(50 mg) was based on an earlier study[3] in which this regimen showed the strongest effect on homocysteine levels; this dose is relatively high compared with several other homocysteine-lowering trials. We are aware that vitamin B_2 is a coenzyme of *MTHFR*, and that riboflavin supplementation lowers homocysteine levels in vitamin B_2–deficient patients.[4] However, no data are available on the additional effect of riboflavin next to the combination of folate, vitamin B_{12}, and vitamin B_6. Only 1 study shows a small additional effect of riboflavin next to folate alone.[5]

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To the editor:

RAG1 and *BRCA2* polymorphisms in non-Hodgkin lymphoma

A recent *Blood* paper by Hill et al[1] suggested a link between the risk of developing non-Hodgkin lymphoma (NHL) and polymorphic variations in several genes involved in DNA strand break induction and DNA repair pathways. We examined 2 of these polymorphisms where Hill et al reported statistically significant associations, in the Recombination-activating 1 (*RAG1*) gene (K820R; odds ratio [OR] = 2.7 [AA vs GG], 95% confidence interval [CI], 1.4-5.0) and the *Breast cancer 2* (*BRCA2*) gene (N372H; OR = 1.5 [AA vs CC], 95% CI, 1.0-2.1), in a United Kingdom case-control study of lymphoma.

Local ethical approval was obtained for this research. Informed consent was obtained in accordance with the Declaration of Helsinki.

A total of 741 white patients with NHL and 806 white control participants randomly selected from population registers were recruited as part of a lymphoma case-control study conducted in parts of north and southwest England.[2] Our study participants consented to give a blood sample, and represented 67% of patients with incident NHL aged 16 to 69 years in the study area and 66% of the control participants who were contacted successfully. We genotyped the participants' DNA while blinded to case-control status using TaqMan SNP genotyping assays (Applied Biosystems, Warrington, United Kingdom) and ABI PRISM 7000 software (Applied Biosystems). To assess the reliability of the Taqman assays, 20 samples were randomly selected for direct DNA sequencing: concordance with TaqMan was 100% for both polymorphisms. Among our control population, *RAG1* K820R and *BRCA2* N372H were in Hardy-Weinberg equilibrium, and the distributions of variants were consistent with those reported by Hill et al and the cancer genome anatomy project SNP500 cancer database.[3] Unmatched statistical analyses to estimate ORs and 95% CIs were conducted using unconditional logistic regression adjusting for age and sex,[4] and the likelihood ratio test was used to test for interactions.

Table 1. Number of patients and control participants, adjusted ORs, and 95% CIs for *BRCA2* N372H and *RAG1* K820R by immunophenotype

Genes and variants	Controls, no. (%)	NHL		B-cell lymphoma		T-cell lymphoma	
		Patients, no. (%)	OR (95% CI)	Patients, no. (%)	OR (95% CI)	Patients, no. (%)	OR (95% CI)
Total	806 (100)	741 (100)	NA	665 (100)	NA	59 (100)	NA
BRCA2 N372H, A > C*							
AA	387 (51.1)	375 (55.5)	1 (reference)	340 (56.4)	1 (reference)	28 (48.3)	1 (reference)
AC	307 (40.6)	253 (37.4)	0.85 (0.68-1.05)	224 (37.1)	0.83 (0.66-1.03)	22 (37.9)	1.03 (0.58-1.85)
CC	63 (8.3)	48 (7.1)	0.79 (0.53-1.18)	39 (6.5)	0.71 (0.46-1.09)	8 (13.8)	1.61 (0.70-3.75)
AC + CC	370 (48.9)	301 (44.5)	0.84 (0.68-1.03)	263 (43.6)	0.81 (0.65-1.00)	30 (51.7)	1.14 (0.67-1.96)
RAG1 K820R, A > G*							
AA	622 (81.4)	557 (81.2)	1 (reference)	496 (81.3)	1 (reference)	46 (78.0)	1 (reference)
AG	136 (17.8)	124 (18.1)	1.01 (0.77-1.33)	109 (17.9)	1.00 (0.76-1.32)	13 (22.0)	1.38 (0.72-2.65)
GG	6 (0.8)	5 (0.7)	0.94 (0.29-3.10)	5 (0.8)	1.07 (0.32-3.52)	0 (0.0)	0 (0-8.84)†
AG + GG	142 (18.6)	129 (18.8)	1.01 (0.78-1.33)	114 (18.7)	1.00 (0.76-1.32)	13 (22.0)	1.31 (0.69-2.51)

B-cell lymphoma includes International Classification of Diseases for Oncology version 3 codes 9673/3, 9679/3, 9680/3, 9684/3, 9689/3, 9690/3, 9691/3, 9695/3, 9698/3, and 9699/3; T-cell lymphoma includes 9700/3, 9701/3, 9702/3, 9705/3, 9708/3, 9709/3, 9714/3, 9716/3, 9717/3, 9718/3, 9719/3, and 9827/3.

Immunophenotype was not known for 17 patients. ORs and 95% CIs were calculated using unconditional logistic regression adjusting for age and sex.

NA indicates not applicable.

**BRCA2 N372H* and *RAG1 K820R* were in Hardy-Weinberg equilibrium among controls ($\chi^2 = 0.04$, $P = 0.85$; $\chi^2 = 0.23$, $P = 0.63$, respectively). Samples did not amplify for 65 patients and 49 control participants for *BRCA2 N372H,* and 55 patients and 42 control participants for *RAG1 K820R.*

†OR and 95% CI were calculated using exact methods.

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.

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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.

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