8831 pediatric ALL patients enrolled in Children's Cancer Group therapeutic protocols from 1983 to 1995, the cumulative incidence of SPMs was 1.18% at 10 years, more than a sevenfold increased risk compared with that of the general population.[10]

Our study is the first to report SPMs in adult ALL patients. We found a 43% relative increase in SPMs in ALL patients (O/E = 1.43; 95% CI, 1.01-1.95) compared with the general population. The risk of specific SPM depends on the patient's age and the latency period. Cancer-specific screening during follow-up of ALL survivors may help diagnose the SPM at an earlier stage.

The strengths of our study include the large number of patients with long-term follow-up from a large geographic area. There are several limitations. The SEER database does not have information on the chemotherapy used, comorbid conditions, social habits, exposure to carcinogens, or family history.

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To the editor:

Genome-wide scan identifies variant in 2q12.3 associated with risk for multiple myeloma

Common inherited genetic variants associated with disease risk may uncover important biological mechanisms behind neoplastic development. Here, we report a novel susceptibility locus associated with multiple myeloma (MM) risk and an additional promising locus, and we replicate 6 previously published associations.

Germ line DNA was isolated from leukapheresis products obtained from a test set of 972 newly diagnosed patients of European ancestry with MM and from a validation set of 252 more recent patients treated at the Myeloma Institute for Research and Therapy. In the test set, genotyping was performed using Illumina HumanOmni1-Quad BeadChips, and genotypes have been submitted to the database of Genotypes and Phenotypes (accession no. phs000545.v1.p1). Control data for our study were downloaded from the database of Genotypes and Phenotypes and consisted of 1064 unrelated cancer-free patients of European ancestry recruited in the south-central United States for the High Density Single Nucleotide Polymorphism (SNP) Association Analysis of Melanoma (accession no. phs000187.v1.p1).[1]

We excluded SNPs with greater than 2% missingness or with minor allele frequency less than 1%, as well as SNPs that violated Hardy-Weinberg equilibrium ($P < .001$) among control patients. We removed 2 SNPs strongly suspected of genotyping error

Table 1. Two novel SNPs associated with MM risk

		MM cases					Controls							
SNP	**Risk allele**	**N**	**Genotypes**			**RAF**	**N**	**Genotypes**			**RAF**	**OR**	***P****	***P*†**
rs12614346 (2q12.3)	A		AA	AG	GG			AA	AG	GG				
Discovery		972	126	462	384	0.37	1064	89	449	526	0.29	1.39	7.1E−07	1.7E−05
Replication		249	38	102	109	0.36						1.33	.007	
rs73486634 (9q22.33)	G		GG	GA	AA			GG	GA	AA				
Discovery		971	5	85	881	0.05	1064	0	47	1017	0.02	2.28	4.7E−06	6.3E−04
Replication		249	0	14	235	0.03						1.28	.416	

OR, odds ratio; RAF, risk allele frequency.
*Cochran-Armitage trend test.
†Logistic regression assuming additive inheritance and including 4 genome-wide multidimensional scaling parameters as covariates.

because of unusual patterns of segregation in genotype clustering plots (see supplemental Data, available on the *Blood* Web site) and highly significant risk associations ($P < 10^{-22}$) in regions containing no other risk-associated SNPs. The resulting data included 972 case subjects, 1064 control subjects, and 777 681 SNPs. Gene expression profiling on CD138-selected plasma cells was available for a subset of 650 patients.[2] The validation set of 252 patients was genotyped at selected SNPs by LGC Genomics, LLC (Beverly, MA), using quantitative PCR (polymerase chain reaction).

The genomic scan identified 2 regions containing multiple SNPs with significant association with MM risk ($P < 10^{-5}$). The most significant genetic variant was a SNP located in 2q12.3 (rs12614346; $P = 7.1 \times 10^{-7}$; odds ratio, 1.39) upstream of the ST6 β-galactosamide α-2,6-sialyltranferase 2 (*ST6GAL2*) gene, which encodes a sialyltransferase that catalyzes the transfer of sialic acid from cytidine monophosphate to an oligosaccharide substrate. Sialic acids are expressed on the cell surface and play a fundamental role in cell–cell and cell–microenvironment interactions. The protein encoded by the gene is widely distributed in normal human tissue, and its expression is increased by cytokines such as interleukin 6.[3] The risk association was replicated by the validation sample of 252 patients (Table 1; $P = .007$). There was no relationship between the risk allele and expression of *ST6GAL2* in CD138-selected plasma cells.

At the 9q22.33 locus, the most significant association was at rs73486634 ($P = 4.7 \times 10^{-6}$; odds ratio, 2.28), located both between and upstream from the genes forkhead box E1 (*FOXE1*) and xeroderma pigmentosum, complementation group A (*XPA*). *FOXE1* is an intronless gene belonging to the forkhead family of transcription factors, and changes in the gene may be involved in carcinogenesis.[4] *XPA* encodes a zinc finger protein that participates in DNA nucleotide excision repair of DNA toxicants,[5] and variants in *XPA* are associated with lung and colorectal cancer.[6,7] Gene expression of *FOXE1*, but not *XPA,* was significantly lower among risk allele carriers ($P = .026$). The validation sample failed to replicate the association with statistical significance because of the SNP's low minor allele frequency (Table 1; $P = .416$).

We also replicated 6 of 7 previously published genome-wide association study–discovered MM associations[8,9] ($P < .05$; supplemental Data). In the current study, we studied risk-associated genotypes from patients eligible for high-dose melphalan (mean age, 57.7 years; mean age at diagnosis for patients in the MyelomA Genetics International Consortium [MAGIC],[9] 61.0 years). In MM, an age-related risk has been shown for genetic variants in the *IL6* gene.[10] Along with the geographic difference between study populations and the known heterogeneity of MM disease, this may explain why our currently reported associations have not previously been identified. Our current study strengthens the evidence for 6 previously identified susceptibility loci and introduces 2 novel loci toward a greater understanding of the genetic etiology of multiple myeloma.

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