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Mitochondrial DNA G10398A Polymorphism and Invasive Breast Cancer in African-American Women

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To the Editor:

In the September 1, 2005 issue of Cancer Research, Canter et al. (1) describe an association between invasive breast cancer in African-American women and a mitochondrial DNA polymorphism (*10398A* allele) that alters the structure of complex I in the electron transport chain. The authors propose that this polymorphism increases free radical generation and local oxidative injury facilitating neoplastic transformation. We are investigating the possibility that a similar mechanism explains the increased incidence and severity of prostate cancer in African-American men as compared with other ethnic groups. Several large studies have reported a relationship between increased dietary antioxidants and decreased risk of prostate cancer. As pointed out by Canter et al., a major source of cellular reactive oxygen species is the mitochondrion, where electrons leak from the electron transport chain and reduce oxygen to superoxide anion, thus initiating free radical generation. Polymorphisms in the human mitochondrial genome have been used to elucidate phylogenetic relationships among ethnic groups and define mitochondrial haplotypes. As compared with other ethnic groups, African mitochondrial haplotypes exhibit tightly coupled oxidative phosphorylation which increases energy production, but increases production of superoxide radicals (2).

As part of a larger study examining polymorphisms in genes related to oxidative stress, we determined the mitochondrial macrohaplotype of 88 African-American men with organ-confined prostate cancer and 60 healthy African-American men in the same age group. Patients and controls were recruited at Baylor College of Medicine with assistance from the Baylor Prostate Specialized Programs of Research Excellence. At the 10398 polymorphic site, the *10398A* allele was present in 12 of 88 cancer patients (13.64%), but none of the 60 controls. The Sheehe corrected odds ratio of 19.8 (95% confidence interval, 2.5–155.4) suggests an increase in prostate cancer risk for African-American men who carry the *10398A* allele. The one-sided Fisher exact test yielded a *P* value of 0.0014, demonstrating a statistically significant difference in the frequency of the 10398A variant between cases and controls.

The mechanism of the adverse effect of the *10398A* allele is unknown; however, it is presumed to be increased free radical generation leading to somatic mutations. This hypothesis seems plausible based on experiments in which an oxidative phosphor-ylation inhibiting mutation in the mitochondrial gene for ATP synthase was introduced into PC3 prostate cancer cells and tested for tumor growth in nude mice. Mutant tumors were seven

times larger than wild-type tumors, and generated significantly more reactive oxygen species (3). Thus, in African-Americans, mitochondrial mutations and oxidative stress may play a role in the development of both breast and prostate cancers. We propose that the *10398A* allele may be more deleterious in African-Americans because African mitochondrial haplotypes are prone to generate more reactive oxygen species than mitochondria in other ethnic groups or because coexistent mutations in other mitochondrial or nuclear genes decrease cellular capacity to manage oxidative stress. From an evolutionary standpoint, prooxidant mutations may have been beneficial because they increased resistance to malaria, but might be deleterious later in life, following reproduction, via promotion of breast or prostate cancer.

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