

# UC Office of the President

## Recent Work

### Title

A promoter polymorphism in the CASP8 gene is not associated with cancer risk

### Permalink

<https://escholarship.org/uc/item/0m06g80z>

### Authors

Haiman, Christopher A.  
Garcia, Rachel R.  
Kolonel, Laurence N.  
et al.

### Publication Date

2008

### DOI

10.1038/ng0308-259

Peer reviewed

# A promoter polymorphism in the *CASP8* gene is not associated with cancer risk

## To the Editor:

A common missense variant (*D302H*) in the *CASP8* gene has been reported to be a common low-penetrance susceptibility allele for breast cancer<sup>1</sup>, highlighting the role of the immune system in this common cancer. More recently, Sun *et al.*<sup>2</sup> identified a 6-bp deletion polymorphism (–652 6N del) in the promoter of the *CASP8* gene that abolishes an Sp1 transcription factor binding site and is associated with decreased RNA expression in lymphocytes and lower caspase-8 and T lymphocyte apoptotic activity. This deletion variant was found to be associated with a ~25% reduced risk (per copy) of lung, esophageal, stomach, colorectal, breast and cervical cancer in a Chinese population (4,938 cases and 4,919 controls,  $P = 4.3 \times 10^{-16}$ )<sup>2</sup>. To further examine the hypothesis that this polymorphism is a susceptibility marker for multiple cancers, we genotyped 7,161 incident cases of breast, prostate or colorectal cancer and 6,266 controls drawn from multiple populations with different ancestral backgrounds.

Subjects for this report include those of three studies. The largest consists of a case-control study of breast (2,098 cases and 2,318 controls), prostate (2,825 cases and 2,548 controls) and colorectal cancer (1,139 cases and 4,631 controls) nested in the Multiethnic Cohort Study (MEC)<sup>3–5</sup>. The MEC is a prospective cohort study that includes over 215,000 men and women in Hawaii and California and is comprised predominantly of self-declared African Americans, Japanese Americans, Native Hawaiians, Latinos and European Americans who were between the ages of 45 and 75 years at enrollment (1993–1996)<sup>6</sup>. Incident cancers in the MEC are identified by cohort linkage to popula-

**Table 1 Association of the *CASP8*–652 6N ins/del variant with breast, colorectal and prostate cancer risk**

| Site              | Study and population | Number of cases/<br>controls | Minor allele frequency<br>in controls | OR (95% CI) <sup>a</sup>      |
|-------------------|----------------------|------------------------------|---------------------------------------|-------------------------------|
| Breast cancer     | <u>MEC</u>           |                              |                                       |                               |
|                   | African American     | 432/457                      | 0.53                                  | 1.04 (0.86–1.26)              |
|                   | Japanese American    | 560/567                      | 0.17                                  | 0.95 (0.76–1.19)              |
|                   | Native Hawaiian      | 148/295                      | 0.44                                  | 0.86 (0.65–1.14)              |
|                   | Latino               | 425/425                      | 0.36                                  | 0.92 (0.75–1.13)              |
|                   | European American    | 533/574                      | 0.47                                  | 0.97 (0.82–1.15)              |
|                   | <u>LABC</u>          |                              |                                       |                               |
|                   | Chinese American     | 263/376                      | 0.23                                  | 0.97 (0.75–1.25)              |
|                   | Japanese American    | 176/314                      | 0.17                                  | 1.03 (0.76–1.40)              |
|                   | Filipino American    | 304/297                      | 0.19                                  | 1.00 (0.76–1.32)              |
|                   | <u>All groups</u>    | 2,841/3,305                  |                                       | 0.98 (0.91–1.06)              |
| Colorectal cancer | ins/del <sup>b</sup> |                              |                                       | 0.99 (0.88–1.12) <sup>b</sup> |
|                   | del/del <sup>b</sup> |                              |                                       | 0.96 (0.80–1.14) <sup>c</sup> |
|                   | <u>MEC</u>           |                              |                                       |                               |
|                   | African American     | 217/1,074                    | 0.54                                  | 0.92 (0.75–1.13)              |
|                   | Japanese American    | 386/1,200                    | 0.16                                  | 1.10 (0.86–1.36)              |
|                   | Native Hawaiian      | 61/355                       | 0.45                                  | 1.16 (0.79–1.69)              |
|                   | Latino               | 251/1,027                    | 0.35                                  | 1.24 (1.01–1.51)              |
|                   | European American    | 224/975                      | 0.48                                  | 0.96 (0.78–1.18)              |
|                   | <u>LACC</u>          |                              |                                       |                               |
|                   | European American    | 356/413                      | 0.50                                  | 0.94 (0.77–1.15)              |
|                   | <u>All Groups</u>    | 1,495/5,044                  |                                       | 1.03 (0.94–1.13)              |
| Prostate cancer   | ins/del <sup>b</sup> |                              |                                       | 0.99 (0.86–1.14)              |
|                   | del/del <sup>b</sup> |                              |                                       | 1.08 (0.90–1.30)              |
|                   | <u>MEC</u>           |                              |                                       |                               |
|                   | African American     | 890/629                      | 0.54                                  | 0.98 (0.84–1.13)              |
|                   | Japanese American    | 722/728                      | 0.16                                  | 1.00 (0.82–1.22)              |
|                   | Native Hawaiian      | 111/112                      | 0.50                                  | 0.70 (0.47–1.04)              |
|                   | Latino               | 637/633                      | 0.36                                  | 1.10 (0.94–1.30)              |
|                   | European American    | 465/446                      | 0.50                                  | 0.83 (0.68–1.01)              |
|                   | <u>All Groups</u>    | 2,825/2,548                  |                                       | 0.97 (0.89–1.05)              |
|                   | ins/del <sup>b</sup> |                              |                                       | 1.04 (0.92–1.18)              |
|                   | del/del <sup>b</sup> |                              |                                       | 0.91 (0.76–1.08)              |

<sup>a</sup>OR per allele. Pooled ORs were adjusted for ancestral background and study. <sup>b</sup>ins/del and del/del genotypes are compared to ins/ins genotype.

tion-based cancer surveillance, epidemiology and end results (SEER) registries covering Hawaii and Los Angeles County, California and to the California state cancer registry covering all of California. Associations

with the *CASP8* deletion variant were also examined in population-based case-control studies of incident breast (LABC) and colorectal cancer (LACC) among women in Los Angeles County, California. The breast

cancer study (743 cases and 987 controls) includes Chinese, Japanese or Filipino cases between the ages of 25 and 74 years at the time of diagnosis (1995–2001)<sup>7</sup>. Cases in the colorectal cancer study (356 cases and 413 controls) were diagnosed at ages 55–74 years during 1998–2002 (ref. 5). In both studies, cases were identified through the Los Angeles County and statewide cancer registries, and controls were selected from the neighborhoods where the cancer cases resided at the time of diagnosis (**Supplementary Table 1** online). All three of these studies were approved by the appropriate institutional review boards at the University of Southern California and the University of Hawaii. In these studies, the 6-bp insertion/deletion polymorphism was genotyped using the TaqMan assay (Applied Biosystems). We assessed genotype data quality by typing 2–5% blinded replicate samples; the concordance rate was 99.4% (**Supplementary Methods** online).

The deletion variant was common in all populations examined and ranged in frequency from 16% in Japanese to 54% in African Americans (**Table 1**). No deviation from Hardy-Weinberg equilibrium was observed (at  $P < 0.05$ ) in any racial or ethnic group. We found no significant inverse association between this deletion variant in the *CASP8* gene with risk of any of these three common cancers in pooled analyses (breast, odds ratio (OR) = 0.98, 95% confidence interval (CI) = 0.91–1.06; prostate, OR = 0.97, 95% CI = 0.89–1.05; colorectal, OR = 1.03, 95% CI = 0.94–1.13; **Table 1**); nor were

significant associations noted for heterozygous or homozygous carriers of the deletion allele (**Supplementary Table 2** online). The effects in each population were consistent, with the exception of a nominally significant positive association observed with colorectal cancer in Latinos, which may possibly be due to chance (**Table 1**). For each site, we had >99.7% power to detect an OR of 0.75 per copy of the deletion allele, which had been reported previously by Sun *et al.*<sup>2</sup> (assuming a log additive model, a two-sided test using  $\alpha = 0.05$  and a variant allele frequency of 16%, the lowest allele frequency in any one of the populations examined). With this conservative scenario, we also had reasonably good power ( $\geq 80\%$ ) to detect effects as small as 0.85 per allele for each cancer site. In addition to its large size and multiple cancer endpoints, this study included groups of various ancestral backgrounds with very different disease risks and allele frequencies. Thus, the likelihood that the lack of any significant association is attributable to bias or population stratification is much reduced.

Our inability to replicate the findings of Sun *et al.*<sup>2</sup> may be due to possible genetic and/or environmental modifiers that vary in frequency between populations of various ancestries in the United States and the Chinese populations studied by Sun *et al.*<sup>2</sup>, or it may be because the initial association was a false positive. A recent breast cancer study by Frank *et al.*<sup>8</sup> (7,753 cases and 7,921 controls) also found no significant evidence that this variant has an effect on breast cancer risk among Europeans. Although we cannot com-

ment on the other cancer sites studied by Sun *et al.*<sup>2</sup> (lung, stomach, esophagus, cervix), our results do not support the hypothesis that this specific polymorphism, which has been proposed to be biologically functional, is an independent marker of breast, colorectal or prostate cancer risk in populations of Asian, European or African origin.

Christopher A Haiman<sup>1</sup>, Rachel R Garcia<sup>1</sup>, Laurence N Kolonel<sup>2</sup>, Brian E Henderson<sup>1</sup>, Anna H Wu<sup>1</sup> & Loïc Le Marchand<sup>2</sup>

<sup>1</sup>Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California 90089, USA. <sup>2</sup>Epidemiology Program, Cancer Research Center of Hawaii, University of Hawaii, Honolulu, Hawaii 96813, USA. Correspondence should be addressed to C.H. (haiman@usc.edu).

#### ACKNOWLEDGMENTS

The Multiethnic Cohort Study was supported by National Cancer Institute (NCI) grants CA63464 and CA54281. The Los Angeles-based case-control studies were supported by NCI grant CA17054 and by grants from the California Breast Cancer ReSEARCH Program (1RB-0287, 3PB-0102, 5PB-0018 and 10PB-0098).

1. Cox, A. *et al.* *Nat. Genet.* **39**, 352–358 (2007).
2. Sun, T. *et al.* *Nat. Genet.* **39**, 605–613 (2007).
3. Freedman, M.L. *et al.* *Hum. Mol. Genet.* **13**, 2431–2441 (2004).
4. Haiman, C.A. *et al.* *Nat. Genet.* **39**, 638–644 (2007).
5. Haiman, C.A. *et al.* *Nat. Genet.* **39**, 954–956 (2007).
6. Kolonel, L.N. *et al.* *Am. J. Epidemiol.* **151**, 346–357 (2000).
7. Wu, A.H. *et al.* *Int. J. Cancer* **120**, 844–852 (2007).
8. Frank, B. *et al.* *Breast. Cancer. Res. Treat. Epub* (2007).

#### Sun *et al.* reply:

We recently identified a 6-bp insertion/deletion polymorphism (–652 6N ins/del) in the promoter of the *CASP8* gene that removes an Sp1 binding site and that was shown to be associated with reduced *CASP8* transcription in lymphocytes. We further demonstrated that T lymphocytes with the deletion variant had lower caspase-8 activity and lower cancer cell antigen-induced cell death. We also reported that this genetic variant was associated with significantly reduced risk of several human cancers in a large case-control study in homogenous Han Chinese populations<sup>1</sup>. Haiman *et al.* now report a case-control study seeking to replicate our findings of this *CASP8* variant in breast, prostate or colorectal cancers in multiple US populations of various ancestries and self-declared ethnic identification (African Americans, Japanese Americans, Latinos, European Americans,

Native Hawaiians and Chinese Americans), but they did not find statistical evidence for any association<sup>2</sup>. Although the reasons for the discrepancies between their findings and ours are currently unknown, we have some thoughts that may offer some explanation.

First, the inconsistency may be related to sample sizes of selected populations. The overall sample sizes for each cancer site in Haiman *et al.* seem large (2,841 breast cancer cases, 1,529 colorectal cancer cases and 2,825 prostate cancer cases<sup>2</sup>), and comparable to those in our study (which included 1,125 individuals with breast cancer and 930 individuals with colorectal cancer<sup>1</sup>). We are concerned, however, that the number of cases included in some of the ancestry-specific groups for a specific cancer type may still be too limited to make a conclusive direct comparison. Perhaps most relevant for comparison to our study, the Chinese

American group (from the LABC study) in Haiman *et al.* included only 263 breast cancer cases<sup>2</sup>. Given that any single study may generate some spurious results<sup>3</sup>, such initial findings need to be validated or replicated in much larger studies for each ancestry or ethnic group.

Second, the discrepant findings may be related to population-specific differences not only in genetic variation, but also in gene–environment interactions. Other variants have also recently been suggested to have population-specific differences in association with different cancers. For example, the *CASP8* D302H and *CASP10* V410I SNPs have been shown to be associated with reduced risk of breast cancer in populations of predominantly European ancestry<sup>4</sup>; however, both SNPs seem extremely rare (*CASP8* D302H) or nonexistent (*CASP10* V410I) in some Asian populations (from a search of