We observed a modest but nonsignificant decrease in risk of NHL with *BRCA2* N372H AC and CC variants compared with the AA variant, and no evidence of any association between NHL and the *RAG1* K820R polymorphism (Table 1). Risks for B-cell lymphoma, and the 2 major diagnostic subgroups of diffuse large B-cell lymphoma and follicular lymphoma (data not shown), were similar to those for total NHL for both variants, while risk estimates were elevated for T-cell lymphoma, but were not significant (Table 1). Risks were generally similar among men and women, and varied little by age (data not shown). However, for T-cell lymphoma, men who carried at least 1 copy of the *BRCA2* N372H C allele had a significantly increased risk (OR = 2.30, 95% CI, 1.08-4.87 based on 23 patients and 194 control participants with the C allele compared with 11 patients and 208 control participants), while women were at decreased risk (OR = 0.43, 95% CI, 0.17-1.06 based on 7 patients and 176 control participants with the C allele compared with 17 patients and 179 control participants) (test for interaction: $\chi^2 = 8.42$, $P = .004$).

Our data suggest that there is little association between NHL and either of these 2 polymorphisms. However, we cannot exclude the possibility of an association, and further investigation is required using larger datasets to elucidate the role of these polymorphisms in determining the risk of developing NHL.

Kathryn Scott, Peter J. Adamson, Sharon L. Barrans, Lisa J. Worrillow, Eleanor V. Willett, and James M. Allan

Correspondence: Kathryn Scott, Department of Biology, University of York, York. United Kingdom YO10 5YW; e-mail: KS27@YORK.AC.UK

Conflict-of-interest disclosure: The authors declare no competing financial interests.

References

1. Hill DA, Wang SS, Cerhan JR, et al. Risk of Non-Hodgkin lymphoma (NHL) in relation to germline variation in DNA repair and related genes. Blood. 2006; 108:3161-3167.
2. Willett EV, Smith AG, Dovey GJ, et al. Tobacco and alcohol consumption and the risk of non-Hodgkin lymphoma. Cancer Causes Control. 2004;15: 771-780.
3. National Cancer Institute. Cancer Genome Anatomy Project SNP500 Cancer Database. Available at: http://snp500cancer.nci.nih.gov. Accessed June 2006.
4. Breslow NE, Day NE. Classical methods of analysis of matched data. Statistical methods in cancer research: the analysis of case-control studies volume 1. Lyon: International Agency for Research in Cancer. 1980:162-189.

Response:

NHL and genomic variability in *RAG1* and *BRCA2*

In the letter by Scott and colleagues in this issue of *Blood*, the authors failed to identify an association between *RAG1* K820R or *BRCA2* N372H variant alleles and risk of non-Hodgkin lymphoma (NHL), while we had observed a relationship in a previous study. Small differences in the ethnicity distribution between the 2 studies probably do not account for the discordant findings, as we did not detect risk estimate heterogeneity according to ethnicity. The 2 studies reported a similar gene variant prevalence among controls, which was also consistent with that seen in other populations.[1,2] The similar prevalence suggests another potential explanation for the discrepancy: that small differences in control genotype prevalence, coupled with slightly larger differences in case genotype distributions (as in our studies) can create apparently spurious positive (or null) results. This highlights the possibility that sampling variability may play a major role in seemingly discordant findings. If a slightly different sample of our respective eligible participants had been enrolled, we might have had concordant results. Resolution of this issue in genetic association studies will require very large datasets and thousands of study participants to develop large-scale evidence for genotype-disease associations, as several authors have noted.[3-5] Such initiatives are beyond the scope of most single investigations, and have led to the creation of consortia to address these questions, not only through standard meta-analyses, (which can be subject to publication bias), but by pooled analyses of individual-level data from both published and unpublished sources.[6] Few results are yet available from these undertakings. The International Lymphoma Epidemiology Consortium (Interlymph), which includes related initiatives focused on other hematopoietic malignancies, is only one of many such consortia,[7] and welcomes other investigators to join this collaborative effort.

Deirdre A. Hill, Sophia Wang, Patricia Hartge, and Nathaniel Rothman

Correspondence: Deirdre A. Hill, Department of Internal Medicine, University of New Mexico School of Medicine, 1 University of New Mexico, Albuquerque, NM 87131-0001; email: dahill@salud.unm.edu.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

References

1. Wu X, Gu J, Grossman HB, Amos CI, et al. Bladder cancer predisposition: a multigenic approach to DNA-repair and cell-cycle-control genes. Am J Hum Genet. 2006;78:464-479.
2. http://snp500cancer.nci.nih.gov, accessed 12/12/06.
3. Colhoun HM, McKeigue PM, Davey Smith G. Problems of reporting genetic associations with complex outcomes. Lancet.2003;361:865-872.
4. Wacholder S, Chanock S, Garcia-Closas M, El Ghormli L, Rothman N. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. J Natl Cancer Inst. 2004;96:434-442.
5. Ioannidis JP, Trikalinos TA, Khoury MJ. Implications of small effect sizes of individual genetic variants on the design and interpretation of genetic association studies of complex diseases. Am J Epidemiol. 2006;164:609-614.
6. Ioannidis JP, Gwinn M, Little J, et al. A road map for efficient and reliable human genome epidemiology. Nat Genet. 2006;38:3-5.
7. Rothman N, Skibola CF, Wang SS, et al. Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the InterLymph Consortium. Lancet Oncol. 2006;7:27-38.