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Research Report

Breast Cancer, Alzheimer's Disease, and *APOE4* Allele in the UK Biobank Cohort

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Abstract.
Background: Cognitive problems are common in breast cancer patients. The apolipoprotein E4 (*APOE4*) gene, a risk factor for Alzheimer's disease (AD), may be associated with cancer-related cognitive decline.
Objective: To further evaluate the effects of the *APOE4* allele, we studied a cohort of patients from the UK Biobank (UKB) who had breast cancer; some also had AD.
Methods: Our analysis included all subjects with invasive breast cancer. Single nucleotide polymorphism (SNP) data for rs 429358 and rs 7412 was used to determine *APOE* genotypes. Cognitive function as numeric memory was assessed with an online test (UKB data field 20240).
Results: We analyzed data from 2,876 women with breast cancer. Of the breast cancer subjects, 585 (20%) carried the *APOE4* allele. Numeric memory scores were significantly lower in *APOE4* carriers and *APOE4* homozygotes than non-carriers ($p = 0.046$). 34 breast cancer subjects (1.1%) had AD. There was no significant difference in survival among genotypes $\varepsilon 3/\varepsilon 3$, $\varepsilon 3/\varepsilon 4$, and $\varepsilon 4/\varepsilon 4$.
Conclusion: UKB data suggest that cognitive problems in women with breast cancer are, for the most part, mild, compared with other sequelae of the disease. AD, the worst cognitive problem, is relatively rare (1.1%) and, when it occurs, *APOE* genotype has little impact on survival.

Keywords: *APOE*, chemobrain, dementia, heterozygote

INTRODUCTION

Cognitive problems are common in breast cancer patients [1]. Not all have these problems, and they can be subtle in the 75% older than 60. Aging, too, is related to cognitive decline, and it can be difficult to separate the effects of getting old from the effects of chemotherapy and hormonal treatment.

Chemotherapy can cause muddled thinking patients call 'chemobrain' [2]. Tamoxifen can produce mental fogging that is difficult to distinguish from Alzheimer's disease (AD) but which clears when tamoxifen is withdrawn [3].

The *APOE* genotype accounts for most of the AD risk. There are three common alleles of the *APOE* gene: *APOE2*, *APOE3*, and *APOE4*. In the general U.S. population, the $\varepsilon 4$ allele prevalence is approximately 13%, about 2% being $\varepsilon 4$ homozygous (2% of the U.S. population), and 11% being heterozygous (22% of the US population). Possession of one $\varepsilon 4$ allele increases the risk of developing AD by 3 to 4-fold, and possession of two $\varepsilon 4$ alleles increases risk by 15-fold, as compared with the $\varepsilon 3/\varepsilon 3$ genotype, with a large part of the variation being related to early age of onset. Over 60% of patients with non-familial AD carry the $\varepsilon 4$ allele [4].

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The ε4 allele may be associated with cancer-related cognitive decline. In one study, older women with breast cancer who were treated with chemotherapy and were carriers of the *APOE4* allele were more likely to have cognitive problems than women without cancer who were also carriers of the *APOE4* allele [1].

To further evaluate the effects of the *APOE4* allele, we studied a cohort of patients from the UK Biobank (UKB) who had breast cancer; some also had AD.

METHODS

The UK Biobank is a large prospective observational study comprising approximately 500,000 men and women (N = 229,134 men, N = 273,402 women), more than 90% white, aged 40–69 years at enrollment. Participants were recruited from across 22 centers located throughout England, Wales, and Scotland between 2006 and 2010 and continue to be longitudinally followed for capture of subsequent health events [5]. This methodology is like that of the Framingham Heart Study [6], with the exception that the UKB program collects postmortem samples, which Framingham did not.

Our UK Biobank application was approved as UKB project 57245 (S.L., P.H.R.).

Our analysis included all subjects with invasive breast cancer. Cancer diagnoses were ascertained through linkage to national cancer registries in England, Wales, and Scotland. Invasive breast cancer was coded using the 10th Revision of the International Classification of Diseases. Alzheimer's disease was coded using the 10th Revision of the International Classification of Diseases. Death was ascertained via linkage to death registries. Complete follow-up was available through June 2020.

Single nucleotide polymorphism (SNP) data for rs429358 and rs7412 were used to determine *APOE* genotypes. Cognitive function as numeric memory was assessed with an online test (UKB data field 20240). Longest number correctly recalled during the numeric memory test was recorded, minimum score 2, maximum score 11. A value of –1 was assigned if the participant chose to abandon the test before completing the first round (Fig. 1).

We used the English Indices of Deprivation 2010 Index of multiple deprivation (UKB data field 26410) to correct for the effects of economic deprivation on numeric memory. The English Indices of Deprivation are measures of multiple deprivation at the small area

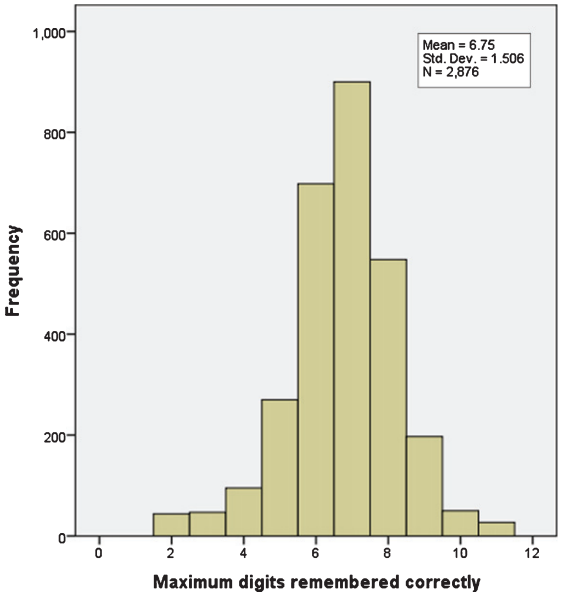

Fig. 1. Numeric memory scores from 2,876 women with breast cancer. There are 10 distinct values, maximum 11, minimum 2.

level [7]. The model of multiple deprivation which underpins the Indices of Deprivation 2010 is based on the idea of distinct domains of deprivation which can be recognized and measured separately. These domains are experienced by individuals living in an area. People may be counted in one or more of the domains, depending on the number of types of deprivation that they experience. Each domain represents a specific form of deprivation experienced by people and each can be measured individually using indicators. Seven distinct domains have been identified in the English Indices of Deprivation: Income Deprivation, Employment Deprivation, Health Deprivation and Disability, Education Skills and Training Deprivation, Barriers to Housing and Services, Living Environment Deprivation, and Crime.

We used the English Indices of Deprivation Education score 2010 (UKB data field 26414) in a separate analysis to correct only for the effects of education on numeric memory. This score measures the extent of deprivation in terms of education, skills and training in an area. The indicators are structured into two sub-domains: one relating to children and young people and one relating to adult skills. The two subdomains are designed to reflect the 'flow' and 'stock' of educational disadvantage within a region. Flow shows change during a period whereas stock indicates the quantity of education at a point in time. Seven indicators were used to calculate the score: 1)

Average points score of pupils taking English, Math and Science Key Stage 2 exams; 2) Average points score of pupils taking English, Math and Science Key Stage 3 exams; 3) Average capped points score of pupils taking Key Stage 4 (General Certificate of Secondary Education or equivalent) exams; 4) Proportion of young people not staying on in school or non-advanced education above age 16; 5) Secondary school absence rate, the proportion of authorized and unauthorized absences from secondary school; 6) Proportion of those aged under 21 not entering Higher Education; 7) Proportion of adults aged 25–54 with no or low qualifications.

RESULTS

We analyzed data from 2,876 women with breast cancer. The age at enrollment was 57 ± 7 (mean $\pm$ SD). The women were 98% white and British.

Numeric memory scores from 2,876 women with breast cancer are shown in Table 1. Data were analyzed by multivariate weighted least squares regression. Numeric memory score was dependent variable. *APOE4* genotype (homozygous ε4/ε4, ε4 carrier, ε4 non-carrier), English Indices of Deprivation score were independent variables weighted by age. *APOE4* carrier status had a significant effect on numeric memory score ($p = 0.046$). Women homozygous ε4/ε4 had the lowest score, ε4 carriers had an intermediate score, and ε4 non-carriers had the highest score. English Indices of Deprivation score significantly affected numeric memory score ($p = 0.005$) and was independent of the effect of *APOE4* carrier status.

A second analysis was done, substituting the English Indices of Deprivation Education score for the English Indices of Deprivation 2010 Index of multiple deprivation score. *APOE4* carrier status had a significant effect on numeric memory score ($p = 0.05$). Women homozygous ε4/ε4 had the lowest score, ε4 carriers had an intermediate score, ε4 non-carriers had the highest score. English Indices of Deprivation Education score significantly affected numeric memory score ($p < 0.001$) and was independent of the effect of *APOE4* carrier status.

Of the 2,876 breast cancer subjects, 34 (1.1%) had AD. Their age was 76 ± 4. We were able to determine *APOE* genotype in 31 of the subjects. 3 were missing rs7412 data. There was no significant difference in survival among genotypes ε3/ε3, ε3/ε4, and ε4/ε4 ($p = 0.258$, Fig. 2).

Table 1
Numeric memory scores from 2,876 women with breast cancer. Data were analyzed by multivariate weighted least squares regression. Numeric memory score was dependent variable. Genotype (homozygous ε4/ε4, ε4 carrier, ε4 non-carrier), English Indices of Deprivation 2010 Index of multiple deprivation score were independent variables weighted by age. *APOE4* carrier status had a significant effect on numeric memory score ($p = 0.046$). English Indices of Deprivation score had a significant effect on numeric memory score ($p = 0.005$) that was independent of the effect of *APOE4* carrier status. A second analysis was done, substituting the English Indices of Deprivation Education score for the English Indices of Deprivation 2010 Index of multiple deprivation score. *APOE4* carrier status had a significant effect on numeric memory score ($p = 0.05$). Women homozygous ε4/ε4 had the lowest score, ε4 carriers had an intermediate score, and ε4 non-carriers had the highest score. English Indices of Deprivation Education score significantly affected numeric memory score ($p < 0.001$) and was independent of the effect of *APOE4* carrier status

		Memory	Score
Genotype	N	Mean	SD
non-ε4 carrier	2,291	6.77	1.488
ε4 carrier	541	6.67	1.555
ε4/ε4 homozygote	44	6.57	1.784

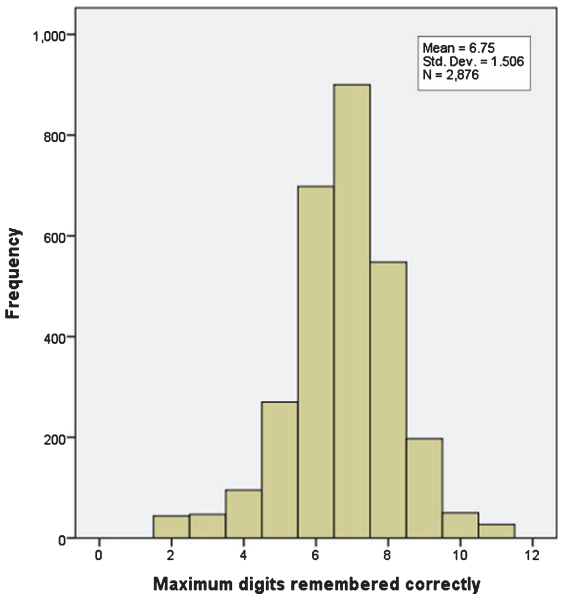

Fig. 2. Survival of 31 subjects with breast cancer and AD by *APOE* genotype. 12 subjects were ε3/ε3, 11 subjects were ε3/ε4, and 8 subjects were ε4/ε4. The survival difference was not significant ($p = 0.258$, log rank test).

DISCUSSION

Cancer survivors have difficulties with memory, attention, learning, and processing of information months or even years after completing treatment, and the *APOE4* allele is a prime suspect. An *APOE* mouse

model of cancer-related cognitive problems showed that the mice developed chemotherapy-related changes in spatial learning and memory as well as physical changes in brain regions involved in those functions [8].

Findings regarding the effects of *APOE* genotype on cognition in normal individuals have been inconsistent. It is difficult to substantiate whether cognitive deficits in *APOE4* carriers are related to prodromal dementia, the *prodromal hypothesis*, or a direct contribution of *APOE* genotype to individual differences, the *phenotype hypothesis*. Multiple studies suggest that both prodromal and phenotype factors might be implicated [9]. Young $\varepsilon 4$ carriers show a slight superiority in mental acuity as compared with $\varepsilon 3$ homozygotes. At some point in middle age or late middle age, $\varepsilon 4$ carriers start showing cognitive deficits as compared with $\varepsilon 3$ homozygotes [10].

In our UKB cohort, the small significant decline in numeric memory scores of women with breast cancer and the *APOE4* allele is consistent with a previous observation that older breast cancer patients with the $\varepsilon 4$ allele who received chemotherapy, with or without hormonal therapy, experience minor cognitive declines over time [1].

Dementia prevalence in the UK is 6.6% in women age 75–79 [11], considerably greater than the 1.1% we found in the breast cancer patients with AD. The UK Biobank cohort is not representative of the general population regarding several sociodemographic, physical, lifestyle, and health-related characteristics. UK Biobank participants generally live in less socioeconomically deprived areas; are less likely to be obese, to smoke, and to drink alcohol daily; and have fewer self-reported health conditions. All-cause mortality is approximately half that of the UK population, and total cancer incidence rates are approximately 10%–20% lower. However, valid assessment of exposure-disease relationships may be widely generalizable and do not require participants to be representative of the population at large [12].

The much lower incidence rate of AD (1.1%) in the UKB cohort of white women of high education and socioeconomic status supports the current lifestyle recommendations for the prevention of AD. Because we analyzed UK white women of high education and socioeconomic status (SES), age at first birth and overall nulliparity rate in this high SES cohort would be higher than age at first birth and nulliparity rates in a lower SES ethnically matched group of women. On a relative basis, the UKB cohort has followed lifestyle recommendations for the prevention of AD: a heart-healthy lifestyle, good diet, exercise, control of blood pressure and blood sugar, prevention of obesity. These AD prevention recommendations like avoiding obesity (and its pro-estrogenic effects) would not be expected to prevent breast cancer when counteracted by late first birth and nulliparity effects. Stem cells in the breast are differentiated by pregnancy hormones, thereby removing them as candidate cells for malignant transformation, although the effect is only seen at younger ages of first birth [13].

Weaknesses in our analysis:

- UKB does not identify which subjects received chemotherapy and/or hormonal therapy. If it did, we might have been able to demonstrate a larger effect on numeric memory scores.
- UKB does not have information about pathology or stage. Our study cohort is well-educated and of high SES. We assume that most of the women follow the mammogram recommendations in the UK. Pathological stage at case presentation would almost certainly be at least somewhat earlier than in a cohort with lower education and SES. Impoverished patients often present at quite late stages of breast cancer. Despite the comparatively early diagnosis in UKB subjects, a significant fraction would still have required chemotherapy or, based on hormone receptor status of tumor, hormonal treatment.
- $\varepsilon 3/\varepsilon 4$ and $\varepsilon 3/\varepsilon 2$ are fundamentally different. We had too few $\varepsilon 2$s to include statistical analysis of $\varepsilon 2$ carriers and non-carriers. A larger sample would be required.

The UKB data we present above suggest that cognitive problems in women with breast cancer are, for the most part, mild, compared with other sequelae of the disease. AD, the worst cognitive problem, is relatively rare (1.1%) and, when it occurs, *APOE* genotype has little impact on survival.

Mild cognitive changes can be quite upsetting to patients experiencing them. Brain training, computer games, yoga, and physical activity may improve cognitive function in these patients [14].

It will be important to learn why some people are more vulnerable to cancer-related cognitive impairment. No doubt genetics plays a major role, probably greater than stress or treatment modality.

Further studies of the biology may allow prediction of which patients will be affected and how best to manage them.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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