

## Prevalence of Monoclonal Gammopathy of Undetermined Significance Among Men in Ghana

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**OBJECTIVES:** To determine the prevalence of monoclonal gammopathy of undetermined significance (MGUS), a precursor of multiple myeloma (MM), in Ghanaian men vs white men and to test for evidence to support an underlying race-related predisposition of the 2-fold higher prevalence of MGUS in African Americans vs whites.

**PARTICIPANTS AND METHODS:** Between September 1, 2004, and September 30, 2006, 917 men (50-74 years) underwent in-person interviews and physical examinations. Serum samples from all participants were analyzed by electrophoresis performed on agarose gel; any serum sample with a discrete or localized band was subjected to immunofixation. Age-adjusted and standardized (to the 2000 world population) prevalence estimates of MGUS and 95% confidence intervals (CIs) were computed in the Ghanaian men and compared with MGUS prevalence in 7996 white men from Minnesota. Associations between selected characteristics and MGUS prevalence were assessed by the Fisher exact test and logistic regression models.

**RESULTS:** Of the 917 study participants, 54 were found to have MGUS, yielding an age-adjusted prevalence of 5.84 (95% CI, 4.27-7.40) per 100 persons. No significant variation was found by age group, ethnicity, education status, or prior infectious diseases. The concentration of monoclonal immunoglobulin was undetectable in 41 (76%) of the 54 MGUS cases, less than 1 g/dL in 10 patients (19%), and 1 g/dL or more in only 3 patients (6%). Compared with white men, the age-adjusted prevalence of MGUS was 1.97-fold (95% CI, 1.94-2.00) higher in Ghanaian men.

**CONCLUSION:** The prevalence of MGUS in Ghanaian men was twice that in white men, supporting the hypothesis that race-related genetic susceptibility could explain the higher rates of MGUS in black populations. An improved understanding of MGUS and MM pathophysiology would facilitate the development of strategies to prevent progression of MGUS to MM.

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CI = confidence interval; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma

**M**ultiple myeloma (MM), which is characterized by an overproduction of monoclonal immunoglobulins, remains an incurable clonal neoplasm of differentiated B cells (plasma cells). The median survival for patients with MM is 3 to 4 years.<sup>1</sup> Usually, MM is preceded by the premalignant plasma cell disorder monoclonal gammopathy of undetermined significance (MGUS), which is defined by a serum monoclonal immunoglobulin concentration of 3 g/dL or less; the absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the proliferation of

monoclonal plasma cells; and 10% or fewer plasma cells in the bone marrow.<sup>2</sup> It progresses to MM at a rate of 1% per year.<sup>3</sup>

Although most hematopoietic neoplasms are more prevalent in whites, the age-adjusted incidence of MM is 2-fold higher in African Americans than in whites.<sup>4</sup> This increased incidence in African Americans could be due to 2 factors: increased prevalence of MGUS or an increased risk of progression of MGUS to MM. In a study based on data from the US Department of Veterans Affairs hospital network, we found the cumulative risk of MM during the first 10 years of follow-up to be similar ( $P=.37$ ) for 734 African American veterans with MGUS (17%) and 1312 white veterans with MGUS (15%), suggesting that the excess risk of MM in African Americans results from an increased risk of MGUS rather than an increased risk of progression from MGUS to MM.<sup>5</sup> Indeed, the standardized prevalence of MGUS was 3.0-fold (95% confidence interval [CI], 2.7-3.3) higher in African American than in white veterans.

To elucidate whether the increased risk of MGUS in African Americans is due to inherent race-related genetic susceptibility or, alternatively, to differences in environmental factors between African Americans and whites in the United States, we wanted to study MGUS among West Africans because they share similar genetic ancestry with African Americans. To our knowledge, ours is the first

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population-based study of MGUS in Africa. The aims of the study were to estimate the age-specific prevalence of MGUS in Ghana and to compare it with the prevalence of MGUS in more than 20,000 predominantly white people 50 years or older in Olmsted County, MN (4.0% for men, 2.7% for women).<sup>6</sup> In addition, we defined characteristics of MGUS among Ghanaian men.

## PARTICIPANTS AND METHODS

### STUDY PARTICIPANTS

Informed consent was obtained from all study participants, and the study sample collection was approved by the institutional review boards of the National Cancer Institute and the University of Ghana.

To enroll a population-based probability sample into the study, we used (in collaboration with the Ghana Census Bureau) the 2000 Ghana Population and Housing Census data to construct a sampling frame of men aged 50 to 74 years in the Greater Accra Region (population of approximately 3 million). We estimated that 7500 households would need to be sampled to identify approximately 1000 eligible men for the study. To achieve this, probability samples were selected in 3 consecutive stages from well-defined geographic boundaries in Accra, households in the enumeration areas, and men aged 50 to 70 years living in the household. At the first stage of sampling, 300 enumeration areas were selected randomly with probability proportional to size; size was determined by the number of households in each enumeration area. At the second stage, a listing of households in each enumeration area was produced by the Ghana Census Bureau and 25 households were selected randomly from each enumeration area to produce a total of 7500 households from the Greater Accra Region. The third stage involved door-to-door visits to the 7500 selected households to enumerate all members of the household and identify eligible men for the study. The respondent for the survey was selected from the eligible men (aged 50-74 years) of the household; when there was more than one eligible respondent, the one with the earliest month of birth was selected.

Initially, between September 1, 2004, and September 30, 2006, we identified 971 eligible men from these households. Of these, 3 were too sick to be screened and 9 refused to participate, yielding a 98.8% (959/971) response rate. We further excluded 42 men with a history of cancer from the MGUS investigation, leaving 917 men for the current analysis. We compared prevalence estimates of MGUS in Ghanaian men, standardized to the 2000 world population, with standardized prevalence estimates from our recent screening study of residents of Olmsted County, MN, including almost 8000 white men 50 to 74 years of age.<sup>6</sup>

### INTERVIEW OF PARTICIPANTS AND COLLECTION OF BIOLOGICAL SAMPLES

Consenting participants were brought to the Korle-Bu Hospital for interview and physical examination. Using a structured questionnaire, trained interviewers elicited information in person from all study participants regarding risk factors, including smoking, use of alcohol, body size, family history of cancer, and medical history, as well as screening practices and use of the medical care system. A 20-mL blood specimen was collected from all participants after they fasted overnight. Collected blood was brought to the central laboratory within 2 hours of collection for processing and then stored at  $-70^{\circ}\text{C}$  at the Korle-Bu Hospital. Subsequently, specimens were shipped on dry ice by express mail to the National Cancer Institute repository in Frederick, MD, for long-term storage.

### LABORATORY TESTS

All serum samples were identically processed and analyzed in the same laboratory (Protein Immunology Laboratory, Mayo Clinic, Rochester, MN) as those obtained from Olmsted County residents for the population-based study of MGUS<sup>6</sup> with which the rates of MGUS in Ghanaian men were to be compared. The samples were thawed and analyzed on average 1.5 years (range, 1.0-2.5 years) after blood collection. Electrophoresis was performed on an agarose gel (REP; Helena Laboratories, Beaumont, TX). The agarose strip was inspected by a technician and by 2 of the authors (J.A.K. and R.A.K.). Any serum sample that was thought to have a discrete or localized band was subjected to immunofixation (Hydrasys and Hydragel; Sebia, Lisses, France).<sup>7</sup> The definition of MGUS used in our study, derived from a previous definition, was identical to that used in the study of the prevalence of MGUS in Olmsted County residents.<sup>3,6,8,9</sup>

### STATISTICAL ANALYSES

Age-specific prevalence rates for Ghana and Olmsted County data were calculated by dividing the number of participants with MGUS in each age stratum by the number of participants in that stratum. Standardized prevalence rates and 95% CIs were obtained by direct standardization to the overall world population (>50 years) in 2000. Associations of MGUS prevalence with demographic and patient characteristics were assessed by the Fisher exact test and in logistic regression models (PROC GENMOD, SAS 9.1; SAS Institute Inc, Cary, NC) adjusted for age in quartiles. All *P* values are 2-sided.

## RESULTS

Selected characteristics of the 917 study participants are given in Table 1. The mean age of the study participants

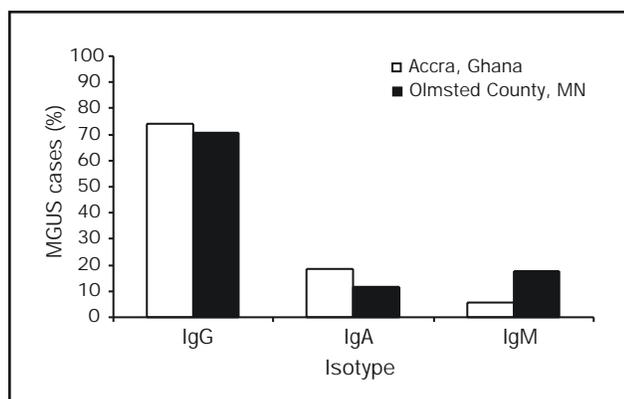


FIGURE 1. Distribution of monoclonal gammopathy of undetermined significance (MGUS) isotypes among men in Accra, Ghana, and Olmsted County, MN.

was 60 years (range, 50-74 years). Most (almost 98%) were born and currently living in Accra. The largest ethnic groups were the Ga-Adangbe people and those from the middle regions. Approximately 11% of the men had no formal education, whereas more than 60% had either a middle or junior secondary education level or a secondary or senior secondary education level. Approximately 15% of participants were found to have a higher education level (Table 1).

More than 80% of the participants reported a history of malaria, and almost 11% had previously had yellow fever. Approximately half of the study participants reported having a history of sexually transmitted diseases; gonorrhea was the most common. The prevalence of selected previous infectious conditions is listed in Table 1.

**PREVALENCE OF MGUS**

Of the 917 study participants, MGUS was detected in the serum of 54 (5.9%). The age-adjusted prevalence of MGUS was 5.89 (95% CI, 4.36-7.42) per 100 persons (50-74 years) (Table 2). The age-specific prevalence rates of MGUS per 100 persons for Ghanaian men were 5.33 (50-54 years), 5.74 (55-59 years), 5.42 (60-64 years), 7.74 (65-69 years), and 5.38 (70-74 years). No significant variation by age was found ( $P=.94$ ,  $\chi^2$  test) (Table 2).

The overall prevalence of MGUS (standardized to the 2000 standard world population [50-74 years]) among Ghanaian men (5.84 per 100 persons; 95% CI, 4.27-7.40) was significantly higher ( $P<.001$ ) compared with the rate among 7996 white men aged 50 to 74 years (2.97 per 100 persons; 95% CI, 2.59-3.34) in Olmsted County, MN,<sup>5</sup> with a relative risk of 1.97 (95% CI, 1.94-2.00).

When we conducted internal comparison analyses to examine the age-specific prevalence pattern by ethnicity, education status, or history of selected infectious diseases

TABLE 1. Selected Characteristics of Study Participants at Screening\*

Characteristics	Study participants (N=917)
Mean age, y (range)	60 (50-74)
Country of birth	
Ghana	897 (97.8)
Other than Ghana	15 (1.6)
Missing	5 (0.6)
Living in Accra	
Yes	885 (96.5)
No	7 (0.8)
Data missing	25 (2.7)
Ethnic group	
Ga-Adangbe	350 (38.2)
South	177 (19.3)
Middle	286 (31.2)
North	47 (5.1)
Data missing	57 (6.2)
Education status	
None	104 (11.3)
Primary	55 (6.0)
Middle or junior secondary	411 (44.8)
Secondary or senior secondary	169 (18.4)
Higher	129 (14.1)
Data missing	49 (5.3)
History of selected infectious conditions†	
Malaria	753/898 (83.8)
Tuberculosis	14/895 (1.6)
Cholera	26/889 (2.9)
Yellow fever	94/878 (10.7)
Measles	220/816 (27.0)
Meningitis	3/863 (0.3)
Syphilis	30/853 (3.5)
Gonorrhea	375/902 (41.6)
Hepatitis A	29/822 (3.5)
Hepatitis B or C	9/817 (1.1)
Genital herpes	58/887 (6.5)
Genital warts	4/900 (0.4)

\*Unless otherwise indicated.

†Denominator varies with number of participants for whom information is available.

among the Ghanaian men, we found no evidence of statistical variation (Table 3).

**CHARACTERISTICS OF MONOCLONAL IMMUNOGLOBULINS IN GHANAIAN MEN**

Among 54 men with evidence of MGUS, the isotype of the monoclonal immunoglobulin was IgG in 40 (74%), IgA in 10 (19%), IgM in 3 (6%), and biclonal in 1 (2%) (Table 4). In Olmsted County the proportion of IgM MGUS was higher (14%); however, the difference was not statistically significant ( $P=.11$ ) (Figure 1). The serum light chain type was  $\kappa$  in 26 (48%),  $\lambda$  in 27 (50%), and biclonal in 1 (2%) of the MGUS cases in Ghana. The fraction of patients with  $\lambda$  serum light chain MGUS was somewhat lower in Olmsted County (43%) than in Ghana ( $P=.36$ ).

The monoclonal immunoglobulin concentration was undetectable in 41 (76%) of the 54 Ghanaian men with MGUS, less than 0.49 g/dL in 2 (4%), 0.50 to 0.99 g/dL in

TABLE 2. Prevalence of MGUS in 917 Men in Accra, Ghana, and in 7996 Men in Olmsted County, MN\*

Variable	Ghana			Olmsted County <sup>6</sup>		
	Total No.	No. (%) with MGUS	Prevalence (95% CI) <sup>†</sup>	Total No.	No. (%) with MGUS	Prevalence (95% CI) <sup>†</sup>
Age (y)						
50-54	244	13 (5)	5.33 (2.51-8.15)	2181	40 (2)	1.83 (1.27-2.40)
55-59	209	12 (6)	5.74 (2.59-8.90)	1857	42 (3)	2.26 (1.59-2.94)
60-64	166	9 (5)	5.42 (1.98-8.87)	1520	52 (3)	3.42 (2.51-4.33)
65-69	168	13 (8)	7.74 (3.70-11.8)	1344	53 (4)	3.94 (2.90-4.98)
70-74	130	7 (5)	5.38 (1.50-9.26)	1094	56 (5)	5.12 (3.18-6.42)
Total, unadjusted	917	54 (6)	5.89 (4.36-7.42)	7996	243 (3)	3.04 (2.66-3.42)
Total, adjusted <sup>‡</sup>			5.84 (4.27-7.40)			2.97 (2.59-3.34)

\*CI = confidence interval; MGUS = monoclonal gammopathy of undetermined significance.

<sup>†</sup>Per 100 persons.

<sup>‡</sup>Standardized to the 2000 standard world population (50-74 years).

8 (15%), 1.00 to 1.49 g/dL in 1 (2%), and at least 2.00 g/dL in 2 (4%). Individual values ranged from undetectable to 2.92 g/dL; the median was 0.01 g/dL or 0.97 g/dL if the undetectable proteins were excluded (Table 4). In contrast, the monoclonal immunoglobulin was undetectable in only 12% of men 50 to 74 years of age in the Olmsted County MGUS study, and the differences are statistically significant ( $P < .001$ ).

### DISCUSSION

In this first population-based study of MGUS in Africa, we found a significant 2-fold (95% CI, 1.94-2.00) higher risk of MGUS among Ghanaian men aged 50 to 70 years (5.84

per 100 persons) compared with white men from Olmsted County (2.97 per 100 persons) of a comparable age group. Further, in contrast to white men, in whom the prevalence of MGUS increases significantly with age,<sup>6</sup> no age-associated differences in prevalence of MGUS were noted in Ghanaian men ( $P = .94$ ). To our knowledge, there is no available information on MGUS prevalence rates among Ghanaian men younger than 50 years. However, we have speculated that the flat MGUS prevalence pattern by age observed in our study might reflect a race-related earlier onset of MGUS among Ghanaian men. In further support of this hypothesis, African American men appear to be diagnosed with MM on average approximately 5 to 10 years earlier than white men.<sup>4</sup> Future studies that include younger persons are needed to show increasing prevalence by age.<sup>6</sup> Other differences include the lower rates of IgM MGUS, more frequent  $\lambda$  light chain use, and the smaller monoclonal proteins seen in MGUS among Ghanaian men.

TABLE 3. Risk of MGUS Stratified by Ethnic Group, Education Status, and History of Selected Infections\*

Variable	No. of MGUS cases	OR (95% CI) <sup>†</sup>
Ethnic group		
Ga-Adangbe	16	1.00
South	11	1.42 (0.64-3.15)
Middle	19	1.52 (0.76-3.04)
North	3	1.45 (0.41-5.20)
Education status		
None or primary	11	1.00
Middle or junior secondary	22	1.04 (0.45-2.38)
Secondary, senior secondary, or higher	19	1.20 (0.54-2.68)
Self-reported history of selected infections		
None <sup>‡</sup>		1.00
Malaria	46	1.53 (0.64-3.68)
Tuberculosis	2	2.79 (0.60-12.94)
Cholera	2	1.37 (0.31-6.03)
Yellow fever	7	1.36 (0.59-3.13)
Measles	12	0.82 (0.41-1.65)
Syphilis	3	1.87 (0.54-6.45)
Gonorrhea	20	0.82 (0.45-1.47)
Genital herpes	2	0.61 (0.14-2.58)

\*CI = confidence interval; MGUS = monoclonal gammopathy of undetermined significance; OR = odds ratio.

<sup>†</sup>Adjusted for age.

<sup>‡</sup>Each infectious condition was assessed separately, using the people without the condition as the reference group.

TABLE 4. Characteristics of Monoclonal Gammopathy of Undetermined Significance Among 54 Men in Accra, Ghana

Variable	No. (%) <sup>*†</sup>
Mean monoclonal protein concentration, g/dL (range) <sup>‡</sup>	0.97 (0.29-2.92)
Monoclonal immunoglobulin isotype	
IgG	40 (74)
IgA	10 (19)
IgM	3 (6)
Biclonal	1 (2)
Serum light chain type	
$\kappa$	26 (48)
$\lambda$	27 (50)
Biclonal	1 (2)
Monoclonal immunoglobulin concentration, g/dL	
Undetectable	41 (76)
$\leq 0.49$	2 (4)
0.50 to 0.99	8 (15)
1.00 to 1.49	1 (2)
1.50 to 1.99	0 (0)
$\geq 2.00$	2 (4)

\*Unless otherwise indicated.

<sup>†</sup>Percentages do not total 100% because of rounding.

<sup>‡</sup>Excluding cases with undetectable monoclonal protein concentration.

In the United States, a distinct racial disparity pattern is seen for MM incidence, reflected in an approximately 2-fold higher incidence for African Americans (9.5 per 100,000 person-years) than whites (4.1 per 100,000 person-years).<sup>4</sup> This increase is related to the increased prevalence of MGUS, the precursor premalignant condition to MM, among African Americans rather than an increased conversion of MGUS to MM.<sup>5</sup> In our study, we report that African men in Ghana also had an increased prevalence of MGUS relative to that in white men, further suggesting that the difference in MM incidence in whites vs African Americans in the United States is likely due to race-related genetic susceptibility because Africans and African Americans have similar but not identical genetic make-up. The increased incidence likely also reflects unknown environmental influences that might interact with host (genetic) factors.

Although currently there are no established risk factors for MGUS other than age, some, but not all, smaller studies have indicated an increased incidence of MGUS among people with a history of certain infections (for example, hepatitis C and *Helicobacter pylori*).<sup>10-12</sup> However, on the basis of self-report, we found no statistically significant association between MGUS and a history of 12 infectious diseases (Table 3). Studies based on larger numbers are needed to better assess the association between immune-mediated and inflammatory conditions in relation to MGUS risk. Prevalence of MGUS did not vary by demographic features, ethnicity, or education status.

On the basis of estimates derived from white populations, we previously reported that the annual risk of progression of MGUS to MM or a related tumor is approximately 1%; this risk is unaffected by age or duration of MGUS but increases as the concentration of serum M protein increases.<sup>3</sup> Thus, the absolute risk of malignancy for a patient aged 50 years with a projected 25-year life span is 25%; MGUS is therefore more likely to progress to cancer in younger people because they have more years at risk. However, the proportion of men with MGUS who had an undetectable M protein level was significantly higher in Ghana than in Olmsted County (75.9% vs 12.4%).<sup>3</sup> This discrepancy is striking, and underlying mechanisms need to be explored in future studies.

Of the immunoglobulin types, IgG was most common in the Ghanaian MGUS cases (almost 75%), confirming the findings of both the Olmsted County survey<sup>6</sup> and a previous French study.<sup>13</sup> However, IgM MGUS was found in 6% of the Ghanaian men compared with 14% of the men from Olmsted County (50-74 years), 24% of the participants in the French study,<sup>13</sup> and 8% in a Swedish study.<sup>14</sup> Although we cannot explain the observed discrepancy, the pattern is consistent with the incidence ratio of Waldenström macroglobulinemia when stratified by race.

Waldenström macroglobulinemia, a malignancy associated with IgM, is approximately twice as common in whites as in African Americans in the United States.<sup>15</sup> The isotype of the immunoglobulin has been found to be associated with risk for cancer progression (IgG is associated with lower risk than IgM and IgA).<sup>3</sup> It is thus unclear what the risk of cancer progression is in the Ghanaian population that we studied. Long-term follow-up studies of MGUS cases in people of African descent are needed to define the annual risk of MGUS progression to MM.

Major strengths of this large population-based study include its inclusion of probability samples from the population, its high response rate, its high-quality in-person interviews, its rigorous quality-control procedures, and the highly sensitive and specific monoclonal analyses performed at Mayo Clinic. Limitations include the unavailability of a fully detailed medical history, which prevented full ascertainment of comorbidities (such as infections other than those included in the protocol) and of data on medication use. Also, we lack information on the prevalence of MGUS in women. Additional investigations are needed to confirm our findings and to expand the study population to include women and patients younger than 50 years.

Future studies, including genetic mapping by admixture linkage disequilibrium applied to African American populations with MM or MGUS, could provide insights into the etiology and pathogenesis of MGUS and risk factors for MM progression.<sup>16-18</sup> A better description of the mechanisms that mediate monoclonal plasma cell proliferation, survival, and migration in the bone marrow microenvironment could ultimately enhance our understanding of MGUS and MM pathophysiology and allow identification of novel molecular targets.<sup>19</sup>

## CONCLUSION

We found a significant 2-fold elevated risk of MGUS in Ghanaian men, which is supportive of the hypothesis that race-associated differences in genetic susceptibility could explain higher incidence rates of MGUS and in part explain higher incidence rates of MM among African Americans. Because no curative MM therapy is currently available, we must improve our understanding of MGUS and MM pathophysiology with the aim of developing strategies to prevent progression of MGUS to MM.

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