Acknowledgments: Informed approval for this research was obtained from the Fred Hutchinson Cancer Research Center's Institutional Review Board. Informed consent for the relevant studies was obtained according to the Declaration of Helsinki.

Contribution: J.R.V and E.E. designed the research; J.R.V. and V.S. performed the research; J.R.V., P.S.B., J.M.P., F.R.A., and E.E. analyzed the data; and J.R.V., P.S.B., F.R.A., and E.E. wrote the paper.

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To the Editor:

MGUS prevalence in a cohort of AML patients

The increased incidence of acute myeloid leukemia (AML) and myelodysplastic syndromes following multiple myeloma (MM) has been observed for more than 4 decades[1,2] and has been largely attributed to mutagenic induction therapy for myeloma.[3-6] Recent data from a large population study (N = 5652) showed that patients with the myeloma precursor disease, monoclonal gammopathy of unknown significance (MGUS), have an eightfold statistically increased risk of developing AML/myelodysplastic syndromes, suggesting nontreatment-related factors may contribute to excess risk.[7]

Because AML is a rare malignancy (3.6 cases/100 000/year in the United States),[8] previous prospective studies of MGUS patients have included relatively few AML cases; as such, the extent to which MGUS precedes development of AML remains unclear. To overcome this challenge, we used the prospective Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, which includes 77 469 healthy men and women with available baseline peripheral blood samples, to identify 96 individuals (aged 55 to 74years at baseline) who developed AML during follow-up. We then assessed evidence of monoclonal (M) proteins and abnormal free light-chain (FLC) ratios in serum collected up to 14 years prior to diagnosis of AML using serum protein electrophoresis (SPEP) (Helena SPIFE-3000, Helena Laboratories, Beaumont, TX) and κ− and λ-FLC assays (SPA-Plus, The Binding Site, Birmingham, United Kingdom). Patients with an abnormal FLC ratio and/or suspicious SPEP were subjected to immunofixation electrophoresis (IFE).[9,10] Patients with an abnormal FLC ratio and elevated free κ (FK) or free λ (FL) values, without M protein on SPEP or IFE, were classified as light-chain (LC)-MGUS.[11] Exact 95% binomial confidence intervals (CIs) were computed for estimates of proportions.

Among patients with AML, the prevalence of MGUS in baseline sera was 4/96 (4.2%; 95% CI, 1.2% to 10.3%), including 1 immunoglobulin G (IgG) λ, 1 biclonal IgMλ/IgGκ, and 2 patients satisfying criteria for LC-MGUS.[11] Blood draw date ranged 3.7 to 14 years prior to AML diagnosis. In addition, there were 8/96 patients with elevated FK or FL with normal FLC ratio. Two patients had hypogammoglobinemia, defined as IgG γ < 9.5% of total protein on SPEP. Thus, 14/96 (14.5%) patients were found to have any immunoglobulin abnormality (Table 1).

Our prospective screening study of MGUS prior to diagnosis of AML does not demonstrate evidence of increased overall prevalence. In an age-matched comparison with the Olmsted County study conducted by the Mayo Clinic, the prevalence of MGUS + LC-MGUS among individuals aged 50 to 79 years was 593/16 347

Table 1. Study subjects

Patient No.	Age	Sex	Race	Category	Isotype	M Protein (g/dL)	FLC ratio (0.26–1.65)	FK (mg/L) (3.3–19.4)	FL (mg/L) (5.7–26.3)	Time from blood draw to AML diagnosis (y)
1	63	M	White	MGUS	Biclonal (IgM λ+ IgG κ)	<0.1	1.08	18.69	17.27	9.6
2	67	M	White	MGUS	IgG λ	0.81	0.5	10.1	20.19	8.7
3	70	M	Black	*MGUS*	Light-chain	/	12.68	335.9	26.49	14.0
4	60	F	Black	*MGUS*	Light-chain	/	1.81	25.42	14.01	3.7
5	64	M	White	Polyclonal*	/	/	0.94	26.05	27.58	5.6
6	68	F	White	Polyclonal*	/	/	0.75	24.09	32.04	13.6
7	70	M	White	Polyclonal*	/	/	0.77	20.93	27.08	8.9
8	65	M	White	Polyclonal*	/	/	0.73	20.05	27.31	5.3
9	72	M	White	Polyclonal†	/	/	0.97	24.05	24.79	0.5
10	74	M	White	Polyclonal†	/	/	1.61	23.58	14.66	0.8
11	65	M	White	Polyclonal†	/	/	1.01	23.54	23.31	1.7
12	65	M	White	Polyclonal†	/	/	1.23	19.89	16.12	9.9
13	67	F	White	Hypogammaglobulin	/	/	0.16	1.01	6.48	9.4
14	69	M	White	Hypogammaglobulin	/	/	0.61	5.05	9.04	6.6

*κ + λ elevated.
†κ elevated.

(3.6%; 95% CI, 3.4% to 3.9%) overlapping with our proportion ($P = .56$, Fisher exact test).[10] Given that 32/96 (33%) of the patient samples were collected >10 years prior to AML diagnosis, some individuals may have developed MGUS at a time closer to AML diagnosis. Furthermore, an increase in prevalence cannot be excluded because our statistical calculation is limited by number of AML patients, despite drawing from one of the largest cancer screening trials.

Interestingly, 8/96 (8.3%; 95% CI, 3.7 to 15.8) patients had FK and/or FL elevations with preserved FLC ratio and no M spike, reflective of chronic polyclonal B-cell stimulation.[12] Such percentage is comparable to findings in chronic lymphocytic leukemia.[13] Taken together, we speculate our finding may reflect some underlying immune stimulation that could play a role in the development of both AML and plasma-cell dyscrasias.

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Contribution: S.P.W. analyzed data and drafted the report; R.C. designed research, processed samples, and ran arrays; J.N.H., M.P., N.K., and S.M. designed research; O.L. designed the research, analyzed data, and drafted the report; and all authors reviewed the manuscript, gave input, and approved the final version.

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