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RESEARCH ARTICLE

# Cancer risk and gammopathies in 2123 adults with Gaucher disease type 1 in the International Gaucher Group Gaucher Registry

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## Abstract

There are numerous reports of cancers in Gaucher disease (GD) from mostly small single-center studies; however, precise risk estimates and cancer types involved have not been delineated. We conducted a study involving 2123 patients with GD type 1 (GD1) to assess the incidence of hematological malignancies, gammopathies, and solid tumors in an international observational study, the International Cooperative Gaucher Group Gaucher Registry (Clinicaltrials.gov: NCT00358943). Risk for cancer overall and for each type of malignancy was compared to the United States (US) population using the Surveillance, Epidemiology, and End Results database. Natural history of gammopathy was determined through assessing the progression from a diagnosis of monoclonal gammopathy of unknown significance (MGUS) to multiple myeloma (MM). Risk for hematological malignancies was more than four times higher than expected compared to the general population: non-Hodgkin lymphoma was approximately three times higher; MM was approximately nine times higher. Age-specific incidence rates of MGUS were unexpectedly high among younger patients. The 10-year cumulative incidence of MM after diagnosis of MGUS was 7.9%, comparable to the general population. Compared to the general US population, GD1 patients were at higher risk for solid malignancies of liver (2.9 times), kidney (2.8 times), melanoma (2.5 times), and breast (1.4 times). Colorectal, prostate, and lung cancer risks were lower than expected. These findings help advance care of patients with GD1 by supporting recommendations for individualized monitoring for malignancies and antecedents such as MGUS for MM and provoke important questions of the role of glucosylceramide and related sphingolipids in cancer biology.

## 1 | INTRODUCTION

Gaucher disease (GD) is a rare, autosomal recessive inborn error of metabolism caused by deficient lysosomal acid β-glucosidase activity (EC 3.2.1.45) that underlies the accumulation of glucosylceramide and its bioactive metabolite glucosylsphingosine within lysosomes of tissue macrophages, triggering chronic metabolic inflammation.[1] GD is known for its phenotypic diversity with three broad phenotypes (types 1 [OMIM #230800], 2 [#230900], and 3 [#231000]). GD type 1 (GD1) is the most common type with multisystemic manifestations including splenomegaly, hepatomegaly, anemia, thrombocytopenia, marrow infiltration, and complex bone disease. Although overt, early-onset neurodegenerative disease is absent in GD1 compared to types 2 and 3,[1] late-onset synucleinopathies may occur in GD1 patients.[2] Treatment for GD1 includes macrophage-mannose-receptor-targeted, recombinant enzyme replacement therapy (ERT) (e.g., imiglucerase, velaglucerase alfa, or taliglucerase) and oral substrate reduction therapy (SRT) with inhibitor of glucosylceramide synthase (GCS; e.g., eliglustat or miglustat).

GD1, as with other inborn errors of metabolism, is associated with increased cancer risk.[3] The tissue microenvironment of GD presents an aggregation of factors that promote carcinogenesis, for example: simultaneous occurrence of accumulation of growth promoting metabolite, glucosylceramide, cancer promoting metabolite shunting (Warburg effect), M2 polarization of glucosylceramide-laden macrophages, chronic B-cell stimulation, chronic metabolic inflammation, masked metabolic syndrome with insulin resistance, iron overload, lysosomal dysfunction, and endoplasmic reticulum stress.[3–5] Inborn errors of metabolism generally exhibit increased cancer risk in the site of metabolic defect (e.g., hepatocellular carcinoma in alpha1 antitrypsin deficiency or hemochromatosis). GD is primarily a bone marrow disease, hence hematological malignancies are expected to be increased, but the types and magnitude of risk are not clear. Moreover, whether the risk of solid organ cancers is increased in GD1 is also not clear. Reliable data on the types of malignancies and magnitude of risk are important to improve patient care and inform scientific investigations into the role of glucosylceramide and its downstream metabolites in carcinogenesis.

We conducted a study in a large, multicenter, international sample from the International Cooperative Gaucher Group (ICGG) Gaucher Registry (NCT00358943, Sanofi-funded) for comprehensive delineation of the relative risk of hematological and solid organ malignancies and the relationship between gammopathies and multiple myeloma (MM). The ICGG Gaucher Registry is a global, observational, voluntary program for patients with GD created in 1991 which has tracked the natural history and outcomes of GD patients for over 30 years regardless of treatment status. In 2017, the ICGG Gaucher Registry team began a focused retrospective and prospective collection of gammopathy- and malignancy-related data. We investigate the relative risk for hematologic malignancies and solid tumors among GD1 patients compared to a representative general population as well as the incidence of polyclonal gammopathies and monoclonal gammopathies of undetermined significance (MGUS), and the frequency with which GD1 patients with MGUS progress to MM.

## 2 | METHODS

### 2.1 | Study population

The study population included all patients who were diagnosed with GD1 and had a non-missing response to "Has the patient been diagnosed with a malignancy?" or "Has the patient been diagnosed with a gammopathy?" and whose most recent Registry date of record or death was 1993 or later. Malignancies reported prior to 1993 are excluded from all analyses to reduce recall bias. The study was conducted according to the principles of the Declaration of Helsinki.[6] Informed consent was obtained from all patients per study site regulations and verified by study monitors. Data are reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[7]

### 2.2 | Gammopathy and malignancy categorization

Diagnoses of gammopathy and malignancy, date of diagnosis, and type of gammopathy (MGUS and polyclonal) or malignancy (hematologic and solid) were collected. Hematologic malignancies included MM, plasmacytoma, non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myelodysplastic syndrome, and "any other hematologic malignancy." Solid malignancies included liver, renal cell, thyroid, cervical, breast, ovarian, lung, colorectal, pancreatic, prostate, testicular, vascular tumors, sarcoma, melanoma, skin (squamous and basal cell type), and "any other solid tumors."

### 2.3 | Analytical methods

Crude incidence rates of malignancy among GD1 patients were calculated as the number of cases diagnosed during the study period (January 1993–January 2021) divided by the total person-years of time observed during the study period. Incidence rates were calculated for overall malignancies (excluding basal and squamous cell skin cancer), hematologic malignancies, solid tumor malignancies, and MM, NHL, liver cancer, renal cell cancer, melanoma, breast cancer (women only), colorectal cancer, prostate cancer (men only), and lung cancer separately. Person-time was calculated as the time from the start of the study period until either end of follow-up date or (1) for overall malignancies, the earliest malignancy diagnosis date or (2) for specific cancers, until the first date of diagnosis of that cancer type.

Age-adjusted rates were calculated by weighting the crude incidence rate within 5-year age groups according to the 2000 United States (US) Standard Population (Census P25-1130). This allowed for comparison to age-adjusted incidence rates of malignancy in the US general population using the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (SEER 13 database[8]), which is also adjusted to the 2000 US Standard Population. We compared age-adjusted incidence rates in the Registry

to SEER incidence data from three time points (1995, 2005, 2015) to account for evolving rates of malignancy in the general population over the study period. Results are shown from the 2015 SEER data comparison (Figure 1); results were similar for the 1995 and 2005 SEER comparisons (see Figure S2).

Crude incidence rates of MGUS and polyclonal gammopathy among GD1 patients ≥18 years were calculated by dividing number of events by person-time, defined as the time from study entry until the patient's first diagnosis of MGUS/polyclonal gammopathy or last reported follow-up. Incidence rates of MGUS and polyclonal gammopathy were calculated by age category and were age-adjusted using the 2000 US Standard Population. Age-adjusted incidence rates were calculated overall and by N370S genotype (homozygous or heterozygous/other). The cumulative incidence function of MGUS and polyclonal gammopathy by age was also calculated, overall and by the length of time between GD1 diagnosis and treatment initiation. Time between GD diagnosis and treatment initiation was categorized as: 0–<5 years, 5–<15 years, 15–<25 years, and ≥25 years. A difference in cumulative incidence between categories was tested for statistical significance using Gray's test.[9]

To further investigate whether the risk of MGUS and polyclonal gammopathy (analyzed separately) varied depending on the time between GD1 diagnosis and treatment initiation, we used multivariable Cox proportional hazard (PH) analyses with age as the time scale, adjusting for age at treatment initiation, sex, time-period of diagnosis, and splenectomy status. Interaction between each covariate and "time between GD1 diagnosis and treatment initiation" was assessed; no significant interactions were found.

The risk of progression from MGUS to MM was assessed using the cumulative incidence function of MM among patients who reported MGUS. Follow-up was defined as the time from MGUS diagnosis to the date of MM diagnosis or the date of last follow-up if no MM diagnosis. A swimmer plot illustrated the disease-related journey of each patient with MGUS and MM.

Statistical analyses were performed using SAS, version 9.4 (Cary, North Carolina) and a significance level of $\alpha = .05$. Registry data cutoff was January 28, 2021.

## 3 | RESULTS

### 3.1 | Study population

Of the 5035 GD1 patients enrolled in the Registry, 2123 patients had a yes/no response for report of malignancy and/or gammopathy within the study timeframe. Forty-six percent were male; mean (standard deviation [SD]) age at GD diagnosis was 23.7 (18.5) years; and 88.9% had received treatment for GD at a mean (SD) age of

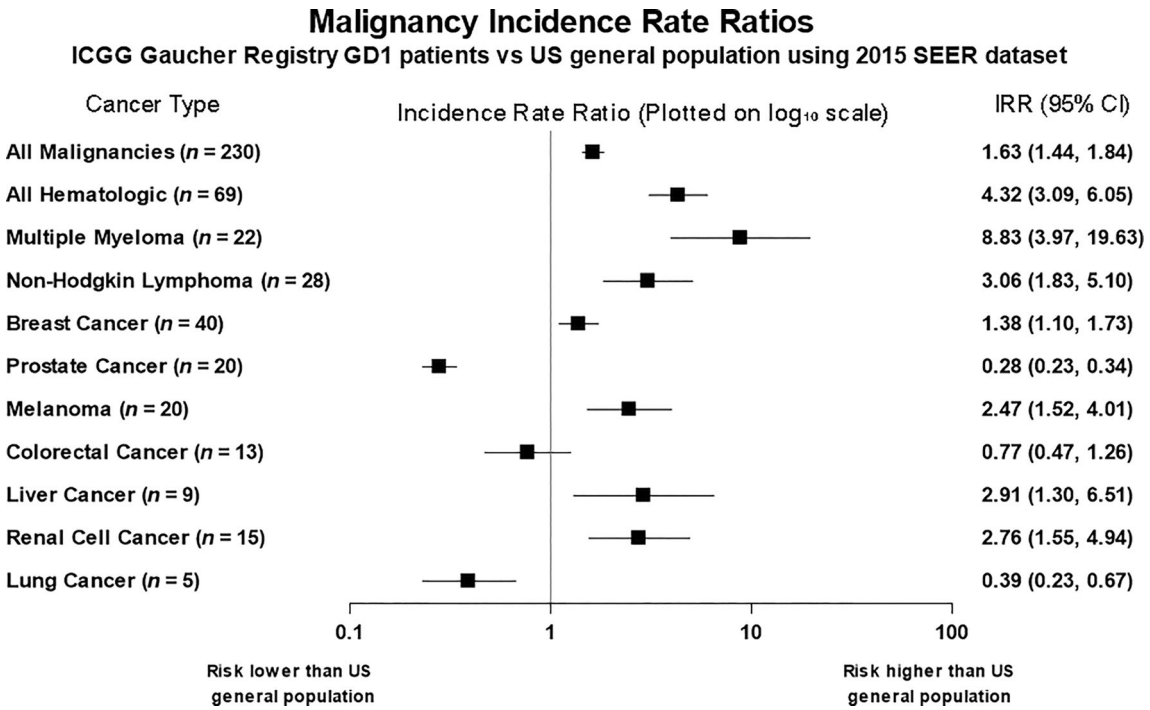


**FIGURE 1** Malignancy rates and comparison of risk for solid and hematologic malignancies of GD1 patients with the United States general population using the SEER data from 2015 are shown for those solid and hematological malignancies where a difference in rates was observed. Incidence rates are age-adjusted to the 2000 US Census population for comparison. The log of the incidence rate ratios is graphed. Only females are included for breast cancer. Only males are included for prostate cancer. Disease type reported by physician. *$n$ is the number of cases for each malignancy type in the ICGG Gaucher Registry. "All malignancies" include all malignancies except basal cell and squamous cell skin cancer, which are not reportable to the SEER database. CI, confidence interval; GD1, Gaucher disease type 1; ICGG, International Cooperative Gaucher Group; IRR, incidence rate ratio

32.9 (19.4) years. Mean (SD) age at last follow-up was 48.1 (20.3) years. Most patients had an intact spleen (80.7%); for those patients who were splenectomized, the mean (SD) age of splenectomy was 23.2 (15.9) years. Of the 158 patients who had died, the mean (SD) age at death was 68.1 (16.28) years. Patients included in the analyses were generally similar to the overall Registry GD1 population except for a somewhat greater proportion of treated patients, older at last follow-up, a larger percentage of patients from North America, and a lower representation from the Middle East, Africa, and Latin America (Table S1).

## 3.2 | Malignancies

All comparisons described below are to the US general population unless stated otherwise.

### 3.2.1 | Total malignancies

Of the 2121 patients with a yes/no response to malignancy, 258 (12%) had at least 1 malignancy. Age of first malignancy diagnosis, time between GD treatment initiation and malignancy diagnosis, and splenectomy data, by type of malignancy and other characteristics are reported in Tables S2 and S3. Seventy-six (29%) of those with a malignancy have died (any cause). Mean (SD) age at death was 68.4 (14.50) years. For 38 (15%) patients, the primary cancer was reported as metastasized. Forty-six (18%) patients had >1 malignancy (Table S4). Age-adjusted risk for malignancy overall was 1.63 times higher for GD1 patients (Figure 1).

### 3.2.2 | Hematologic malignancies and gammopathies

Sixty-nine (27%) of the 258 patients had at least one hematologic malignancy (see Table S3 for descriptive characteristics); NHL and MM were the most frequent hematologic malignancies (Table 1). The age-adjusted risk of hematologic malignancy was >4 times higher in patients with GD1 (Figure 1). Risk of MM was approximately nine times higher. Risk for NHL was approximately three-fold higher.

Of the 2080 patients with gammopathy data (yes/no response), 223 (11%) reported gammopathy. Of these, 114 patients (51%) reported MGUS alone, 96 patients (43%) polyclonal gammopathy alone, and 13 patients (6%) both MGUS and polyclonal gammopathy.

The age-adjusted incidence rate of MGUS ($n = 127$) was 445 per 100 000 person-years for patients ≥18 years (Table 2). Age-specific incidence rates of MGUS increased with age, increasing sharply in patients aged ≥50 years. The cumulative incidence of MGUS by age 60 was 6.6% (Figure 2A) and did not differ across categories of time from GD1 diagnosis to treatment initiation (Figure 2B, Gray's test $p = .8389$), which was confirmed in the Cox PH analysis (Table S5).

Ten of 126 patients with MGUS had a subsequent diagnosis of MM; one additional patient reported MGUS after diagnosis with MM and is excluded from the cumulative incidence analysis. Among 126 MGUS patients, the 10-year cumulative incidence of MM was 7.9% (Figure 2C). The mean (SD) time between MGUS and MM diagnosis was 3.5 (4.26) years. See Figure S1 for individual patient journeys. Given the higher rate of MGUS and MM in the African American population,[10] we examined this population separately. There were 42 African American/Black patients in the study population; none were reported with MGUS or MM.

**TABLE 1** Number and percentage of patients with Gaucher disease type 1 with each type of solid tumor and hematologic malignancy

| Solid tumors ($N = 199$) | | Hematologic malignancies ($N = 69$) | |
|---|---|---|---|
| **Type** | ***n* (%)** | **Type** | ***n* (%)** |
| Breast | 41 (20.6) | Non-Hodgkin lymphoma | 28 (40.6) |
| Skin (basal cell type) | 31 (15.6) | Multiple myeloma | 22 (31.9) |
| Melanoma | 20 (10.1) | Myelodysplastic syndrome | 5 (7.2) |
| Prostate | 20 (10.1) | Acute myeloid leukemia | 4 (5.8) |
| Skin (squamous cell type) | 16 (8.0) | Chronic lymphocytic leukemia | 3 (4.3) |
| Renal cell | 15 (7.5) | Hodgkin lymphoma | 3 (4.3) |
| Colorectal | 13 (6.5) | Acute lymphoblastic leukemia | 1 (1.4) |
| Liver | 9 (4.5) | Chronic myeloid leukemia | 1 (1.4) |
| Thyroid | 6 (3.0) | Other hematologic malignancy | 7 (10.1) |
| Lung | 5 (2.5) | | |
| Ovarian | 5 (2.5) | | |
| Pancreatic | 5 (2.5) | | |
| Cervical | 1 (0.5) | | |
| Sarcoma | 1 (0.5) | | |
| Other solid tumor | 44 (22.1) | | |

*Note*: A patient may have more than one malignancy, so may be counted in more than one malignancy type. Disease type reported by physician.

**TABLE 2** Age-specific incidence of MGUS by age group

| Age (years) | ICGG Gaucher registry # of MGUS cases | Person-years | Age-specific incidence rate per 100 000 person-years |
|---|---|---|---|
| <18 | 0 | 9885 | 0.00 |
| 18–29 | 4 | 9154 | 43.70 |
| 30–39 | 17 | 8525 | 199.41 |
| 40–49 | 25 | 8408 | 297.34 |
| 50–59 | 26 | 6772 | 383.93 |
| 60–69 | 29 | 3962 | 731.95 |
| 70–79 | 21 | 1444 | 1454.29 |
| 80+ | 5 | 255 | 1960.78 |
| Total for ages 18+ years | 127 | 38 520 | 329.70 |
| Age-adjusted incidence rate for age 18+ years[a] | - | - | 444.68 per 100 000 person-years |

*Note*: Study period start is 1993; all MGUS and person-years prior to 1993 have been excluded. Records with missing dates for assessment or MGUS are excluded. Age is missing for some patients, so not all patients could be assigned to an age category. Age category is based on the age of patient's first MGUS diagnosis or last follow-up. Person-years column includes all follow-up time from 1993 or entry into study (if after 1993) until the patient's first event (MGUS) or last follow-up. A patient may contribute person-time in more than one age category.
Abbreviations: ICGG, International Cooperative Gaucher Group; MGUS, monoclonal gammopathy of unknown significance.
[a]Age-adjusted to the 2000 US Census population.

The age-adjusted incidence rate of polyclonal gammopathy ($n = 109$ at any age; $n = 104$ at age ≥18 years) was 287 per 100 000 person-years for patients ≥18 years (Table S3 for descriptive characteristics and Table S6 for analyses). Overall, the cumulative incidence of polyclonal gammopathy was 5.1% by age 50 and 7.5% by age 60 (Figure 2D). Cumulative incidence of polyclonal gammopathy was significantly different across categories of time from GD1 diagnosis to treatment initiation (Figure 2E, Gray's test $p = .0075$). Those with <5 years between diagnosis and treatment initiation had a lower cumulative incidence of polyclonal gammopathy compared to patients with longer intervals. However, this result was not confirmed in the Cox PH analysis adjusted for confounding factors (Table S7).

Additionally, an earlier study had shown that patients with the *N370S/N370S* genotype may have a higher rate of MGUS.[11] We examined the age-adjusted incidence rate for MGUS and polyclonal gammopathy for patients who were homozygous for *N370S*. Among 1959 GD1 patients with genotype information, 704 patients were homozygous for *N370S*, and the remaining 1255 were heterozygous for *N370S* or had other genotypes. Mean (SD) age at Gaucher diagnosis was 31.2 (19.20) years for *N370S* homozygotes and 19.4 (16.58) years for others (data not shown). Mean age at last follow-up was 52.6 (21.33) years for *N370S* homozygotes and 45.5 (19.22) years for others. *N370S* homozygotes were less likely to ever have been treated (77.2% vs. 95.1% of patients with other genotypes).

Among patients homozygous for *N370S* aged ≥18 years, age-adjusted incidence rates for MGUS ($n = 40$) and polyclonal gammopathy ($n = 24$) were 325 and 183 per 100 000 person-years, respectively. Among patients heterozygous for *N370S* or with other genotypes aged ≥18 years, age-adjusted incidence rates for MGUS ($n = 77$) and polyclonal gammopathy ($n = 72$) were 497 and 388 per 100 000 person-years, respectively. Five occurrences of polyclonal gammopathy were at age <18 years and were not included in the age-adjusted incidence rates.

### 3.2.3 | Solid tumors

Of the 258 patients with reported malignancy, 199 (77%) had solid tumors (see Tables S3 and S8 for descriptive characteristics). The most common malignancies were non-melanoma skin cancer, breast cancer, melanoma, and prostate cancer (Table 1).

GD1 patients were at approximately 2.5–3 times higher risk for liver cancer, renal cell cancer, and melanoma (Figures 1 and S2). The risk for breast cancer was somewhat increased in the Registry GD1 population. Among patients with breast cancer and ancestry data ($n = 29$ of 40 total breast cancer cases), 22 (75.9%) were of Ashkenazi Jewish ancestry. Colorectal, prostate, and lung cancer rates were lower in GD1 patients (Figures 1 and S2).

## 4 | DISCUSSION

The metabolic defect in GD leads to accumulation of bioactive glycosphingolipids that have long been held to drive carcinogenesis.[12] With earlier diagnosis and transformative therapies, outcomes for patients with GD1 have significantly improved[13]; therefore, maintenance of long-term health in this growing population of patients underscores the importance of reliable data on cancer risk to stratify patients for appropriate monitoring. Previous studies have been hindered by inadequate ascertainment, inadequate patient cohorts, and/or differences in length and depth of follow-up, often leading to contradictory conclusions.[14–18] This is the first analysis of the risk of malignancy in the GD1 population using a large, multicenter, international population with a sufficient follow-up time for malignancies to develop.

The overall risk for hematological malignancies was higher in GD1 patients compared to the general US population, particularly the risk

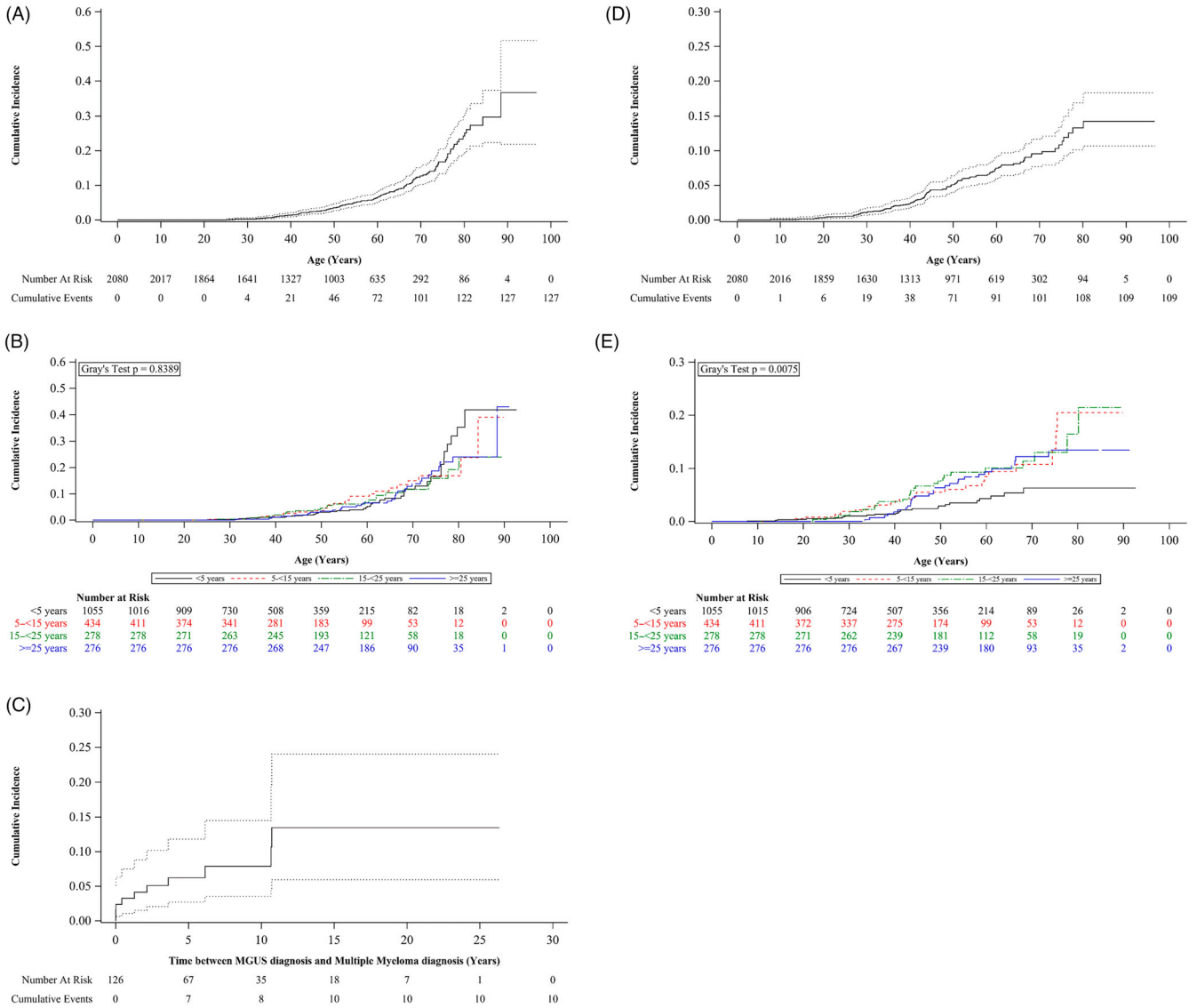


**FIGURE 2** Cumulative incidence curves for MGUS, for multiple myeloma for patients with MGUS diagnosis, and for polyclonal gammopathies. (A) Overall cumulative incidence curve for MGUS. (B) Cumulative incidence curves for MGUS with age as time scale by category of time from GD1 diagnosis to first treatment. (C) Cumulative incidence curve for MM among GD1 patients with MGUS diagnosis. One patient reported diagnosis of MGUS after MM and is not included in the analysis. Eleven of the 22 patients with MM had a "no" response to MGUS and are not included in this analysis. (D) Overall cumulative incidence curve for polyclonal gammopathy. (E) Cumulative incidence curves for polyclonal gammopathies with age as time scale by category of time from GD diagnosis to first treatment. Records with missing dates of diagnosis of the relevant malignancy for the analysis or date of birth are excluded. If a patient was diagnosed more than once with the relevant malignancy for the analysis, the earliest date for the type of event is used for the analysis. Disease type is as reported by physician. GD1, Gaucher disease type 1; MM, multiple myeloma; MGUS, monoclonal gammopathy of unknown significance [Color figure can be viewed at wileyonlinelibrary.com]

of B cell neoplasms. A higher risk for MM has been reported previously, ranging from 5.9 to 51.1 times greater risk.[11,14,15] Our study estimated the relative risk for MM as approximately nine times higher in GD1 patients compared to the general population. The age stratification we used may yield a more representative risk estimate as MM is an age-related phenotype. Previous risk studies of GD1 patients have shown that patients with MM were >50 years old.[11,14,15] Our large international cohort extended the age of occurrence of MM to younger ages, emphasizing the need for regular comprehensive evaluations of adults with GD1.

Higher age-adjusted incidence rates of MGUS, a precursor of MM, were also observed which reflects the chronic B cell lymphoproliferation known to occur in GD.[19] These findings are consonant with the emerging role of Gaucher lipids driving B cell proliferation and generation of anti-lipid antibodies.[20,21] In the general population <50 years old, the incidence rate for MGUS is 120 per 100 000 person-years in men and 60 per 100 000 person-years in women.[22] MGUS occurs in the older population generally due to age-related immune dysregulation. Our data show that with GD1, MGUS occurs more frequently than expected at younger ages.

Number of years between GD1 diagnosis and initiation of treatment did not significantly affect the cumulative incidence of MGUS. The limited number of African American/Black patients were not reported to have MGUS or MM thus a cumulative incidence for this subset of patients could not be calculated. Patients who were homozygous for *N370S* genotype had a lower incidence of MGUS and polyclonal gammopathy, counter to a previous study that found an increased lifetime risk of MGUS for patients homozygous for *N370S*.[11] The discrepancy between the results of this study and our findings is most likely due to a higher proportion of patients who were homozygous for *N370S* in the previous study compared to the Registry. A recent French GD Registry study also found that the only independent predictor of monoclonal gammopathy in a multivariate analysis was age at GD diagnosis (higher risk for >30 years at diagnosis); splenectomy, GD treatment, sex, genotype, and baseline disease characteristics were not significant.[23]

Future studies should examine the effect of ERT and SRT on the incidence of MGUS in GD1 and determine whether a correlation with levels of immunogenic Gaucher lipids, glucosylceramide, and glucosylsphingosine levels exists. Our findings suggest monitoring all adults with GD1 annually for immunoglobulins, free light chains, and M spike. Even in the face of a finding of MGUS, detecting lytic lesions in a patient with GD does not necessarily mean that myeloma is developing. Although presently therapeutic intervention for MGUS does not offer clinical or survival benefit, current practice could change given the pace of development of therapies for plasma cell dyscrasias.[18,24] Additionally, preliminary pre-clinical data and experience of amelioration of MGUS in GD1 patients on SRT are emerging.[20,21]

The 10-year risk for MM after MGUS diagnosis among Registry GD1 patients (approximately 8%) is similar to the general population (approximately 10%).[25] Half of the patients with MM did not have a report of MGUS, possibly contributing to an underestimate of risk of progression to MM given that all patients with MM presumably experience an MGUS phase.[26] Cytogenetic data for MGUS and MM diagnoses are not collected in the Registry and may not have even been available at the time the diagnosis was made. Current hematology practice is for cytogenetic studies to be conducted for patients with MM and should be conducted for patients with GD diagnosed with MM. There is considerable interest in the cytogenetic abnormality amplification of chromosome 1 q21 as a negative risk factor for conversion of MGUS to MM, which is also the locus of *GBA* (which encodes for glucocerebrosidase). However, there is no indication of any relationship thus far as that locus has a total of approximately 2100 genes.

The cumulative incidence of polyclonal gammopathy was about 5% by 50 years of age. Cumulative incidence may be lower among patients who began treatment within 5 years of GD1 diagnosis, although caution is warranted since the multivariable-adjusted model did not confirm this result. The incidence of polyclonal gammopathies reported across six previous GD studies ranges from 14% to 64%.[27] The largest study ($N = 507$) found an incidence of 14% and 25% in treated and untreated GD patients with ≥2 years of data, respectively; among treated patients, incidence of polyclonal gammopathies decreased significantly per year of ERT, but not for monoclonal gammopathies.[28] Our low cumulative incidence of polyclonal gammopathy likely reflects the effect of GD-specific treatment and limited information about pre-treatment immunoglobulin concentrations in many of our patients. Assessing the risk of MGUS or MM in patients with polyclonal gammopathy is not possible due to the assessment as a "one-time" event which may change with GD treatment.

In the setting of lipid antigenic stimulation, polyclonal activation of B cells and polyclonal gammopathy occur initially. This type of hypergammaglobulinemia reverses with ERT. Unabated lipid antigenic stimulation leads to MGUS, which is not likely to be eliminated once developed.[29–31] Early studies do suggest, however, that lipid-reactive M spike decreases significantly with SRT.[20] Our findings of markedly increased risk of B cell malignancies and precursor MGUS in GD1 have been recapitulated in murine GD1 models.[20,21,32,33] As in preliminary studies of human GD1 and MGUS, SRT with GCS inhibitor (Genz-161) aids in ameliorating B cell malignancies in murine GD1 models,[21,34] validating a long-held view on the role of glycosphingolipids in driving carcinogenesis.[12,18,20,21,24,32,33] If MGUS develops because of antigenic stimulation to lysolipids and B cell activation, then early initiation of GD treatment may abrogate the exposure to lysolipids and reduce the risk of MGUS. In a study of 63 patients of whom 50 received ERT, no patients developed MGUS during ERT and immunoglobulin levels either decreased or remained stable in patients with and without monoclonal gammopathy.[27] Encouragingly, SRT (eliglustat) in a GD mouse model reduced disease-associated gammopathy.[21] The effects of eliglustat on GD patients with existent MGUS are still unknown, although anecdotal reports exist of MGUS concentrations decreasing.[32] Eliglustat is also highly effective in reducing plasma concentrations of lyso-GL1 in patients with GD,[35] a potential antigen for the development of monoclonal antibodies.[36]

Worldwide, NHL is the most common hematologic malignancy (4.3% of all cancers in US).[37] The risk for NHL in patients with GD1 may not encompass the entire spectrum of subtypes that comprise the NHL super-family.[38] Epidemiologic studies of NHL have identified subtype-specific, predisposing risk factors that are also characteristic of GD pathophysiology. B cell NHL subtypes (diffuse large B-cell lymphoma [DLBCL], marginal zone lymphoma [MZL], lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia [LL/WM]) are strongly associated with B-cell activating, chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, and Sjogren's syndrome.[39] These conditions are often associated with phospholipid antibodies (lupus anticoagulants) whose presence has been documented in most histological subtypes of NHL (e.g., splenic MLL and LL).[40] GD-associated NHL by lymphoma subtypes has not been reported and are not collected in the Registry. Whether monoclonal lipid-reactive antibodies, characteristic of GD-associated MGUS, are present in GD patients with NHL is unknown.

Viral risk factors for NHL include hepatitis C (HCV) and Epstein–Barr (EBV).[38,41] Only three cases of HCV were found among 14 GD patients with concurrent hepatocellular carcinoma (HCC),[42] and, as in the general population, chronic EBV infection after infectious mononucleosis is also rare in GD patients.[43] Therefore, the increased risk for NHL in the GD1 population is unlikely due to viral factors.

Vitamin D deficiency may play a role in lymphomagenesis.[39] GD1 patients have a high prevalence of moderate-to-severe vitamin D insufficiency and may fail to normalize blood levels of 25-hydroxyvitamin D despite standard therapeutic doses of cholecalciferol or calcitriol.[44–46] Vitamin D deficiency in GD1 may result from intestinal malabsorption and poor skin production or decreased hepatic production of calcidiol.[47] Presence of a specific vitamin D receptor (VDR) genotype (*ApaI aa*) was also observed more frequently in GD1 patients with various cancers than a group of GD1 patients without cancer.[48] Further study is needed, however, as the *APaI* genotype may be more often associated with decreased cancer risk, and studies are inconsistent and often restricted to specific ethnicities (e.g., Ashkenazi Jews)[48] who may substantially vary in terms of VDR genotypes.[49]

For solid tumors, greater risk was found for liver and renal cell malignancies, breast cancer, and melanoma. Generally, increased cancer risk is confined to the organ harboring the metabolic defect in patients with inborn errors of metabolism. The increased risk of malignancies for solid organs and hematological malignancies in GD1 underscores the important role of the pathological accumulation of lipids, glucosylceramide/glucosylsphingosine, tissue macrophage dysfunction, lysosomal dysfunction, and type of chronic metabolic inflammation that occur in GD, creating a cancer-permissive environment in multiple organ systems beyond the primary site of defect (e.g., bone marrow).

HCC in the absence of preexisting cirrhosis in GD patients has been reported with a standardized rate ratio of 141.3 (95% CI 17.1–510.5).[14] Renal cell carcinoma has also been reported in GD patients[11,14,50] with an increased proportional mortality rate[51] but no estimates of relative risk. Our results confirm increased rates of liver and renal malignancies with approximately three times higher risk of both liver cancer and renal cell carcinoma compared to the general US population. Important differences between these studies investigating relative risk and ours preclude direct comparisons of risk ratios; however, the consistency of increased risk for liver and renal malignancies is noteworthy. In a case series, risk factors for GD patients included splenectomy, iron overload, and hepatitis.[42] Seventy-eight percent of patients in our study who had liver malignancy had been splenectomized. Our study suggests that increased risk of HCC persists in the era of macrophage-targeted ERT given that HCC risk appears to persist across different eras of ERT (1995, 2005, 2015). Insulin resistance and masked metabolic syndrome due to body burden of Gaucher cells may contribute to increased risk of HCC. GCS inhibitors have been shown to reverse metabolic syndrome in murine models.[52] However, the increased prevalence of obesity, metabolic syndrome, and nonalcoholic steatohepatitis found even in the GD population may negatively offset any benefits of GD treatment.[42] Assessing the risks in patients who are treated with GCS inhibitor SRT will be informative.

We found a higher risk of melanoma as has been found in other studies.[11,17] The links between melanoma and Parkinson's disease[53–55] and between Parkinson's disease and *GBA1* mutations may also be related to increased risk for melanoma.[56] Alpha-synuclein, a neuronal protein that regulates synaptic vesicle trafficking and neurotransmitter release, may provide a common pathogenic interaction. In Parkinson disease and melanoma, key enzymes of tyrosine metabolism and L-dopa biosynthesis may interact with α-synuclein.[57] Alpha-synuclein accumulation is also observed in GD patient neurons, probably initiated in lysosomes that accumulate glucosylceramide.[58] Increased melanoma risk may also be related to T cell dysfunction and impaired immune surveillance in GD patients, possibly related to lyso-GL1.[59]

With respect to breast cancer, incidence was somewhat elevated in GD1 patients, with a 38% higher risk compared to the US general population. Since risk of both GD1 and breast cancer is greater for women of Ashkenazi Jewish origin,[60] comparison to the US general population may bias the results. A study in a large tertiary GD center in US with >95% Ashkenazi Jewish patients found no increase of breast cancer in GD when compared to the Israeli National Cancer Registry.[16] Women with GD should follow standard guidelines for early detection of breast cancer.

Our epidemiologic finding of lower risk for lung cancer is interesting because the lungs have a large population of resident alveolar macrophages which, if they share the characteristics of other Gaucher macrophages as alternatively activated (M2), might be expected to be tumor growth permissive rather than suppressive.[61] Weinreb et al. found that mortality from lung cancer in untreated patients with GD1 was one-third what would have been expected in the general population.[51] The evolution of lung cancer in an experimental GD murine model would be worthy of future investigation.

Limitations to our study include those expected for a voluntary, observational registry study. Participating sites vary in following the recommended protocol for assessments, attrition may not be random, and underreporting of some malignancies may occur. However, the size of the sample and the international nature of the Registry make it a very comprehensive database of GD patients. There are limitations to the amount and type of data that are collected by the Registry; data which may have strengthened our analyses are not always collected, for example the lymphoma subtypes of NHL or cytogenetics of MGUS or MM. One of the strengths of our study is its international composition and an international comparison sample would have been preferable if one had been available. The sample size of patients with MGUS diagnosis and MM is small and conclusions regarding the progression from MGUS to MM should be interpreted with caution; however, our study includes the largest sample of MM patients compared to other studies of patients with GD.

## 5 | CONCLUSIONS

The modest increased risk for neoplasia in GD1 patients is confined to specific malignancies, which corroborates the link between GD pathophysiology and malignancies, supporting investigation of sphingolipid substrates and metabolites in carcinogenesis and cancer immunology. The younger ages at which MGUS developed is particularly interesting. The GD community should advocate for the creation of a dedicated GD Cancer Registry to house patient and tumor genomic information based on evolving cancer classifications, annotate presence of known or future risk factors for neoplasia, and monitor evolution of malignancies in the context of treatments for both GD and cancer. Patients should be registered when pre-malignant or early malignant states are detected (e.g., MGUS, monoclonal B lymphocytosis,[38] clonal

hematopoiesis of indeterminate potential[62]) or via cell-free serum DNA epigenomics.[63] Such rigorous follow-up would justify a recommendation of monitoring for MGUS and other clonal states at an earlier age than currently recommended. Monitoring for any early signs of liver or renal malignancies when examining imaging results during patients' 1- to 3-year evaluations of GD1 is also prudent.

## AUTHOR CONTRIBUTIONS

All authors contributed to the development of the study, interpretation of the analyses, and the review and editing of the manuscript. Additionally, Julie L. Batista conducted the statistical analyses. All authors had access to the study data.

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## CONFLICT OF INTEREST

Barry E. Rosenbloom: Was a principal investigator in the eliglustat ENCORE trial and has received honoraria and travel reimbursement from Sanofi. Maria Domenica Cappellini: Is a member of the advisory board for Sanofi, BMS, Vifor, Vertex, and Silence. Neal J. Weinreb: Has received honoraria for consultancy or participation on Advisory Boards for Sanofi, Pfizer and Shire and fees or honoraria from speaking at the invitation of Sanofi, Pfizer, and Shire. He has received grant support from Sanofi. Marta Dragosky: She was a Principal Investigator in the eliglustat Phase 2 and ENCORE clinical trials and has received speaker fees and travel support from Sanofi and Shire. Shoshana Revel-Vilk: Has received research grants, speaker fees, and travel support from Pfizer, Sanofi and Takeda/Shire. Davorka Sekulic: Employee of Sanofi and owns stock and/or stock options in the company. Julie L. Batista: Employee of Sanofi and owns stock and/or stock options in the company. Pramod K. Mistry: Has received research grant, travel support from Sanofi. He was a principal investigator in the ENGAGE clinical trial.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available to ICGG Gaucher Registry participants in aggregate format and can be requested through a Data Analyses Request form. The data are not publicly available due to privacy or ethical restrictions. For additional information, please contact rarediseaseregistries@sanofi.com.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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