Effect of *APOE* polymorphisms, smoking status, and chemotherapy on cognition in breast cancer survivors

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Rationale

Many breast cancer survivors experience decline in cognitive function after treatment. Cognitive effect of chemotherapy may be modulated by genetics and cigarette smoking. The *APOE* gene has been associated to cognitive decline in brain cancer survivors and Alzheimer's disease.

Aim

To investigate the role of a common *APOE* polymorphism, smoking and treatment history on the cognitive performance among older, long-term breast cancer survivors.

Methods

• MSK Participants: 90 breast cancer cases enrolled 5-15 years post treatment who were either treated or not treated with chemotherapy, and 39 controls (Table 1, Figure 1)

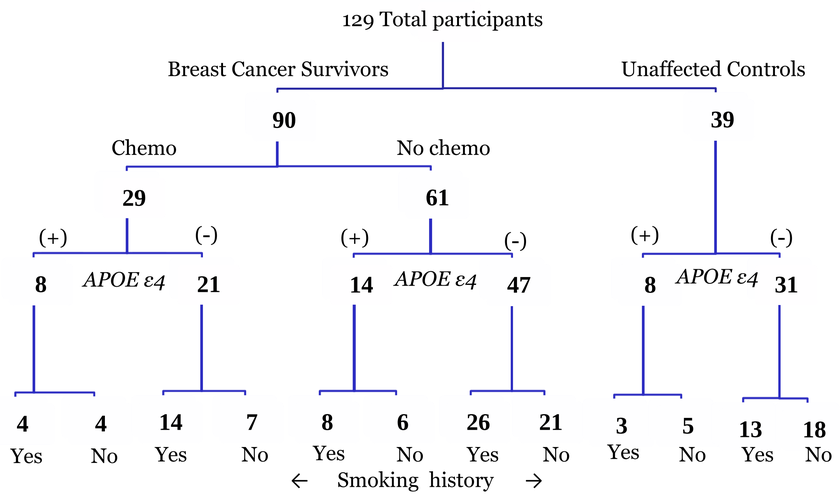
•All subjects completed standardized neuropsychological testing: Driving Scenes from the NAB for attention and executive function, Logical Memory I and II Weschler Memory Scale (W MS-4) Stories A & B for learning and memory

•All participants provided blood samples for *APOE* genotyping

• Information regarding smoking status, treatment, and demographics was obtained at enrollment

Table 1 and Figure 1: Demographic characteristics of study participants

	Chemotherapy (n=29)	No Chemotherapy (n=61)	Control (n=39)
Age: mean ± sd	73.5 ± 3.9	73.5 ± 5.5	73.6 ± 6.6
Smoking History			
Smoker	18	34	16
Nonsmoker	11	27	23
APOE4+ (n, %)	8 (27.6%)	14 (22.9%)	8 (20.5%)



Results

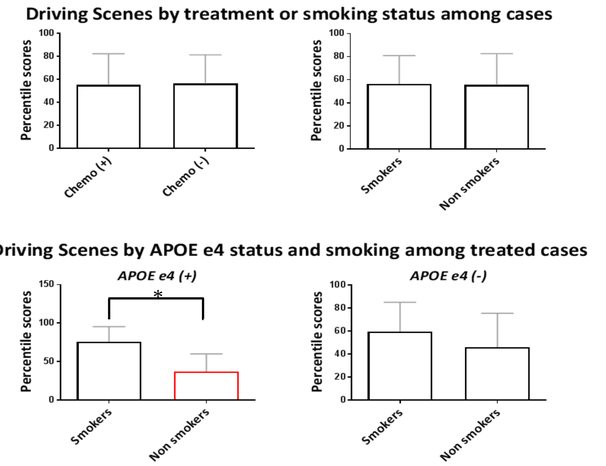


Figure 2: Standarized neuropsychological test scores according to exposure and genetics. Note the difference among chemotherapy treated patients that were *APOE ε4* (+), between smokers and non smokers (* p = 0.043). The *APOE ε4* (-), chemotherapy patients show no difference between smokers and no smokers. For both, attention and executive function and learning and memory tests

Summary

APOE ε4 carriers exposed to chemotherapy without a smoking history scored lower on attention and executive function, learning and memory tests; however, the effect of *APOE-ε4* was moderated if they had a history of smoking. This effect was not observed in non *APOE-ε4* carriers, nor was it observed among patients not exposed to chemotherapy

Conclusion

Our preliminary results, in a small number of participants, suggest that smoking may have a protective effect on cognitive function among *APOE ε4* (+) who were treated with chemotherapy. We hypothesize that nicotine may be compensating for a deficit in the activation of dopamine receptors (Figure 3)

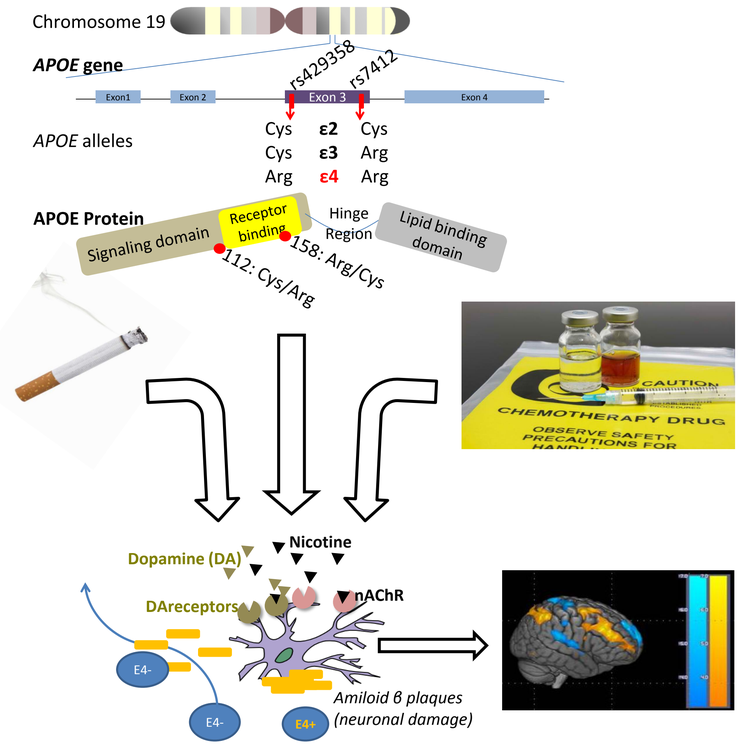


Figure 3: APOE, smoking, and chemotherapy in relation to cognitive decline. Top, *APOE* within chromosome 19. The "Epsilon" variants are determined by the combination of amino acids on residues 112 and 158, which overlap with the functional domains.

Bottom, APOE ε4(+) may increase amyloid deposition and oxidative damage, disrupt neuronal repair, and alter the regulation of lipids after brain injury. Nicotine binds to nicotine acetyl choline receptors (nAChr) and dopamine receptors and induces the release of dopamine, which has a beneficial effect on cognition. Thus, it is possible that in *APOE ε4* carriers who are smokers, the nicotine compensates for the defective APOE function.

Future steps

• Accrual is ongoing to meet the target (n = 480)

•Formal statistical analysis, controlling for covariates

•Analyses of other *APOE* polymorphisms

•Longitudinal analysis to assess trajectory, or evolution of cognitive capacity

Acknowledgements

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