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Mitochondrial DNA G10398A variant is not associated with breast cancer in African-American women

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Abstract

Mitochondria play important roles in cellular energy production, free radical generation and apoptosis. In a previous report in *Cancer Research*, the mitochondrial DNA (mtDNA) G10398A (Thr → Ala) polymorphism was associated with breast cancer risk in African-American women. Here, we seek to replicate the association by genotyping the G10398A polymorphism in three established population-based case-control studies of breast cancer in African-American women. The 10398A allele was not significantly associated with risk in any of the studies [San Francisco study (542 cases, 282 controls, odds ratio (OR) = 1.73; 95% confidence interval (CI): 0.87, 3.47, P = 0.12); Multiethnic Cohort (391 cases, 460 controls, OR = 1.08; 95% CI: 0.62, 1.86, P = 0.79); CARE/LIFE study (524 cases, 236 controls, OR = 0.81; 95% CI: 0.43, 1.52, P = 0.50)]. When pooling the data across the three studies (1456 cases and 978 controls), no significant association was observed with the 10398A allele (OR = 1.14; 95% CI: 0.80, 1.62, P = 0.47, P heterogeneity=0.30). In analysis of advanced breast cancer cases (n=674), there also was no significant association (OR = 1.18; 95% CI: 0.76, 1.82, P = 0.46). Our results do not support the hypothesis that the mtDNA G10398A polymorphism is a marker of breast cancer risk in African Americans as previously reported.

1. Introduction

Mitochondria play important roles in cellular energy production, free radical generation and apoptosis [1]. The mitochondrial DNA (mtDNA) G10398A polymorphism results in a nonconservative amino acid substitution (Thr → Ala) within the NADH dehydrogenase 3

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(ND3) subunit of complex I of the electron transport system, and this change is thought to result in increased oxidative stress [2]. Canter *et al* reported that the mtDNA 10398A genotype is associated with an increased risk of breast cancer in African-American women (OR = 1.6; 95% CI, 1.10, 2.31, $p = 0.013$) [3]. In the present analysis, we utilized data from established population-based breast cancer case-control studies (1456 cases and 978 controls) to test the association of mtDNA G10398A and breast cancer.

2. Material and methods

The first study from the San Francisco Bay area (SF) included African-American participants in a population-based case-control study [4,5] and African-American cases and controls enrolled at the Northern California site of the Breast Cancer Family Registry [6]. Invasive breast cancer cases were identified through the Greater San Francisco Bay area regional Surveillance, Epidemiology and End Results (SEER) cancer registry. The case-control study included cases aged 35 to 79 years and diagnosed between 1997 and 1999 and the family registry included cases aged <65 years and diagnosed between 1995 and 1998. Controls were identified through random digit dialing in the same region and were frequency-matched to cases in 5-year age groups. A total of 542 African-American cases and 282 African-American controls were available for the present analysis.

The second study was African-American breast cancer cases and controls nested within the Multiethnic Cohort Study (MEC) [7]. Beginning in 1994, blood samples were collected from incident breast cancer cases identified by cohort linkage to SEER registries, as well as a random sample of MEC participants, frequency-matched on age, to serve as controls for genetic analyses. For the present analysis, we included 391 invasive breast cancer cases aged 42 to 82 years and diagnosed up to December 2003 and 460 controls free of cancer up to December 2003.

The third study from Los Angeles was comprised of African-American invasive breast cancer cases and controls aged 35 to 64 years from the Los Angeles component of the Women's Contraceptive and Reproductive Experiences Study (CARE) [5] and invasive African-American breast cancer cases aged 20 to 49 years from a case-control study (the LIFE study) [8]. Incident cases were identified from the Los Angeles SEER registry (diagnosed between 1994 and 1998 in the CARE study and diagnosed between 2000 and 2003 in the LIFE study). Random digit dialing was used to identify controls from the same geographic area for CARE, and neighborhood controls were used for LIFE. For the present analysis, we included 524 invasive breast cancer cases and 236 controls. Details about these case-control studies including methods for identifying/selecting cases and controls and participation rates have been previously described [9,10].

The mtDNA G10398A variant was genotyped using TaqMan (Applied Biosystems, Foster City, CA); primers, probes, and assay conditions are available upon request. The genotyping success rate was 98.1%. Blinded repeat samples (~5% in each study) were included for quality control; genotype concordance was $\geq 99\%$.

Odds ratios (OR) and 95% confidence interval (CI) were estimated using unconditional logistic regression adjusting for age. Prior to pooling the data, tests of homogeneity of the ORs across the studies were conducted using a likelihood ratio test following the inclusion of an interaction term between genotype and study in the logistic model. All analyses were conducted in SAS 9.0 (SAS Institute, Cary, NC).

All subjects were previously enrolled under Institutional Review Board approved protocols at the Northern California Cancer Center, the University of Southern California, and the University of Hawaii.

3. Results and discussion

The frequency of the 10398A allele in control groups ranged from 4% to 7% and was comparable to frequencies reported in previous studies of African Americans [3,11,12]. The 10398A allele was not significantly associated with risk in any of the three studies. In the SF study, women with the 10398A allele were at a non-significantly increased risk compared to noncarriers (OR = 1.73; 95% CI: 0.87, 3.47, P = 0.12) (Table 1). The association was similar among advanced disease cases (OR = 1.75; 95% CI: 0.83, 3.71, P = 0.14). In the MEC and CARE/LIFE studies women with the 10398A allele were not at increased risk compared to women with the 10398G allele (MEC: OR = 1.08; 95% CI: 0.62, 1.86, P = 0.79; CARE/LIFE: OR = 0.81; 95% CI: 0.43, 1.52, P = 0.50). No evidence of heterogeneity for effects was noted across studies (P = 0.30). When pooling the data across the three studies (1456 cases and 978 controls), no significant association was observed with the 10398A allele (OR = 1.14; 95% CI: 0.80, 1.62, P = 0.47). Analyses among advanced cases (n=674) also did not reveal a significant association (OR = 1.18; 95% CI: 0.76, 1.82, P = 0.46).

The pooled data provided $\geq 96\%$ power (a two-sided test and using $\alpha=0.05$) to detect an OR of 1.6 [the reported OR in the previous study [3]] for a variant with 5–7% allele frequency.

The mtDNA G10398A variant has been implicated as having a role in reactive oxygen species production in neurodegenerative diseases and cancers [2,3,13]. A study in North Carolina found increased breast cancer risk associated with the mtDNA 10398A allele only among African Americans and not among Whites [3]. The authors suggested that interaction with unknown genetic and environmental risk factors may cause the discrepancy between ethnic groups. The differing results between our study and that study may also be explained by differences in risk modifiers that exist in diverse geographical areas (Southeastern US vs. California).

In summary, our results do not support the hypothesis that the mtDNA G10398A polymorphism is a marker of breast cancer risk in African Americans.

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Table 1

Associations of the mtDNA G10398A variant in African American breast cancer cases and controls and associations with breast cancer risk.

	SF		MEC		CARE/LIFE		ALL STUDIES		<i>P</i> ^{***}
	Co [*] (n=282) (%)	OR [†] (95%CI)	Ca [*] (n=391) (%)	Co [*] (n=460) (%)	Ca [*] (n=524) (%)	Co [*] (n=236) (%)	Ca [*] (n=1456) (%)	Co [*] (n=978) (%)	OR (95%CI) §
94.3)	266 (96.0)	1.00	355 (93.2)	427 (93.6)	479 (94.3)	219 (93.2)	1327 (93.5)	912 (94.2)	1.00
7.2)	11 (4.0)	1.73 (0.87, 3.47)	26 (6.8)	29 (6.4)	29 (5.7)	16 (6.8)	93 (6.6)	56 (5.8)	1.14 (0.80, 1.62)
		<i>P</i> = 0.12							<i>P</i> = 0.47
93.1)	266 (96.0)	1.00	104 (92.9)	427 (93.6)	243 (94.2)	219 (93.2)	630 (93.5)	912 (94.2)	1.00
6.9)	11 (4.0)	1.75 (0.83, 3.71)	8 (7.1)	26 (6.4)	15 (5.8)	16 (6.8)	44 (6.5)	56 (5.8)	1.18 (0.76, 1.82)
		<i>P</i> = 0.14							<i>P</i> = 0.46

ns. Numbers do not add up to total due to missing genotype data.

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