intelligence, we found that factors related to greater lifetime hormone exposure (oral contraceptive use, greater years since menopause, and longer duration of hormone therapy) predicted cognitive function (executive function, verbal learning and memory, attention, psychomotor efficiency, and visual sustained attention) in women with and without breast cancer but did not explain the differences in cognitive function observed at pretreatment in women with breast cancer.

Conclusions—Other factors may explain the poorer pretreatment cognitive function in women with breast cancer, including persistent effects of surgical operation and anesthesia, sleep problems, and tumor-related factors. Additional studies are needed to explicate the basis of poorer pretherapy cognitive function in this population.

Keywords

Breast cancer; Cognitive function; Pretreatment; Adjuvant therapy; Hormone exposure

Changes in cognitive function in women with breast cancer are frequently attributed to adjuvant therapy.[1–3] The basis for these changes is likely to be multifactorial and is not completely understood. Moreover, results of longitudinal studies that include pretreatment

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Financial disclosure/conflicts of interest: S.L.B. reports consultancies for Noven Pharmaceuticals medical advisory board and Shionogi Inc. All other authors report no conflicts of interest.

cognitive assessments indicate that, before the start of adjuvant therapy, some women with breast cancer perform more poorly in cognitive measures than their healthy counterparts, suggesting that other factors influence pretreatment cognition.[3–6]

Multiple factors may predict pretreatment cognitive function in women with breast cancer, including their lifetime exposure to hormones.[7] Substantial biological evidence indicates that estrogen has a positive influence on brain functioning, although, clinically, evidence for a relationship between estrogen and cognitive function is conflicting.[8,9] The basis for this conflicting evidence may partly reflect a failure to take into account estrogen exposure factors during the course of a woman's life. The influence of estrogen on the brain seems to begin prenatally and persists throughout a woman's life.[10] Endogenous factors (such as parity, age at menarche, and menopause or, collectively, the number of reproductive years) and exogenous factors (such as oral contraceptive use and hormone therapy [HT] use) all contribute to a woman's lifetime exposure to hormones. Cognitive benefits of estrogen exposure may be specific for certain domains of cognitive function. Results of several studies suggest that greater lifetime exposure to estrogen is associated with better verbal memory in healthy women.[11,12] Others have found that lifetime estrogen exposure is associated with better global cognitive function,[13,14] psychomotor efficiency, concentration,[15] and verbal attention[14] in women.

Although estrogen exposure seems to have cognitive benefits for women, exposure to hormones, such as estrogen, also places them at greater risk for breast cancer.[16] However, a closer examination of specific factors that influence estrogen exposure during the course of a woman's life may reveal that individual estrogen exposure factors have differential effects on cognitive function. Examining the influence of the differential effects of estrogen exposure on cognitive function may help to explain pretreatment cognitive function in women with breast cancer. Thus, we examined cognitive function in women with breast cancer before their initiation of systemic adjuvant therapy and compared them with healthy women to determine whether factors related to a lifetime exposure to hormones were associated with poorer cognitive function before therapy. We hypothesized that factors associated with less estrogen exposure (shorter reproductive life and parity) are associated with poorer cognitive function, particularly verbal memory, in women with breast cancer compared with healthy women and, conversely, factors associated with greater estrogen exposure (oral contraceptive use and HT use) are associated with better cognitive function, particularly verbal memory, in women with breast cancer.

METHODS

We analyzed pretreatment data from the Anastrozole Use in Menopausal Women (AIM) study (R01 CA107408), a longitudinal cohort investigation of cognitive function in women with early-stage breast cancer who were matched with healthy women. Cognitive function was assessed after surgical operation, before adjuvant therapy initiation (pretreatment), 6 and 12 months after therapy initiation, and at comparable time points in the control group.

Participants

Breast cancer patients (n = 264) were recruited from the Comprehensive Breast Care Program of the University of Pittsburgh Cancer Institute and the University of Pittsburgh Medical Center Cancer Centers and included postmenopausal women who were eligible to receive HT with or without chemotherapy. Control participants (n = 95) were healthy postmenopausal women matched with treatment participants on age and years of education, recruited via random digit dialing. Participants were not older than 75 years, were able to speak and read English, and had at least 8 years of education. Women were ineligible if they reported hospitalization for psychiatric illness within 2 years before study enrollment or had

a history of neurologic disease or cancer. Institutional Review Board approval was obtained. All participants provided an informed consent form.

Measures

Cognitive function was evaluated with a psychometrically sound battery of measures assessing multiple cognitive domains. Measures in the battery were selected based on demonstrated sensitivity to cognitive changes[2,17] in this population. The assessment battery was administered and scored by project nurses trained by a clinical neuropsychologist.

Our neuropsychological battery is composed of 13 measures, with some measures yielding multiple scores. Owing to the large number of measures in our study battery, we used a data reduction technique to decrease the risk of type I error. Exploratory factor analysis with principal component extraction and orthogonal rotation was applied to 29 scores derived from individual cognitive measures to reduce dimensionality and to cluster individual cognitive measures into domains. Six factors were derived from this exploratory factor analysis, accounting for almost 60% of the total item variance. Individual measures with the highest loadings (>0.400) were included in each domain. The six factors and the measures composing each factor that best characterized the domains evaluated by our cognitive function battery were labeled: visual learning and memory (Rey Complex Figure Test[18] and Cambridge Neuropsychological Test Automated Battery [CANTAB] Paired Associate Learning Test[19]), executive function (Delis Kaplan Color Word Interference and Verbal Fluency Tests[20] and Trail Making Test-B[21]), verbal learning and memory (Rivermead Behavioral Memory Test Story Recall[22] and Rey Auditory Verbal Learning Test[23]), attention (CANTAB Stockings of Cambridge and Spatial Working Memory Tests[19] and Digit Vigilance Test[24]), psychomotor efficiency (Grooved Pegboard[24] and Digit Symbol Substitution Test[25]), and visual sustained attention (CANTAB Rapid Visual Information Processing mean latency and total hits[19]). The sign or direction of several measures was reversed (eg, timed tests, counts of errors) so that higher mean scores were indicative of better cognitive performance. Cognitive function composites were derived as a mean of the identified individual measures *Z*-score–transformed relative to the baseline values of healthy control participants.

During pretreatment evaluation, we obtained data from medical records and participants' self-reports about factors related to lifetime exposure to hormones, including pregnancy and menopause history, duration of reproductive life (age at menopause minus age at menarche), oral contraceptive use, HT use, and history of oophorectomy. We also examined whether other factors commonly associated with cognitive function contributed to pretreatment performance, including age, estimated verbal intelligence (National Adult Reading Test—Revised),[26] depressive symptoms (Beck Depression Inventory-II),[27] anxiety (Profile of Mood States tension/anxiety subscale), fatigue (Profile of Mood States fatigue/inertia subscale),[28] and antidepressant and antianxiety medication use.

Data analysis

Descriptive and exploratory analyses were performed initially to characterize the groups (women with early-stage breast cancer, healthy controls, and the overall combined sample) and to identify any data anomalies that may invalidate the planned analyses. Measures of central tendency and dispersion were computed for continuous variables; frequencies and percentages were computed for categorical variables. Groups were compared on cognitive function factors, variables related to lifetime hormone exposure, and categorical descriptors. Continuous variables were compared using *F* tests based on analysis of variance (or Kruskal-Wallis test if data were severely nonnormally distributed), whereas categorical variables were compared using χ^2 tests of independence (or Fisher's exact tests if sparse

cells existed). Correlational analyses were also conducted to examine the associations among cognitive function factors, variables related to lifetime hormone exposure, and categorical descriptors. Of the covariates considered, only age and estimated verbal intelligence were correlated with cognitive factors; thus, partial correlations were computed, controlling for these factors.

Regression analyses with backward elimination were performed for each cognitive function composite to explore potential predictor variables and associated covariates (age and estimated verbal intelligence) identified from bivariate correlational analyses, using a screening criterion of $P < 0.20$. For each of these regression analyses, standardized regression coefficients and their corresponding P values are reported. For two-sided hypothesis testing when identifying predictor variables, the level of statistical significance was set to 0.05.

RESULTS

We enrolled 359 women: 264 women with breast cancer and 95 healthy women (control group). The two groups differed slightly on age ($P = 0.018$), with our breast cancer group being, on average, 1.76 years older than our control group (Table 1). The control group also had a higher estimated verbal intelligence than the breast cancer group ($P = 0.001$, mean difference, 3.64). The groups did not differ on years of education, depressive symptoms, anxiety, fatigue, or antidepressant or antianxiety medication use.

We also examined between-group differences in each of the factors related to lifetime exposure to hormones. The groups differed only on two of the factors related to oral contraceptive use. Controls used oral contraceptives for a longer duration of time (mean, 4.95 y) compared with the breast cancer group (mean, 3.58 y; $P = 0.03$), whereas the duration of time since oral contraceptive use was greater for the breast cancer group (mean, 42.52 y) than for controls (mean, 36.35 y; $P = 0.003$).

When we compared cognitive function between women with breast cancer at pretreatment and controls, we found that women with breast cancer performed more poorly than controls in the domains of verbal learning and memory ($F = 2.94$, $df = 2$, $P = 0.05$) and attention ($F = 5.28$, $df = 2$, $P = 0.006$).

Cognitive function and factors related to less estrogen exposure

A summary of the descriptive characteristics of the hormone exposure factors is provided in Table 2. Controlling for the covariates age and estimated verbal intelligence, partial correlations between each of the cognitive and hormone exposure factors for which there was a correlation at a maximal level of $P < 0.20$ were computed for the overall, breast cancer, and control samples (Table 3). A similar pattern of significant correlations was observed for the overall and breast cancer samples, and the strength of these associations ranged from $P < 0.05$ to $P < 0.01$. The number of years since oral contraceptive use was negatively correlated with all six of the cognitive factors in the overall and breast cancer samples, and years since menopause was negatively correlated with all six cognitive factors in the overall sample and with five factors in the breast cancer sample. The only cognitive factor that was not significantly correlated with years since menopause was verbal learning and memory. Past oral contraceptive use was positively correlated with the cognitive factors executive function, verbal learning and memory, attention, and visual sustained attention in the overall sample, and with those same factors plus visual learning and memory in the breast cancer sample. Hormone exposure factors related to the number of pregnancies correlated negatively with executive function, psychomotor efficiency, and visual sustained attention in the overall sample, and with executive function and psychomotor efficiency in

the breast cancer group. Years since oophorectomy correlated negatively with visual learning and memory, executive function, and psychomotor efficiency in the overall and breast cancer groups. These same cognitive factors correlated negatively with ever having an oophorectomy in the breast cancer group.

Most significant correlations between cognitive function and hormone exposure factors for the control group were in the same direction as was observed in the overall and breast cancer groups, and the strength of the associations was within the same range. Attention correlated with two hormonal exposure factors: number of pregnancies and years of HT. Verbal learning and memory correlated negatively with the number of pregnancies, whereas psychomotor efficiency correlated positively with oral contraceptive use and negatively with years since oral contraceptive use. Only the number of pregnancies correlated significantly with more than one cognitive factor (attention, sustained attention, and verbal learning and memory) in the control group.

Regression analyses, controlling for the covariates age and estimated verbal intelligence, were performed for instances where there were correlations ($P < 0.20$) between factors related to lifetime exposure to hormones and cognitive factors for the overall, breast cancer, and control samples (Table 4). Hormone exposure factors related to oral contraceptive use, parity, HT use, menopause, and oophorectomy predicted cognitive function in one or more of the study groups; the magnitude of these effects was generally small to moderate. A history of oral contraceptive use predicted better verbal learning and memory and sustained attention in the overall group ($\beta = 0.154$ and $\beta = 0.138$, respectively) and the breast cancer group ($\beta = 0.147$ and $\beta = 0.139$, respectively), and was a marginally significant predictor of better attention in the overall sample ($\beta = 0.110$). More time since oral contraceptive use predicted poorer attention in the breast cancer group ($\beta = -0.144$) and poorer verbal learning and memory ($\beta = -0.206$) and sustained attention ($\beta = -0.201$) in the control group. Greater number of pregnancies predicted poorer psychomotor efficiency in the breast cancer group ($\beta = -0.123$). Longer duration of HT use predicted poorer attention ($\beta = -0.123$) and sustained attention ($\beta = -0.140$) in the overall sample, poorer sustained attention in the breast cancer group ($\beta = -0.153$), and poorer attention in the control group ($\beta = -0.339$). Greater number of years since menopause was a marginally significant predictor of poorer executive function in the overall sample ($\beta = -0.102$) and in the breast cancer sample ($\beta = -0.111$), but predicted better visual learning and memory for the breast cancer sample ($\beta = 0.227$). Finally, greater years since oophorectomy predicted poorer psychomotor efficiency in the overall sample ($\beta = -0.111$).

DISCUSSION

Our findings indicate that, before beginning adjuvant therapy, postmenopausal women with breast cancer have poorer cognitive function than age- and education-matched healthy postmenopausal women. These results are similar to other studies that reported poorer pretreatment cognitive function in women with breast cancer.[3–6] Our results also indicate that factors related to lifetime hormone exposure influence cognitive function in postmenopausal women. However, the influence of these hormone exposure factors on cognitive function did not differ between healthy postmenopausal women and postmenopausal women with breast cancer before the initiation of systemic adjuvant therapy. Therefore, these results do not explain the poorer pretreatment cognitive function observed in postmenopausal women with breast cancer.

It seems reasonable to speculate that lifetime hormone exposure would be related to cognitive function.[15] The influences of sex steroids on cognitive function are well documented; they begin prenatally and seem to persist throughout life.[8,9] We first

hypothesized that factors associated with less estrogen exposure (shorter reproductive life and parity) are associated with poorer cognitive function, particularly verbal memory, in women with breast cancer compared with healthy women. In general, our findings support the hypothesis that factors associated with less estrogen exposure predict poorer cognitive function, although these hormone exposure factors did not predict poorer verbal memory as we postulated. Furthermore, these findings were not limited to our breast cancer group.

We found that greater number of pregnancies predicted poorer psychomotor efficiency in the overall sample. Others have found a significant negative relationship between the number of pregnancies and cognitive function. McLay et al[29] found that, compared with parous women, nulliparous women had better cognitive function, as measured by the Mini Mental State Examination ($\beta = -0.83$, $P = 0.02$). Sobow and Kloszewska[30] found that greater number of pregnancies was associated with a younger age of onset of Alzheimer's disease ($r = -0.065$, $P < 0.01$).

It is not clear why we did not see a significant relationship between the number of pregnancies and cognitive function in our breast cancer group or control group. There was no difference in the number of pregnancies between study groups. It is possible that this variable was highly correlated with other variables in the regression model such that it became nonsignificant when considered jointly with the other variables.

When we computed partial correlations between the duration of reproductive life and cognitive factors, we did not find any significant relationships; thus, this predictor was not entered into the regression models for further evaluation. However, we found that greater number of years since menopause met our screening criteria and was found to be a marginally significant predictor of poorer executive function in the overall and breast cancer groups, compared with better visual learning and memory in the breast cancer group. In addition, greater number of years since oophorectomy was related to poorer psychomotor efficiency in our overall sample. It is not clear why we observed divergent findings related to time since menopause and visual learning and memory versus executive function. Ryan et al[15] also found that younger age at menopause ($P = 0.05$) was associated with poorer executive function in 996 healthy postmenopausal women. They found no relationship between age at menopause and visual learning and memory or any other cognitive domain.

We also hypothesized that factors associated with greater estrogen exposure (oral contraceptive use and HT use) would be associated with better cognitive function, particularly verbal memory, in women with breast cancer. Our findings related to this hypothesis are conflicting. We did find that factors related to oral contraceptive use predicted better verbal memory and attention, but these findings were not limited to the breast cancer group. Interestingly, we found that factors related to HT use predicted poorer attention; again, these findings were not limited to the breast cancer group.

We found that a history of oral contraceptive use predicted better verbal memory and attention in the overall and breast cancer groups. Greater years since oral contraceptive use predicted poorer verbal learning and memory in the control group, and poorer attention in both the control group and the breast cancer group, suggesting that exposure to exogenous estrogen with oral contraceptive use may benefit verbal memory and attention later in a woman's life. There have been previous studies of cognitive function with oral contraceptive use, although these studies were conducted in samples of women who were current oral contraceptive users. Silber et al[31] and Grinspoon et al[32] found that current oral contraceptive use was not related to cognitive function. Mordecai et al[33] compared verbal memory between young women who were naturally cycling (n = 16) and young women who were current oral contraceptive users (n = 20) and found no changes in verbal memory in the

naturally cycling women. However, better verbal memory was observed during the active phase of oral contraceptive use ($P < 0.05$) among women who were current users, and verbal learning and memory was better during the active phase than the inactive phase ($P < 0.0001$).

The synthetic estrogen used in oral contraceptives has not changed over time; however, the progestin formulations used in oral contraceptives have changed, and earlier preparations are different from progestins in current use. We did not have data on the type of oral contraceptive preparation that the women in our study had received in the past and, thus, were not able to examine the potential differential effects of the types of oral contraceptive preparations on cognitive function.

Interestingly, we observed that a longer duration of exposure to another form of exogenous estrogen (HT) predicted poorer attention in all of our study groups. Shumaker et al[34] found no cognitive benefit with HT after a large randomized controlled trial; in fact, their findings also suggest that HT may be detrimental to cognitive function. However, results of several observational studies point to a beneficial role for HT in cognitive function[35] among younger women. The basis for this contradictory evidence may be a consequence of methodological differences across studies. The study conducted by Shumaker et al[34] included women who were at least 65 years of age, older than the mean age of women beginning HT and older than the mean age of women in many observational studies. There is speculation that the cognitive benefits of HT may be best derived when it is taken during the menopausal transition or in the early years of menopause.[21,22]

Differences in age at the time of exogenous estrogen exposure may also explain the fact that past oral contraceptive use was related to better cognitive function in our study, but longer duration of HT use was related to poorer cognitive function later in life. Studies have demonstrated that there is an increased risk of ischemic stroke with HT.[36] There is also an increased risk of stroke with oral contraceptive use, particularly in smokers.[37,38] Ethinyl estradiol (EE) used in oral contraceptive preparations is very different from estradiol. Similarly, conjugated equine estrogens used in some HT preparations are also very different from EE and estradiol. Both EE and conjugated equine estrogens increase the risk for stroke and venous thromboembolism, whereas transdermal estradiol or endogenous estradiol of ovarian origin does not increase the risk for stroke. Women with a documented history of stroke were excluded from participation in our study. However, it is possible that women in our study did experience undetected thrombogenic events and that women exposed to exogenous estrogen in the form of an oral contraceptive at a younger age were more resistant to these events than women exposed to exogenous estrogen with HT use at an older age.

Our findings lend support to the theory that greater lifetime hormone exposure is related to better cognitive function. However, the fundamental question about the basis for poorer pretreatment cognitive function in women with breast cancer remains. The basis for poorer pretreatment cognitive function is probably multifactorial and may include persistent effects of surgical operation and anesthesia, mood, sleep problems, concomitant medications, and tumor-related factors.[7] Previous investigators have examined factors that may influence cognitive function before adjuvant therapy. Wefel et al[5] found that, although not significant, women who were postmenopausal, had no prior HT use, and have had lumpectomy/mastectomy were nearly twice as likely to be cognitively impaired compared with women without these characteristics. However, Ahles et al[4] found that, compared with women who exhibited normal cognitive performance, women categorized as exhibiting “lower-than-expected cognitive performance” did not differ in age, education, menstrual status, surgical

operation type, anesthesia duration, HT use, thyroid function, complete blood count, platelet count, vitamin B_{12} level, and folate level.

Results of our study and those of others suggest that neither depression nor anxiety explains the poorer pretreatment cognitive function observed in women with breast cancer. Sleep problems may exist in women with breast cancer at pretreatment, a time when they are still adjusting to their cancer diagnosis and anticipating therapy. Data suggest that sleep problems are associated with poorer cognitive function in other populations[39–41]; however, these relationships have not been examined in women with breast cancer.

This study has some limitations; thus, caution must be exercised in interpreting these findings. Medical record data were used to acquire some information related to estrogen exposure factors; thus, the accuracy of this information cannot be assured, and we did not have complete information on the specific types of oral contraceptives or HT preparations taken by women. The breast cancer and control groups differed with respect to age and estimated verbal intelligence. However, the mean difference in age and estimated intelligence was 1.76 years and 3.64, respectively, and these are not probably clinically meaningful differences. Moreover, we controlled for age and estimated verbal intelligence in our analyses. Finally, the size of our control group was smaller than that of the breast cancer and overall groups. This may explain the fact that there were fewer significant correlations between cognitive function and hormone exposure factors in the control group. Most of the correlations observed in the control group were in the same direction as what was observed in the overall and breast cancer groups, and the strength of the associations was within the same range.

The strengths of this study include the use of a comprehensive battery of neuropsychological measures that assessed multiple cognitive domains. Our sample was composed exclusively of postmenopausal women and included a matched control group of healthy women.

CONCLUSIONS

To our knowledge, this is the first study to examine whether factors related to lifetime exposure to estrogen predict poorer pretreatment cognitive function in women with breast cancer compared with healthy women. Recent evidence suggests that women who have poorer cognitive function before adjuvant therapy are at greater risk for deterioration with therapy.[6] Research is needed to explicate these factors as the basis for interventions to mitigate or compensate for poorer pretreatment cognitive function.

Acknowledgments

Funding/support: This research was supported by National Cancer Institute grant R01 CA 107408.

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TABLE 1

Participant characteristics

Characteristic	Breast cancer (n = 264)	Control (n = 95)	*P*
Age, mean (SD), y	60.64 (6.2)	58.88 (6.1)	0.018
Education, mean (SD), y	14.84 (2.9)	14.75 (2.9)	0.779
NART-R verbal IQ score, mean (SD)	108.09 (8.9)	111.73 (9.6)	0.001
BDI-II, mean (SD)	5.76 (6.3)	5.34 (6.1)	0.573
POMS tension/anxiety subscale, mean (SD)	7.92 (5.7)	6.78 (6.1)	0.109
POMS fatigue/inertia subscale, mean (SD)	5.56 (5.8)	5.36 (5.4)	0.779
Antidepressant medication use, n (%)	67 (22.5)	21 (17.2)	0.291
Antianxiety medication use, n (%)	31 (10.4)	7 (5.7)	0.188

NART-R, National Adult Reading Test—Revised; BDI-II, Beck Depression Inventory-II; POMS, Profile of Mood States.

TABLE 2

Descriptive characteristics of predictors

	Breast cancer (n = 264)	Control (n = 95)	Overall (n = 359)
Hormone exposure factors			
Number of pregnancies, mean (SD)	2.28 (1.6)	2.44 (1.6)	2.32 (1.6)
Natural menopause, n (%)	217 (84.1)	81 (88)	298 (85.1)
Years since menopause (natural or surgical), mean (SD)	11.86 (7.5)	10.13 (7.2)	11.41 (7.4)
Reproductive life, mean (SD), y	37.18 (4.6)	36.68 (4.6)	37.05 (4.6)
Ever used oral contraceptive, n (%)	169 (64.3)	73 (76.8)	242 (67.6)
Years of oral contraceptive use, mean (SD)[a]	3.45 (4.9)	4.95 (5.8)	3.86 (5.1)
Years since oral contraceptive use, mean (SD)[a]	42.47 (17.8)	36.34 (16.1)	40.78 (17.5)
Ever used hormone therapy, n (%)	140 (53.2)	46 (48.4)	186 (52.0)
Years of hormone therapy, mean (SD)	3.24 (5.2)	2.30 (4.2)	2.97 (4.9)
Years since hormone therapy, mean (SD)	31.68 (28.2)	33.47 (26.4)	32.16 (27.7)
Ever had oophorectomy, n (%)	56 (21.3)	17 (17.9)	73 (20.4)
Years since oophorectomy, mean (SD)	3.41 (8.1)	2.82 (8.2)	3.25 (8.1)
Other predictors			
Age, mean (SD)[a]	60.64 (6.2)	58.88 (6.1)	60.17 (6.2)
NART verbal IQ score, mean (SD)[a]	108.09 (8.9)	111.73 (9.6)	109.11 (9.3)
BDI-II total, mean (SD)	5.76 (6.3)	5.34 (6.1)	5.65 (6.2)
POMS tension/anxiety subscale, mean (SD)	7.92 (5.7)	6.78 (6.1)	7.61 (5.8)
POMS fatigue/inertia subscale, mean (SD)	5.56 (5.8)	5.36 (5.4)	5.50 (5.7)

NART, National Adult Reading Test; BDI-II, Beck Depression Inventory-II; POMS, Profile of Mood States.

[a] $P < 0.05$.

TABLE 3

r values for lifetime estrogen exposure factors and cognitive factors for the overall, breast cancer, and control groups, controlling for age and estimated verbal intelligence

Hormone exposure factor predictors	Visual learning and memory	Executive function	Verbal learning and memory	Attention	Psychomotor efficiency	Visual sustained attention
Number of pregnancies						
Overall	0.068	−0.024	0.158[a]	0.068	−0.103	−0.008
Breast cancer	−0.019	0.035	−0.194	−0.189	−0.159	−0.146
Control	0.034	−0.031	0.062	0.010	−0.119[a]	−0.043
Natural menopause						
Overall	0.121	0.061	−0.048	0.018	0.011	0.033
Breast cancer	−0.108	0.078	−0.020	−0.040	−0.037	0.036
Control	0.052	0.066	−0.038	0.005	0.001	0.034
Years since menopause (natural or surgical)						
Overall	−0.144[a]	−0.175[b]	−0.001	−0.033	−0.141[a]	−0.058
Breast cancer	0.077	−0.172	−0.089	−0.033	0.008	−0.155
Control	−0.067	−0.160[b]	−0.028	−0.032	−0.091	−0.086
Oophorectomy (yes/no)						
Overall	−0.155[a]	−0.110	−0.026	−0.008	−0.121	−0.001
Breast cancer	0.084	−0.045	0.096	0.000	0.013	0.149
Control	−0.082	−0.093	0.007	−0.007	−0.088	0.034
Years since oophorectomy						
Overall	−0.122	−0.101	−0.009	0.060	−0.105	−0.022
Breast cancer	0.034	−0.040	0.021	0.009	−0.118	0.079
Control	−0.074	−0.080	−0.001	0.045	−0.107	0.003
Reproductive life						
Overall	0.130	0.112	−0.012	0.035	0.136	0.005
Breast cancer	−0.159	0.098	−0.038	0.000	−0.055	−0.077
Control	0.051	0.110	−0.024	0.018	0.081	−0.015
Oral contraceptive use (yes/no)						
Overall	0.051	0.121	0.149[a]	0.112	−0.095	0.084

Hormone exposure factor predictors	Visual learning and memory	Executive function	Verbal learning and memory	Attention	Psychomotor efficiency	Visual sustained attention
Breast cancer	−0.077	0.158	0.115	0.000	0.160	0.109
Control	0.009	0.127[a]	0.139[a]	0.086	−0.022	0.090
Years of oral contraceptive use						
Overall	0.022	0.071	0.026	−0.092	−0.102	−0.062
Breast cancer	0.078	0.155	0.174	0.118	0.130	0.143
Control	0.033	0.089	0.074	−0.026	−0.036	−0.008
Years since oral contraceptive use						
Overall	−0.093	−0.122	−0.111	−0.077	0.102	−0.065
Breast cancer	0.052	−0.164	−0.175	0.010	−0.173	−0.150
Control	−0.036	−0.124[a]	−0.129[a]	−0.059	0.023	−0.087
Hormone therapy use (yes/no)						
Overall	−0.026	−0.103	−0.007	−0.127	0.020	−0.148[a]
Breast cancer	−0.041	−0.003	0.149	−0.137	0.064	−0.036
Control	−0.027	−0.054	0.034	−0.134[a]	0.041	−0.117[a]
Years of hormone therapy use						
Overall	−0.005	−0.119	−0.110	−0.097	0.010	−0.150[a]
Breast cancer	−0.046	0.110	0.131	−0.327[b]	0.120	−0.055
Control	−0.008	−0.035	−0.057	−0.159[b]	0.042	−0.126[a]
Years since hormone therapy use						
Overall	0.014	0.097	0.013	0.124	−0.028	0.162[a]
Breast cancer	0.030	−0.066	−0.178	0.155	−0.074	0.005
Control	0.014	0.033	−0.035	0.137[a]	−0.049	0.122[a]

[a] $P < 0.05$.

[b] $P < 0.01$.

TABLE 4

Significant results of linear regression analysis using backward elimination[a] for hormone exposure factors, controlling for age and estimated verbal intelligence, for the overall, breast cancer, and control groups

	Visual learning and memory		Executive function		Verbal learning and memory		Attention		Psychomotor efficiency		Sustained attention	
	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
Number of pregnancies												
Overall									−0.123	0.020		
Breast cancer												
Control												
Years since menopause												
Overall			−0.102	0.053								
Breast cancer	0.227	0.001	−0.111	0.053								
Control												
Years since oophorectomy												
Overall									−0.111	0.032		
Breast cancer												
Control												
Oral contraceptive use (yes/no)												
Overall					0.154	0.003	0.110	0.052			0.138	0.011
Breast cancer					0.147	0.024					0.139	0.033
Control												
Years since oral contraceptive use												
Overall												
Breast cancer							−0.144	0.032				
Control					−0.206	0.045					−0.201	0.045
Duration of hormone therapy use												
Overall							−0.123	0.028			−0.140	0.009
Breast cancer											−0.153	0.017
Control							−0.339	0.001				

β refers to standardized β.

[a] All hormone exposure factors that were statistically significant at $P < 0.20$ were included in the first step. Then, one by one, predictors were eliminated up to $P < 1.0$.