Are antibody deficiency disorders associated with a narrower range of cancers than other forms of immunodeficiency?

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Analysis of cancer risk in primary immune deficiency (PID) offers insight into the relationship between immune function and cancer. Data on Australian patients (n = 1132) notified voluntarily to the Australasian Society of Clinical Immunology and Allergy PID Registry (1990-2008) were linked with national death and cancer registries. Person-years of follow-up commenced from up to 15 years before registration on the PID Registry or January 1982, the inception of national cancer registration. Site-specific, 5-year age-, sex-, calendar year–, and state-standardized incidence ratios (SIRs) with 95% confidence intervals (95% CIs) were calculated for all cancers except nonmelanocytic skin cancer. During an average of 16 person-years follow-up, a 1.6-fold excess relative risk of cancer was observed (n = 58; SIR 1.60, 95% CI 1.22-2.07) for all PID combined. Relative risk was increased for non-Hodgkin lymphoma (n = 16; SIR 8.82, 95% CI 5.04-14.30), leukemia (n = 4; SIR 5.36, 95% CI 1.46-13.73), and stomach cancer (n = 3; SIR 6.10, 95% CI 1.26-17.84). Excess cancer risk was observed for predominantly antibody deficiencies and other well-defined immunodeficiency syndromes. Results suggest that predominantly antibody deficiencies may be associated with a narrower range of solid cancers than immunodeficiency characterized by predominantly T-cell deficiency, such as iatrogenic and HIV-related immunodeficiency, although this requires confirmation in larger cohorts. (*Blood*. 2010;116(8):1228-1234)

Introduction

The contribution of immune dysfunction to cancer risk is receiving increasing attention. Recent findings from population studies in people with HIV and solid-organ transplantation have uncovered a quantifiable contribution of immune deficiency to cancer risk.[1] They suggest that predominantly T-cell deficiency is associated with an increased risk of a wide range of cancers, in particular cancers with a known or suspected infectious etiology. Examinations of immune-related and other risk factors in these cohorts have suggested that impairment of individual immune effector pathways may influence the risk of specific cancers.[2-6] Studies of the cancer profile and risk determinants in primary immune deficiency (PID) have the potential to provide further insight.

PID comprises more than 150 distinct entities caused by genetic defects that primarily affect specific functional immunity.[7] PID has been associated with a markedly increased risk of cancer, in particular non-Hodgkin lymphoma (NHL).[8-13] However, the PID cancer risk profile is not well characterized because most previous studies have been nonpopulation-based, of small sample size, of limited follow-up, and without a matched comparison group. Other cancers that appear to be associated with specific forms of PID include stomach cancer with common variable immune deficiency (CVID),[8,11] leukemia with ataxia-telangiectasia (AT),[10,13] and nonmelanocytic skin cancer with cartilage-hair hypoplasia.[12] Here, we report the overall and site-specific incidence of cancer relative to the general population for a national cohort of Australians with a diverse range of PID, a majority with predominantly antibody deficiencies.

Methods

Study population

The study included Australian children and adults diagnosed with PID, as notified to the Australasian Society of Clinical Immunology and Allergy (ASCIA) PID Registry 1990 to February 1, 2008. The ASCIA Registry receives voluntary case notifications for 56 separate PID syndromes from 79 centers across Australia but does not perform active follow-up or ascertain treatment data.[14,15]

Data collection

Incident deaths were ascertained by the use of data linkage with the Australian National Death Index. The Index records all deaths in Australian residents, as reported to each of the jurisdictional registers of births, deaths, and marriages, since 1980. Incident cancers were ascertained by the use of data linkage with the Australian National Cancer Database, a compilation of data on all incident primary invasive cancers (except nonmelanoma skin cancer, C44) diagnosed in Australian residents from January 1, 1982 to December 31, 2005. Registration of such cancers is mandated throughout Australia. Polymorphic lymphoproliferative disorders (*International Classification of Diseases for Oncology*, 3rd edition [ICDO-3] 9970/1) were not included because they are not routinely registered by Australian cancer registries. Data linkage was determined by patient name code, sex, date of birth, and date of death (if deceased) by the use of a customized algorithm and clerical review rules.[16,17] For each matched record, the date of cancer diagnosis and the topography and morphology codes were obtained (ICDO3, *International Classification of Diseases*, 10th revision [ICD-10]).

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Table 1. Characteristics of the Australian PID cohort

Characteristic	No. of patients (%)	Person-years follow-up for cancer	
		Total	Mean (SD)
Total	1132 (100)	18 055	16.0 (5.4)
Sex			
Male	604 (53.3)	9219	15.3 (5.6)
Female	528 (46.7)	8836	16.7 (5.0)
PID classification*			
Predominantly antibody deficiencies	881 (77.8)	14 313	16.2 (5.0)
Complement deficiencies	78 (6.9)	1298	16.6 (4.8)
Combined T-cell and B-cell immunodeficiencies	54 (4.8)	632	11.7 (7.2)
Other well-defined immunodeficiency syndromes	66 (5.8)	988	15.0 (6.9)
Congenital defects of phagocyte number, function, or both	39 (3.5)	602	15.4 (4.6)
Diseases of immune dysregulation	14 (1.2)	222	15.9 (4.5)
Age at follow-up for cancer, y			
0-9	552 (48.8)	7748	14.0 (5.8)
10-19	108 (9.5)	1963	18.2 (4.2)
20-29	133 (11.8)	2490	18.7 (4.5)
30-39	125 (11.0)	2240	17.9 (4.5)
40-49	102 (9.0)	1697	16.6 (3.4)
50-59	75 (6.6)	1313	17.5 (3.8)
60 and older	37 (3.3)	604	16.3 (3.0)

PID indicates primary immune deficiency; and SD, standard deviation.

*As classified by the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee.[7]

Site-specific general population cancer rates were also obtained by 5-year age, sex, state, and calendar year from 1982 to 2005.

The ASCIA Registry is approved to collect data on the first 2 letters of the first and last name of each patient, as well as the date of birth and sex, enabling probabilistic data linkage. Ethical approval for data linkage was obtained from all relevant institutional ethics committees. The requirement for informed consent from patients was waived because the researchers received only deidentified data.

Statistical analysis

A congenital basis for PID, and therefore immune dysregulation from birth, was assumed for all patients. This assumption extended the person-years (PYs) of follow-up for cancer by adding a retrospective time period (up to 15 years) before the date of ASCIA registration. Thus, PYs at risk of cancer were accumulated from January 1, 1982 (commencement of the Australian National Cancer database), the date of birth, or 15 years before the ASCIA registration date, whichever occurred last, until the date of cancer diagnosis, death, or December 31, 2005. The retrospective PYs were survival-adjusted to account for those with PID who may have developed cancer and died before registration in the ASCIA Registry. The maximum duration of the retrospective period was determined by the available period-specific cancer survival rates (1 to 15 years). Australian national (1982-1997) or South Australian (1977-1998) population-based survival rates were used, these being the most comprehensive available.[18,19] Specifically, PYs were adjusted by applying the period-specific, all-age, sex-, and site-specific cancer survival rates up to 15 years before ASCIA registration. This approach has been used in other registry-based linkage studies involving retrospectively defined follow-up periods.[16,20-22] Cancers were classified according to ICD-10, with the exception of Kaposi sarcoma and lymphoid and hematopoietic neoplasms, which were classified according to ICDO-3 morphology codes.[23]

Standardized incidence ratios

The ratio of the observed to the expected numbers of cancers, the standardized incidence ratio (SIR), was calculated with exact 95% confidence intervals (95% CIs). The expected numbers of cases were computed on the basis of the general population cancer incidence rates, assuming a Poisson distribution.[24] "All cancer" and site-specific cancer SIRs were calculated for the entire cohort, separately for men and women, and also for children (< 16 years of age) and adults.

"All cancer" and site-specific cancer SIRs also were computed for 6 classifications of PID, which grouped individual PID entities with related pathophysiology,[7] as well as for the most common individual PID conditions. The International Union of Immunologic Societies PID classification includes "predominantly antibody deficiencies," "complement deficiencies," "combined T-cell and B-cell immunodeficiencies," "other well-defined immunodeficiency syndromes," "congenital defects of phagocyte number, function, or both," and "diseases of immune dysregulation."[7] The following individual conditions, immunoglobulin G (IgG) subclass deficiency with or without immunoglobulin A (IgA) deficiency, specific defect of IgG, and all isolated IgG subclass deficiency (including isotypes 1-4), were combined into a single classification, "IgG subclass deficiency" for analysis.

Incidence rate ratios

To further explore cancer risk with respect to type of PID, a within-cohort analysis was conducted for NHL, the most common cancer in the cohort. Multivariate Poisson regression was used to calculate incidence rate ratios (IRRs) with 95% CIs for selected PID groupings with adjustment for 5-year age group (time-dependent) and sex. All data analyses were performed with the use of STATA version 10.1 (StataCorp LP).

Results

The study cohort consisted of 1132 patients, 53% of whom were male (Table 1).[7] The median age at ASCIA registration was 25 years (range, newborn to 95 years) and the mean duration of follow-up was 16 years (SD, 5.4 years). A total of 111 (9.8%) deaths were observed during follow-up. Most patients (78%) were classified as having a "predominantly antibody deficiency" (Table 1). CVID was the most common entity (n = 416), followed by IgG subclass deficiency with or without IgA deficiency (n = 215), and there were substantially fewer than 100 patients for most other entities (supplemental Table 1, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article), limiting our ability to make direct comparisons.

Table 2. SIRs for cancer in people with PID in Australia

Cancer site	ICD-10/ICDO-3 codes*	O	E	SIR (95% CI)
Lip	C00	0	0.51	0-7.26†
Oral cavity, oropharynx	C01, C02, C03-C06, C09, C10	0	0.44	0-8.33†
Stomach	C16	3	0.49	6.10 (1.26-17.8)‡
Colon	C18	4	2.99	1.34 (0.36-3.43)
Anus	C21	0	0.10	0-38.0†
Pancreas	C25	1	0.39	2.55 (0.06-14.2)
Trachea, bronchus, lung	C33-C34	2	1.97	1.02 (0.12-3.67)
Thymus gland	C37	2	0.03	67.3 (8.15-243)‡
Melanoma	C43	4	4.95	0.81 (0.22-2.07)
Breast (females only)	C50	12	7.66	1.57 (0.81-2.74)
Vulva, vagina, cervix uteri	C51-C53	0	0.79	0-4.67†
Ovary	C56	1	0.57	1.74 (0.04-9.70)
Penis	C60	0	0.02	0-167†
Prostate	C61	3	3.42	0.88 (0.18-2.57)
Bladder	C67	3	0.75	3.99 (0.82-11.7)
Brain	C71	0	0.46	0-8.02†
Thyroid gland	C73	1	0.75	1.34 (0.03-7.45)
Adrenal gland	C74	1	0.04	26.3 (0.67-147)
Hodgkin lymphoma	ICDO-3 9650-9677	1	0.29	3.47 (0.09-19.4)
Non-Hodgkin lymphoma§	ICDO-3 9591, 9596, 9670-9729, 9761, 9820-9837, 9940, 9948 and 9590 if ICD-10, C82-C85	16	1.81	8.82 (5.04-14.3)‡
Leukemia‖	ICDO-3 9800-9989, excluding 9820-9837, 9940, 9948	4	0.75	5.36 (1.46-13.7)‡
All malignant neoplasms	C00-C96, excluding C44	58	36.2	1.60 (1.22-2.07)‡

95% CI indicates 95% confidence interval; E, expected number of cases; ICD, International Classification of Diseases; ICDO, International Classification of Diseases for Oncology; NHL, non-Hodgkin lymphoma; O, observed number of cases; PID, primary immune deficiency; and SIR, standardized incidence ratio.

*Lymphoid and hematopoietic neoplasms were classified according to current guidelines for epidemiologic studies[23] and include 2 cases with ICDO-3 9960 morphology and ICD-10 D47 topography.

†One-tail, 97.5% CI instead of 95% CI because of zero observations.

‡Statistical significance.

§Diffuse large B-cell lymphoma (n = 1), follicular lymphoma (n = 3), Burkitt lymphoma/leukemia (n = 1), small lymphocytic lymphoma (n = 1), extranodal marginal zone lymphoma type (n = 1; body site location not specified in national cancer registry records), peripheral T-cell lymphoma (n = 1) unclassified, cutaneous T-cell lymphoma unclassified (n = 1), Waldenström macroglobulinemia (n = 1), NHL unclassified (n = 6).

‖Chronic myeloproliferative leukemia (n = 2), acute myeloid leukemia (n = 1), and myeloid neoplasms unclassified (n = 1).

Standardized incidence ratios

All PIDs combined. Linkage identified a total of 58 cancers (5.7%), including 55 first and 3 second primary cancers. SIRs were significantly elevated for all cancers combined (SIR 1.60), cancer of the thymus gland (SIR 67.3), NHL (SIR 8.82), stomach cancer (SIR 6.10), and leukemia (SIR 5.36; Table 2).[23] There were no cases of Kaposi sarcoma nor any oral cavity/oropharyngeal, anogenital, or brain cancers. No cancers occurred at significantly reduced rates relative to the general population.

"All cancer" and site-specific SIRs were similar for men and women, with the exception of thymoma, which occurred in men only (Table 3). The SIRs for "all cancer" and NHL were significantly increased in both children and adults (Table 4).

Major PID classifications. SIRs for "all cancer" and for NHL were significantly increased for patients with "predominantly antibody deficiencies" and "other well-defined immunodeficiency syndromes" (Table 5). The SIR for leukemia was significantly increased for patients with "diseases of immune dysregulation." No other site-specific SIRs were significantly increased for other PID classifications.

Individual PID conditions. SIRs for "all cancer" were significantly increased in patients with CVID (n = 416) and AT (n = 10; Table 6). In patients with CVID, SIRs also were significantly increased for NHL and cancers of the breast (females) and thymus. Both thymus gland cancers were diagnosed in male subjects (aged 48 and 53 years), and both were thymomas. The SIR for stomach cancer was elevated on the basis of 2 cases; a diffuse adenocarcinoma in a 65-year-old subject and a carcinoma of unspecified morphology in a 56-year-old subject. In patients with AT, the SIR for NHL was significantly increased on the basis of a single case.

In patients with IgG subclass deficiency (n = 244), the SIR for leukemia was significantly increased on the basis of 2 cases. There were no cancers diagnosed in patients with selective IgA deficiency. In patients with X-linked agammaglobulinemia (n = 62), the SIR for stomach cancer was significantly increased on the basis of a single case of diffuse adenocarcinoma in a 45-year-old subject.

Table 3. Site-specific and overall cancer risk for men and women with PID

Cancer site	O	E	SIR (95% CI)
Male, n = 604			
All malignant neoplasms†	23	14.0	1.64 (1.04-2.46)*
NHL	8	0.87	9.22 (3.98-18.2)*
Leukemia	2	0.35	5.77 (0.70-20.9)
Stomach	2	0.26	7.57 (0.92-27.3)
Thymus	2	0.02	114 (13.8-412)*
Female, n = 528			
All malignant neoplasms†	35	22.2	1.58 (1.10-2.19)*
NHL	8	0.95	8.46 (3.65-16.7)*
Leukemia	2	0.40	5.01 (0.61-18.1)
Stomach	1	0.23	4.40 (0.11-24.5)
Thymus	0	0.01	0-303‡

95% CI indicates 95% confidence interval; E, expected number of cases; NHL, non-Hodgkin lymphoma; O, observed number of cases; PID, primary immune deficiency; and SIR, standardized incidence ratio.

*Statistical significance.

†C00-C96, excluding C44.

‡One-tail, 97.5% CI instead of 95% CI because of zero observations.

Table 4. Site-specific and overall cancer risk for children and adults with PID

Cancer site	O	E	SIR (95% CI)
Children (< 16 y; n = 613)			
All malignant neoplasms†	4	0.64	6.21 (1.69-15.9)*
NHL	2	0.20	9.78 (1.18-35.3)*
Leukemia	1	0.04	24.6 (0.62-137)
Adults (≥ 16 y; n = 850)			
All malignant neoplasms†	54	35.6	1.52 (1.14-1.98)*
NHL	14	1.61	8.70 (4.76-14.6)*
Leukemia	3	0.71	4.26 (0.88-12.4)

95% CI indicates 95% confidence interval; E, expected number of cases; NHL, non-Hodgkin lymphoma; O, observed number of cases; PID, primary immune deficiency; and SIR, standardized incidence ratio.

*Statistical significance.

†C00-C96, excluding C44.

Incidence rate ratios

The risk of NHL was significantly associated with some PID subtypes after adjustment for age and sex. Compared with predominantly antibody deficiencies excluding CVID, CVID was associated with a 5-fold increased risk (IRR 5.75; 95% CI 1.25-26.5), "other well-defined immunodeficiency syndromes" was associated with a 9-fold increased risk (IRR 9.23; 95% CI 1.23-69.0), and all other PID subtypes combined showed no excess risk (IRR 1.52; 95% CI 0.14-16.8).

Table 5. Site-specific and overall risk of cancer for the major PID classifications

PID classification/cancer site	O	E	SIR (95% CI)
Predominantly antibody deficiencies, n = 881			
All malignant neoplasms*	53	32.9	1.61 (1.21-2.11)†
NHL‡	13	1.60	8.13 (4.33-13.9)†
Leukemia	3	0.67	4.50 (0.93-13.2)
Complement deficiencies, n = 78			
All malignant neoplasms*	1	2.13	0.47 (0.01-2.62)
NHL§	1	0.11	9.42 (0.24-52.5)
Leukemia	0	0.04	0-92.3¶
Combined T-cell and B-cell immunodeficiencies, n = 54			
All malignant neoplasms*	0	0.32	0-11.7¶
NHL	0	0.03	0-117¶
Leukemia	0	0.01	0-395¶
Other well-defined immunodeficiency syndromes, n = 66			
All malignant neoplasms*	3	0.23	13.0 (2.69-38.1)†
NHL‖	2	0.03	62.1 (7.51-224)†
Leukemia	0	0.01	0-376¶
Congenital defects of phagocyte number, function or both, n = 39			
All malignant neoplasms*	0	0.48	0-7.69¶
NHL	0	0.03	0-114¶
Leukemia	0	0.02	0-227¶
Diseases of immune dysregulation, n = 14			
All malignant neoplasms*	1	0.23	4.40 (0.11-24.5)
NHL	0	0.01	0-281¶
Leukemia	1	0.004	238 (6.03-1326)†

95% CI indicates 95% confidence interval; E, expected number of cases; NHL, non-Hodgkin lymphoma; O, observed number of cases; PID, primary immune deficiency; and SIR, standardized incidence ratio.

*C00-C96, excluding C44.

†Statistical significance.

‡Diffuse large B-cell lymphoma (n = 1), follicular lymphoma (n = 2), Burkitt lymphoma/leukemia (n = 1), small lymphocytic lymphoma (n = 1), extranodal marginal zone lymphoma type (n = 1), peripheral T-cell lymphoma (n = 1) unclassified, cutaneous T-cell lymphoma unclassified (n = 1), Waldenström macroglobulinemia (n = 1), and NHL unclassified (n = 4).

§Diffuse large B-cell lymphoma (n = 1).

‖ Follicular lymphoma (n = 1), NHL unclassified (n = 1).

¶One-tail, 97.5% CI instead of 95% CI because of zero observation.

Table 6. Site-specific and overall cancer risk for the most common individual PID conditions

PID condition/cancer site	O	E	SIR (95% CI)
Common variable immune deficiency, n = 416			
All malignant neoplasms*	38	19.6	1.94 (1.37-2.67)†
NHL‡	11	0.91	12.1 (6.03-21.6)†
Leukemia	1	0.40	2.49 (0.06-13.9)
Stomach	2	0.28	7.23 (0.88-26.1)
Thymus	2	0.01	146 (17.7-528)†
Breast (female only)	9	4.03	2.24 (1.02-4.24)†
IgG subclass deficiency, n = 244			
All malignant neoplasms*	11	8.83	1.32 (0.66-2.36)
Leukemia	2	0.15	13.2 (1.60-47.6)†
Breast (female only)	3	2.10	1.43 (0.29-4.17)
Selective IgA deficiencies, n = 90			
All malignant neoplasms*	0	3.58	0-1.03¶
X-linked agammaglobulinemia, n = 62			
All malignant neoplasms*	1	0.32	3.09 (0.08-17.2)
Stomach	1	0.004	236 (5.97-1315)†
Ataxia-telangiectasia, n = 10			
All malignant neoplasms*	2	0.05	41.2 (4.99-149)†
NHL§	1	0.006	165 (4.19-922)†

95% CI indicates 95% confidence interval; E, expected number of cases; IgA, immunoglobulin A; IgG, immunoglobulin G; NHL, non-Hodgkin lymphoma; O, observed number of cases; PID, primary immune deficiency; and SIR, standardized incidence ratio.

*C00-C96, excluding C44.

†Statistical significance.

‡Diffuse large B-cell lymphoma (n = 1), follicular lymphoma (n = 2), Burkitt lymphoma/leukemia (n = 1), small lymphocytic lymphoma (n = 1), extranodal marginal zone lymphoma type (n = 1), peripheral T-cell lymphoma (n = 1) unclassified, Waldenström macroglobulinemia (n = 1), and NHL unclassified (n = 3).

§NHL unclassified (n = 1).

¶One-tail, 97.5% CI instead of 95% CI because of zero observation.

Discussion

This national, population-based cohort study identified a modest excess risk of any cancer and a strong excess risk of a small number of cancers (NHL, stomach, thymus, and leukemia) in patients with PID relative to the general population. Within the statistical power afforded by the study, the data suggest 2 novel insights. First, PID characterized predominantly by antibody deficiency may be associated with a narrower range of solid cancers than predominantly T-cell deficiency after solid organ transplantation or in HIV infection.[1] Second, the excess cancer risk may be confined to certain forms of immunodeficiency within PID, and further, to specific disease entities within those broad phenotypes. This study demonstrates the future potential of PID, with its increasingly well characterized genetic basis and forms of immune deficiency and increasing life expectancy, to contribute to our understanding of the role of immune function in cancer control.

Although there are no previously published estimates of cancer risk relative to the general population for the spectrum of PID disease, an excess risk of NHL is well-established.[25,26] We found an 8-fold increased risk for NHL for all forms of PID combined;

however, the misdiagnosis of lymphoma as PID cannot be excluded. NHL risk was also significantly increased for the PID classifications "predominantly antibody deficiencies" and "other well-defined immunodeficiency syndromes." With respect to individual PID entities, the SIR for NHL was significantly increased for CVID but not for other forms of predominantly antibody deficiency. This finding is consistent with previous studies, in particular a smaller, prospective population-based study that observed 3 cases of NHL in CVID (SIR 11.1, 95% CI 2.3-32.5) and one case of NHL in IgA deficiency (SIR 2.6, 95% CI 0.1-14.3).[11] Notably, these and our population-based SIR estimates are appreciably lower than those obtained for smaller CVID cohorts (n = 377[8] and n = 98)[9] using hospital-based cancer ascertainment, where estimates of 30- and 259-fold excess risk of NHL have been reported.

Despite including only 10 patients with AT, we observed a significantly increased relative risk of NHL, which is consistent with previous, good-quality evidence from larger AT cohorts.[10,13] Apart from cartilage hair hypoplasia,[12] the risk of cancer relative to the general population has not been previously quantified for the remaining PID classifications or PID entities. Although our findings support variation in NHL risk by the form of primary immunodeficiency, we had insufficient statistical power to reliably estimate NHL incidence for the rarer PID subtypes.

Lymphomas of B-cell origin appeared to predominate, and most cases were diagnosed in adulthood. Epstein-Barr virus (EBV) infection causally is associated with NHL in immunocompromised hosts[27] as a result of depleted EBV-specific $CD8^+$ cytotoxic T cells.[28,29] Thus, PIDs with T-cell deficiency are expected to be the most susceptible to EBV-related lymphomas. However, specific genetic defects, such as defective DNA repair in AT[30] and impaired NK cell–mediated cytotoxicity in X-linked lymphoproliferative disease,[31] also are believed to play a role in lymphomagenesis. Our within-cohort analysis suggests that the form of functional immune impairment in CVID and "other well-defined immunodeficiency syndromes" is associated with a significantly greater risk of NHL relative to all other predominantly antibody deficiencies combined.

Our risk estimate for stomach cancer for all PID (SIR 6.10) is similar to the only previous population-based estimate for CVID and IgA deficiency combined (SIR 7.5; n = 562), and is appreciably lower than a hospital-based estimate for CVID (47-fold).[8] The increased risk of stomach cancer suggests that local gastrointestinal effects associated with PID, such as the decreased production of gastric IgA and hydrochloric acid, may facilitate *Helicobacter pylori* colonization and gastric inflammation and promote carcinogenesis. Although there is mixed support for such a pathogenic mechanism,[32-35] and the role for cofactors such as alterations in the p53 gene are yet to be clarified,[36] these data support the regular use of diagnostic tests and treatment of *H pylori* infection in adults with PID, together with endoscopic follow-up of those with premalignant gastric lesions.[37]

We observed a large excess risk for thymoma on the basis of 2 cases occurring in patients with CVID. Goods syndrome, or "thymoma with immunodeficiency," is a rare form of predominantly antibody deficiency characterized by the occurrence of adult-onset hypogammaglobulinemia either before or after the diagnosis of thymoma.[38] Although regarded by some as a subset of CVID, it is now classified as a separate entity.

We found a significantly increased risk of leukemia for all PID, "diseases of immune dysregulation," and "IgG subclass deficiency." Despite the strong previous evidence, we did not observe an excess risk of leukemia in AT.[10,13] Our observation of an increased relative risk of breast cancer in CVID is novel, apart from recent case reports in 2 young women.[39] Although our finding is based on 9 incident breast cancer cases, chance cannot be excluded as an explanation. This finding is worthy of further investigation as mothers of children with AT appear to be at increased risk[10] and no excess risk is observed in acquired and iatrogenic immunodeficiency.[1]

The evidence accumulated to-date suggests that the cancer profile in PID may differ from that observed in iatrogenic and acquired immunodeficiency, where a wide range of solid cancers with an infectious etiology occur at excess risk.[1] Of the many solid cancers with an established infectious cause,[40] only stomach cancer appears to occur at a significantly higher rate in PID.[8-13] The size of our cohort and the comparative rarity of infection-related cancers such as Kaposi sarcoma and anogenital and orpharyngeal cancers cannot be ruled out, but there are also other possible explanations. First, the cancer profile may reflect a lower rate of infection by the causally associated sexually acquired infectious agents[40] in this patient group. Second, in comparison with HIV-related and iatrogenic immunosuppression, primary antibody deficiency disorders may occur in the context of relatively preserved T-cell effector function, and T-cell dysfunction may carry the majority of the attributable risk. For example, in HIV, Kaposi sarcoma risk is strongly inversely associated with $CD4^+$ T-cell count.[41,42] In CVID, however, only a small subset (< 10%) of patients appear to have very low CD4 counts.[43] A final possibility is that Ig-replacement therapy, used in 71% of the cohort,[15] is associated with a reduced risk of cancer in PID. If true, such an effect would be consistent with the reduction in risk of some cancers after the use of highly active antiretroviral therapy in HIV[17] and after the removal of iatrogenic immunosuppression in kidney transplant recipients.[44] It also accords with a case report of regression of Kaposi sarcoma in a HIV patient after IVIG therapy.[45]

This study used one of the world's largest national PID registers and national death and cancer notifications to enable unbiased death and cancer ascertainment relative to the general population. Furthermore, it is the first study to examine site-specific cancer risk across the spectrum of PID subtypes, allowing comparisons between some PID conditions with related pathogenesis. Despite these strengths, several limitations must be considered. Although large by comparison with most previous studies with population-level comparison data, the cohort size and the observed number of cancers are insufficient for comprehensive risk factor modeling and robust comparisons between individual PID conditions and with other forms of immune impairment. Furthermore, in common with other registries of this kind, the ASCIA PID Registry is affected by under-reporting, achieving registration of an estimated 34% to 37% of its target population,[15] and potentially misclassification error because of misdiagnosis.[7] In particular, it is possible that patients originally diagnosed with CVID may be subsequently diagnosed with X-linked lymphoproliferative disease or CD40L deficiency, rare conditions known to be associated with cancer.[30,46]

In addition, our analyses were determined by the assumption that immune dysfunction was present for up to 15 years before ASCIA registration. Although our approach accords with the congenital basis of these conditions, it would over-estimate the PY at risk for cancer if adult-onset disorders arose by somatic genetic error later in life. Nevertheless, our approach does offset the diagnostic delay typically experienced for PID, particularly for conditions such as CVID that are usually diagnosed in adulthood.[47] However, although survival adjustment was performed to account for the retrospective period of follow-up, survival bias may not have been completely eliminated, which would also over-estimate the PY at risk of cancer and weaken the PID-cancer association. Despite these limitations, our risk estimates for CVID and IgA deficiency are of similar magnitude to those obtained for

a smaller cohort on the basis of a well-defined diagnostic criteria and with prospective follow-up for cancer.[11]

Although there is long-standing evidence of a strong link between PID and cancer, the association has been understudied. As the life expectancy of people with PID increases because of improvements in the surveillance, prevention, and treatment of chronic infections, the occurrence of cancer is expected to increase. The population-level collection of detailed information on the extent and type of functional immune impairment, in addition to the type and duration of any immune reconstitution therapy or potentially curative treatment such as hematopoietic stem cell transplantation, has the potential to inform patient management. In addition, large-scale comparisons of the long-term cancer risk in different types of PID and other forms of immune dysfunction may give insight into the immunologic and genetic determinants of specific cancers. Such information would inform the development of models of carcinogenesis and thus cancer prevention strategies in both immune-deficient and non–immune-deficient populations.

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Authorship

Contribution: C.M.V., M.T.v.L., A.E.G., and S.R. designed the research; L.M. and M.T.v.L. performed statistical analysis; C.M.V., L.M., and S.R. drafted the manuscript; and M.T.v.L., P.K., and A.E.G. critically reviewed the manuscript.

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