Risk of Malignant Disease Among 1525 Adult Male US Veterans With Gaucher Disease

Ola Landgren, MD, PhD; Ingemar Turesson, MD, PhD; Gloria Gridley, MS; Neil E. Caporaso, MD

Background: Some, but not all, reports suggest that patients with Gaucher disease are at increased risk of developing malignancies, particularly hematopoietic tumors. The aim of this study was to assess the pattern of Gaucher disease and subsequent malignancies among male veterans admitted to US Veterans Affairs hospitals.

Methods: Among 832,294 African American and 3,668,983 white male veterans with at least 1 hospital admission in US Veterans Affairs hospitals and up to 27 years of follow-up, we identified a total of 1,525 patients with Gaucher disease; 11.7% were African Americans. We used Poisson regression methods for cohort data to estimate relative risks (RRs) and 95% confidence intervals (CIs) after adjusting for attained age and calendar year, race, number of hospital visits, and latency.

Results: When patients with Gaucher disease were compared with patients without Gaucher disease, the RR of any cancer was 0.91 (95% CI, 0.76-1.08 [n=137]). When we stratified our analyses by race, risks were similar for whites (RR, 0.89; 95% CI, 0.74-1.07 [n=120]) and African Americans (RR, 1.00; 95% CI, 0.61-1.64 [n=17]). Patients with Gaucher disease had an elevated risk for non-Hodgkin lymphoma (RR, 2.54; 95% CI, 1.32-4.88 [n=9]), malignant melanoma (RR, 3.07; 95% CI, 1.28-7.38 [n=5]), and pancreatic cancer (RR, 2.37; 95% CI, 1.13-4.98 [n=7]). Among the remaining 19 cases involving defined solid tumors and 7 other hematologic malignancies, we found no statistical association with Gaucher disease.

Conclusion: We found 2- to 3-fold risks of non-Hodgkin lymphoma, malignant melanoma, and pancreatic cancer in patients with Gaucher disease, but no significant association between Gaucher disease and cancer in general or with other specific malignancies such as multiple myeloma.

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Recently, using the International Gaucher Registry,6 Rosenbloom et al10 assessed the cancer incidence among 2742 patients with Gaucher disease. They found 126 cases of cancer, actually suggesting an overall decreased risk of cancer (relative risk [RR], 0.79; 95% confidence interval [CI], 0.67-0.94). However, 10 of the patients had MM, yielding an estimated RR of 5.9 (95% CI, 2.82-10.82); all MM cases were diagnosed after the age of 50 years. Based on their findings, Rosenbloom and colleagues concluded that patients with Gaucher disease, particularly those older than 50 years, should undergo serial serum electrophoresis every 1 to 2 years to rule out MM and/or the precursor condition monoclonal gammopathy of undetermined significance (MGUS), which often precedes MM.21-23

We were motivated by these previous investigations to conduct a study of cancer risk among patients with Gaucher disease using a database of adult male military veterans admitted to US Veterans Affairs (VA) hospitals. Advantages of the study include its large size (>4 million veterans) and long-term follow-up (up to 27 years).

### METHODS

**HOSPITALS, PATIENTS, AND OUTCOMES**

An exemption from institutional review board review was obtained from the National Institutes of Health Office of Human Subjects Research, Bethesda, Md, because we analyzed existing data without personal identifiers. Informed consent was waived because there was no contact with study subjects. The cohort was identified from discharge records for all inpatient hospitalizations at 142 nationwide US VA hospitals between July 1, 1969, and September 30, 1996. Based on US census data, there were an estimated 30 million US veterans entitled to admission data without personal identifiers. Informed consent was waived because there was no contact with study subjects. The cohort was identified from discharge records for all inpatient hospitalizations at 142 nationwide US VA hospitals between July 1, 1969, and September 30, 1996. Based on US census data, there were an estimated 30 million US veterans entitled to admission to VA hospitals during the study period. The target population included all African American (n=832 294) and white (n=3 668 983) male veterans hospitalized at least once during the study period. The subjects were followed up for as long as 27 years with an average of 12.5 and 12.8 years for white and African American patients, respectively. On average, African American men tended to be younger than white men at study entry, and African American men were diagnosed as having Gaucher disease at a slightly younger age than white men. A total of 137 patients (9.0%) with Gaucher disease were hospitalized with a malignant disease. Patients with Gaucher disease tended to visit the hospital more often than patients without a diagnosis of Gaucher disease.

### RESULTS

We identified 1346 white patients (88.3%) and 179 African American patients (11.7%) with Gaucher disease (Table 1). The subjects were followed up for as long as 27 years, with an average of 12.5 and 12.8 years for white and African American patients, respectively. On average, African American men tended to be younger than white men at study entry, and African American men were diagnosed as having Gaucher disease at a slightly younger age than white men. A total of 137 patients (9.0%) with Gaucher disease were hospitalized with a malignant disease. Patients with Gaucher disease tended to visit the hospital more often than patients without a diagnosis of Gaucher disease.

As shown in Table 2, Gaucher disease was not associated with an overall cancer risk (RR, 0.91; 95% CI, 0.76-1.08). When we stratified our analyses by race, risks were comparable for whites (RR, 0.89; 95% CI, 0.74-1.07) and African Americans (RR, 1.00; 95% CI, 0.61-1.64). We observed increased risks for non-Hodgkin lymphoma (NHL) (RR, 2.54; 95% CI, 1.32-4.88 [n=9]), malignant melanoma (RR, 3.07; 95% CI, 1.28-7.38 [n=5]), and pancreatic cancer (RR, 2.37; 95% CI, 1.13-4.98 [n=7]) among patients with Gaucher disease.

#### Table 1. Characteristics of the Study Cohort*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Whites Without Gaucher Disease</th>
<th>Whites With Gaucher Disease</th>
<th>African Americans Without Gaucher Disease</th>
<th>African Americans With Gaucher Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>3 667 637</td>
<td>1346</td>
<td>8 321 15</td>
<td>179</td>
</tr>
<tr>
<td>Mean age at study entry, y†</td>
<td>51.1</td>
<td>49.7</td>
<td>46.7</td>
<td>46.0</td>
</tr>
<tr>
<td>Mean duration of follow-up, y*</td>
<td>11.7</td>
<td>12.5</td>
<td>11.9</td>
<td>12.8</td>
</tr>
<tr>
<td>Person-years at risk*</td>
<td>42 734 763</td>
<td>16 889</td>
<td>9 884 304</td>
<td>2 294</td>
</tr>
<tr>
<td>Median No. of hospital visits</td>
<td>3</td>
<td>7</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

*White and African American male veterans (US Veterans Affairs) with at least 1 hospital admission between July 1, 1969, and September 30, 1996, who were followed up for more than 1 year. The first year of follow-up was censored.

†Age at first discharge record for inpatient hospitalization at Veterans Affairs hospitals between July 1, 1969, and September 30, 1996.
Among the remaining 19 cases of defined solid tumors and 7 other hematologic malignancies, we found no statistical association with Gaucher disease (Table 2). It can be seen from the 95% CIs in Table 2 that this study had the statistical power to detect the common cancers with an RR of approximately 2. However, for rare cancers, such as MM, our study could detect only RRs greater than 5. Also, among the patients with Gaucher disease, we found no cases involving a subsequent diagnosis of MGUS. In a separate analysis of the data that we censored (ie, the first year of follow-up after index hospital discharge), we found no cases of cancer among the patients with Gaucher disease.

In this large registry-based cohort study, which included 1525 adult male patients with a diagnosis of Gaucher disease and a very long follow-up, we found no evidence of an increased general risk of malignant disease. When we considered individual solid and hematopoietic tumors, we found that the risks of NHL, malignant melanoma, and pancreatic cancer were elevated 2- to 3-fold among patients with Gaucher disease compared with those without Gaucher disease. The presence of Gaucher disease was not associated with a significantly elevated risk for any other defined malignancy.

Although there are only sparse data available, a general association between Gaucher disease and subsequent risk of malignant disease has been found in some, but not all, previous studies. In the largest study to date (n=2742), Rosenbloom et al found a borderline decreased risk of cancer among patients with Gaucher disease. Because we had access to a large hospital-based investigation, with data retrieved from a nationwide record linkage of 142 VA hospitals, our results of a null general association between Gaucher disease and cancer add substantially to, and verify the results of, the restricted literature on this topic. Although type 1 Gaucher disease is a panethnic disorder, it is especially prevalent among persons of Ashkenazi Jewish descent (almost 1 per 1000), with a carrier rate of 1 in 17 Ashkenazi Jews. Thus, our results are particularly relevant for this ethnic group.

Regarding the association between Gaucher disease and specific types of malignant disease, there have previously been hospital-based cohorts but not all, previous studies. In 9 patients with Gaucher disease, we found a 2.5-fold significantly elevated risk for NHL. The occurrence of lymphoma following Gaucher disease has been reported in prior studies, although, to our knowledge, elevated risk estimates for NHL have not previously been reported among patients with Gaucher disease. Our findings add new information and may have clinical implications for the treatment and follow-up of patients with Gaucher disease. If replicated, the observed elevated risk of NHL following Gaucher disease suggests that more aggressive workup should be undertaken for patients with Gaucher disease who have a new onset of symptoms, such as lymphadenopathy, fever, weight loss, and/or night sweats, that might be explained by a lymphoma diagnosis. It is particularly important to diagnose NHL at an early stage to improve the probability of cure, to avoid unnecessary trauma for the patient, and to minimize risks of secondary complications due to NHL treatment.

In contrast to previous hospital-based studies, we failed to observe an elevated risk of MM, which is the malignancy that by far has drawn the most attention in the literature. As shown in Table 3, prior studies on Gaucher disease have typically included patient series using data from a single hospital or a limited number of hospitals. Although we had no information on clinical follow-up routines for patients with Gaucher disease in VA hospitals, we believe that skeletal and visceral assessment routines are probably more rigorous in specialist units that have a particular clinical and research interest in Gaucher disease than in VA hospitals with a broader medical approach. Follow-up procedures imply increased surveillance, a potential bias that could be the

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>No. Observed</th>
<th>RR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematopoietic malignancies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>9</td>
<td>2.54 (1.32-4.88)‡</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>1</td>
<td>NE</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>2</td>
<td>1.29 (0.32-5.16)</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>1</td>
<td>NE</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>2</td>
<td>3.40 (0.85-13.60)</td>
</tr>
<tr>
<td>Acute lymphocytic leukemia</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>1</td>
<td>NE</td>
</tr>
<tr>
<td>Waldenström macroglobulinemia</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

Solid malignancies

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>No. Observed</th>
<th>RR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>7</td>
<td>0.94 (0.45-1.97)</td>
</tr>
<tr>
<td>Bone and articular cartilage</td>
<td>1</td>
<td>NE</td>
</tr>
<tr>
<td>Brain</td>
<td>1</td>
<td>NE</td>
</tr>
<tr>
<td>Colon</td>
<td>9</td>
<td>1.14 (0.59-2.20)</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>3</td>
<td>1.55 (0.22-11.03)</td>
</tr>
<tr>
<td>Digestive organs, unspecified</td>
<td>1</td>
<td>NE</td>
</tr>
<tr>
<td>Endocrine glands</td>
<td>1</td>
<td>NE</td>
</tr>
<tr>
<td>Esophagus</td>
<td>1</td>
<td>NE</td>
</tr>
<tr>
<td>Kidney</td>
<td>3</td>
<td>0.59 (0.15-2.38)</td>
</tr>
<tr>
<td>Larynx</td>
<td>3</td>
<td>0.26 (0.04-1.88)</td>
</tr>
<tr>
<td>Lip</td>
<td>1</td>
<td>NE</td>
</tr>
<tr>
<td>Liver and intrahepatic bile ducts</td>
<td>1</td>
<td>NE</td>
</tr>
<tr>
<td>Lung, bronchus, and trachea</td>
<td>38</td>
<td>0.85 (0.62-1.18)</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>5</td>
<td>3.07 (1.28-7.38)‡</td>
</tr>
<tr>
<td>Nervous system, unspecified</td>
<td>1</td>
<td>NE</td>
</tr>
<tr>
<td>Pancreas</td>
<td>7</td>
<td>2.37 (1.13-4.98)‡</td>
</tr>
<tr>
<td>Prostate</td>
<td>22</td>
<td>0.94 (0.61-1.43)</td>
</tr>
<tr>
<td>Rectum, rectosigmoid junction, and anus</td>
<td>6</td>
<td>1.09 (0.45-2.61)</td>
</tr>
<tr>
<td>Sallivary gland</td>
<td>1</td>
<td>NE</td>
</tr>
<tr>
<td>Stomach</td>
<td>2</td>
<td>2.66 (0.37-18.94)</td>
</tr>
<tr>
<td>Testis</td>
<td>1</td>
<td>NE</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>NE</td>
</tr>
<tr>
<td>Any malignancy, total</td>
<td>137</td>
<td>0.91 (0.76-1.08)</td>
</tr>
<tr>
<td>Any malignancy, by race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African Americans</td>
<td>17</td>
<td>1.00 (0.61-1.64)</td>
</tr>
<tr>
<td>Whites</td>
<td>120</td>
<td>0.89 (0.74-1.07)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NA, not applicable; NE, not estimated; RR, relative risk.

‡The first year of follow-up was censored.

*Adjusted for race, latency, attained age, attained calendar year, and number of hospital visits.

P<.05. Results were very similar when we conducted analyses stratified by calendar period.
Table 3. Gaucher Disease and Subsequent Malignant Disease

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>No. of Patients With Gaucher Disease</th>
<th>No. of Subsequent Malignancies</th>
<th>No. of Subsequent Malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al.1982</td>
<td>Postmortem hospital-based case series</td>
<td>35</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Shoenfeld et al.201982</td>
<td>Hospital-based case series</td>
<td>25</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Shiran et al.1993</td>
<td>Hospital-based case series</td>
<td>48</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Zimran et al.6 2005</td>
<td>Hospital-based case series</td>
<td>500</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Rosenbloom et al.10 2005</td>
<td>International Gaucher Registry</td>
<td>2742</td>
<td>10*</td>
<td>5*</td>
</tr>
<tr>
<td>de Fost et al.11 2006</td>
<td>Hospital-based case series</td>
<td>131</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Present study</td>
<td>Registry based (142 Veterans Affairs hospitals)</td>
<td>1525</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

*Including both prevalent (ie, present before or at diagnosis of Gaucher disease) and incident tumors following a diagnosis of Gaucher disease, because the International Gaucher Registry does not have information on the date of cancer diagnosis in most cases.

There are clinical indications to suspect MM in an individual patient, a conventional workup for MM (including serum electrophoresis analysis, bone marrow biopsy, skeletal radiography, and conventional blood tests) appears to be the appropriate route of action.

Immunoglobulin abnormalities have been associated with type 1 Gaucher disease. The most common finding is polyclonal hypergammaglobulinemia; however, an elevated occurrence of the precursor condition MGUS has also been reported. In our study, we observed no MGUS cases among 1525 identified patients with Gaucher disease. Because MGUS is generally asymptomatic and information on subsequent disease was derived from hospital discharge listings (ie, no detailed clinical or laboratory data were available), it is reasonable to conclude that the observed null association is the result of underascertainment of MGUS. Genetic studies have found that almost 50% of MGUS cases have primary translocations in the clonal plasma cells involving the immunoglobulin heavy-chain (IgH) locus on chromosome 14q32,41,42 a locus thought to be important for the initiation and support of clonal proliferation.41-43 It has been suggested that hypermutability and proliferation of key cells associated with infections could be the precipitating events for these translocations.41 In light of the previously reported association between Gaucher disease and MGUS,32,36-38 it may be hypothesized that abnormal macrophages in Gaucher disease could be especially vulnerable to such precipitating events. Results from a mouse model of Gaucher disease suggest that the inflammatory response in Gaucher disease is independent of glucocerebroside deposition,46 but, to our knowledge, the same relationship has not been explored in humans. Progressive glucocerebroside storage in Gaucher disease could plausibly act via chronic stimulatory mechanisms of the immune system, causing lymphoproliferation.42 Gaucher cells themselves might act (1) by inducing local inflammatory response in surrounding inflammatory cells,47 (2) by reducing T-cell functionality,48 or (3) by a combination of both processes. Interestingly, there are indications that decreased numbers and dysfunction of regulatory T cells are of pathogenetic importance in MGUS and MM.49 These and other potential underlying mechanisms remain to be explored in future preclinical studies. It would be of scientific interest to screen a cohort of patients with Gaucher disease to determine the prevalence of MGUS. If the rates for MGUS are found to be highly elevated compared with the currently reported 3.2% age-adjusted prevalence rate among adults older than 50 years,23 further studies may be required to explore underlying mechanisms.

Based on 5 cases, we found a 3.1-fold increased risk of malignant melanoma among patients with Gaucher disease, and based on 7 cases, we found a 2.4-fold increased risk of pancreatic cancer among patients with Gaucher disease. Interestingly, a host-related immunogenetic profile has recently been proposed to be of importance for susceptibility and tumorigenesis in malignant melanoma.50 Also, there are epidemiological indications that
host-related immune response might play a role in the risk for pancreatic cancer. However, previous studies on Gaucher disease have not reported an excess risk for these cancers, so chance is an alternate explanation.

The prevalence of Gaucher disease in our study is higher than previously reported. This finding is not surprising as the present study is hospital based (ie, it involves male US veterans with at least 1 hospital admission) rather than being based on the general population. For example, if we were to have estimated the prevalence of diabetes mellitus in this hospitalized population, it would also have been much higher than population-based rates. Similarly, the prevalence of Gaucher disease that we report is at the time of hospitalization (approximately at the age of 50 years) and not at the age of military service. With regard to Gaucher disease among blacks, there are only limited data in the literature. As pointed out by the authors of a recent investigation on African Americans with Gaucher disease (based on only 7 cases), the current understanding of Gaucher disease in African Americans has been derived from small numbers and is therefore inherently affected by ascertainment bias, with milder patients escaping diagnosis. To our knowledge, no population-based survey has been conducted to determine the age-adjusted prevalence of Gaucher disease among African Americans. In our study, based on 832 294 African American and 3 668 983 white male veterans with at least 1 hospital admission, we found 179 (1/1650) and 1346 (1/2726) individuals with a diagnosis of Gaucher disease, respectively. As discussed above, the general risk of cancer among Gaucher disease cases was very similar for the 2 races (RRs around 1.0).

The strength of the current study includes its larger size in a patient population with relatively stable and standardized access to medical care that is provided to US veterans independent of socioeconomic status. Also, study subjects were older than 18 years at enrollment and they were followed up for intervals as long as 27 years. To evaluate incident rather than prevalent cancer, we estimated the risk of malignancy using all subjects without a prior discharge diagnosis of malignancy and censored the first year of follow-up. Furthermore, in a subanalysis, we assessed the occurrence of malignancy in that censored year (ie, the first year after the index hospitalization), and we found no tumors among patients with Gaucher disease. The limitations of our study include the lack of information about demographic, clinical, treatment, laboratory, or biomarker information for individual patients in the database as well as the lack of specific information on the Gaucher disease phenotype. However, based on the literature, 90% to 95% of the patients with Gaucher disease have type 1 disease. The identification of the cohort from hospital discharge diagnoses, rather than from screening, is likely to have led to underascertainment of Gaucher disease. Individuals with early-onset severe Gaucher disease are likely not included in this study because they were almost certainly disqualified from military service in their younger years. The use of a retrospective cohort might potentially have resulted in some underascertainment of cancer cases. Also, the restriction to male patients might limit the generalizability of our results. The lack of independent validation of cancer diagnosis is another limitation of our study; however, the ascertainment of cancers was similar among patients with and without Gaucher disease, so the chance of significant bias is reduced. In addition, we previously found more than 98% validity for cancer diagnoses in VA discharge records. Because MM is rare before the age of 40 years and the median age at diagnosis is approximately 70 years, the possibility that prolonged follow-up might have disclosed an increased incidence of MM in our study cannot be excluded. Another limitation involves the fact that available ICD-8 and ICD-9 codes for Gaucher disease are not entirely specific and include other lipid storage disorders, such as Niemann-Pick disease and mucolipidosis II. However, these non-Gaucher lipid storage disorders usually manifest at young ages. Therefore, individuals affected with these conditions would likely not serve in the military. Furthermore, Gaucher disease is the most common inherited storage disease, and other lipid storage disorders are not known to be associated with cancer. Although we had the statistical power to detect common cancers with RRs of approximately 2, for rare cancers (such as MM) we were unable to detect RRs of less than 5. Finally, because we studied multiple cancer outcomes and risk estimates were based on small numbers, positive results should be interpreted with caution.

In conclusion, among more than 1500 adult male US veterans with a diagnosis of Gaucher disease, we found no evidence of a generally elevated risk of subsequent hematopoietic or solid tumors. We observed 2- to 3-fold risks of NHL, malignant melanoma, and pancreatic cancer subsequent to Gaucher disease, but we were unable to confirm the previously reported association between Gaucher disease and MM.

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