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Cancer risk among patients with IgA deficiency or common variable immunodeficiency and their relatives: a combined Danish and Swedish study

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SUMMARY

The extremely high risk reported for some types of cancer among patients with common variable immunodeficiency (CVID) is based on a limited number of investigations. Therefore, we examined the risks for cancer among 562 Danish and Swedish patients with CVID or IgA deficiency and 2071 relatives in 1958–96. The patients were identified through an Immunodeficiency Register and hospital records, while the relatives were traced through population registers. Cancer incidence was assessed by linkage to the Cancer Registries and compared with that in the general population. Among 386 patients with IgA deficiency, the incidence of cancer was not increased (standardized incidence ratio (SI) = 1·0); but two cases of stomach cancer were found, resulting in a non-significant increase in risk (SIR = 5·4; 95% CI = 0·7–19·5). Among 176 patients with common variable immunodeficiency (CVID), the incidence of cancer at all sites combined was increased (SIR = 1·8; 95% CI = 1·0–2·9), which was due mainly to significant excesses of malignant lymphoma (obs = 4; SIR = 12·1; 95% CI = 3·3–31·0) and of stomach cancer (obs = 3; SIR = 10·3; 95% CI = 2·1–30·2). Among the 626 relatives of patients with CVID, no increase in risk was found for these types of cancer or for cancer overall (obs = 53; SIR = 1·0; 95% CI = 0·8–1·3). Our data show that the risks for malignant lymphoma and stomach cancer among patients with CVID may be lower than reported previously. The absence of an increased risk among relatives suggests that the increased cancer morbidity in patients with CVID is related to the immunodeficiency *per se* rather than to specific genetic traits shared with their relatives.

Keywords cancer risk common variable immunodeficiency epidemiology IgA deficiency relatives

INTRODUCTION

A high risk for cancer has been described among patients with primary immunodeficiencies of the B-lymphocyte lineage, but only two investigations have allowed estimates of relative risks for cancer. The risk for malignant lymphoma among patients with common variable immunodeficiency (CVID) was found to be increased 30-fold in a British study [1] and 259-fold in a US study [2], whereas the risk for stomach cancer was 47 times higher than expected in the British study [1]. The risk for cancer among patients with IgA deficiency, a defect that is associated genetically with CVID, has not been evaluated previously.

It is not known whether genotypic or phenotypic characteristics underlie the excess risks for cancer. The mode of inheritance of CVID and IgA deficiency has not been elucidated fully, but within the families of the patients there are some gene carriers without symptoms of immunodeficiency. Data on cancer incidence among these gene carriers are sparse. In a study from the United States, the cancer incidence among 1033 adult blood

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relatives of patients with CVID corresponded to that in the general population, but the cancer incidence among female relatives was higher than that of their spouses [3].

In the present study, we investigated the cancer risk of 562 Danish and Swedish patients with CVID or IgA deficiency and more than 2000 family relatives.

MATERIALS AND METHODS

Probands

In 1979, all paediatric departments in Denmark (5 million inhabitants) were asked to report patients known to have primary immunodeficiency to the Rigshospitalet in Copenhagen [4], in order to initiate the Danish Immunodeficiency Register, which covers a wide variety of immunodeficiencies. A set of variables is recorded for each patient including date of birth, full name, hospital department and immunodeficiency diagnosis. For the analysis of cancer among relatives, cases in the Immunodeficiency Register were supplemented by cases from the departments of paediatrics, rheumatology and infectious diseases, and the department of clinical immunology at Rigshospitalet in Copenhagen. The dates of birth and the names of the patients were linked to the Central Population Register to obtain their personal identification numbers. The unique identification number system in Denmark was established in April 1968, and the number is assigned to all permanent residents of Denmark. We identified a total of 158 patients with IgA deficiency or CVID. For 64 of 102 patients from the Immunodeficiency Register, we obtained the year of debut of the immunodeficiency from the register. Only the latter subgroup of patients were included in the cancer analysis of probands (Table 1).

In Sweden (8 million inhabitants), cases of primary immunodeficiency have been collected at the department of clinical immunology, Huddinge Sjukhuset, Stockholm and at the allergy clinic, Sahlgrenska Sjukhuset, Göteborg. Among the patients with IgA deficiency, some had been identified through screening studies (e.g. blood donors), and some had been identified due to symptoms of immunodeficiency. The variables included in the Swedish registration correspond closely to those obtained in Denmark. The registration covered 582 patients with IgA deficiency or CVID born between 1903 and 1990. The year of diagnosis for the immunodeficiency was found in the medical record for 498 patients (Table 1), and only this subgroup was included in the cancer analysis of probands.

In both Denmark and Sweden, IgA deficiency was diagnosed when IgA was less than 0·05 g/l, and CVID was diagnosed when IgG was less than 4 g/l.

Table 1. Characteristics of patients with IgA deficiency or CVID from Denmark and Sweden

	IgAD		CVID		Total	
Characteristic	No.	%	No.	%	No.	%
Total number	386	100	176	100	562	100
Sex						
Men	172	45	86	49	258	46
Women	214	55	90	51	304	54
Year of debut/diagnosis of immunodeficiency						
1950–59	1	0	13	7	14	2
1960–69	10	3	25	14	35	6
1970–79	22	6	53	30	75	13
1980–89	295	76	62	35	357	64
1990–96	58	15	23	13	81	14
Country						
Denmark	21	5	43	24	64	11
Sweden	365	95	133	76	498	89

IgAD, immunoglobulin A deficiency; CVID, common variable immunodeficiency.

Family relatives

Family relatives were traced for all patients with immunodeficiency, for patients for whom we were able to obtain the date of debut or diagnosis of the immunodeficiency and for patients for whom we were unable to obtain these dates. Family relatives were traced and identified from files on the national population in each country. In Denmark, the Central Population Register contains links between parents and offspring and *vice versa*. For the 158 Danish probands, we were able to trace 207 parents, 205 siblings and 93 offspring. In Sweden, first- and second-degree family members were identified in the National Fertility Register and – before 1963 – local population registers. For the 582 Swedish probands, we identified 713 parents, 600 siblings and 253 grandparents.

Cancer risk analyses

Information on the vital status (alive, dead, emigrated) of the probands and relatives was obtained from the Central Population Register and the Death Certificate File (Denmark) and from the Registry of Causes of Death and the Migration Register (Sweden). All study subjects were linked to the respective national Cancer Registries, which were initiated in 1943 in Denmark [5] and in 1958 in Sweden [6]. The period of follow-up for the occurrence of cancer among the probands extended from the year of debut of the immunodeficiency (Danish patients), the year of diagnosis of the immunodeficiency (Swedish patients) or the date of inception of the computerized national cancer or population registration (1 April, 1968 in Denmark and 1 January, 1958 in Sweden), whichever came last. For the offspring and siblings the period of follow-up extended from their date of birth or the date of inception of the national cancer or population registration, whichever came last. Similar rules were applied to the groups of parents and grandparents, except that follow-up was started at the earliest at the date of birth of the proband (parents) or the relevant parent in direct line to the proband (grandparents). All subjects were followed until date of death, date of emigration or the end of the study (31 December 1996 in Denmark and 31 December 1995 in Sweden), whichever came first. For the subset of patients who developed stomach cancer or malignant lymphoma during follow-up, medical records were traced in order to confirm information on year of debut and year of diagnosis of the immunodeficiency and to verify the cancer diagnosis. After medical record review one case labelled as non-Hodgkin's lymphoma was deleted, when the diagnosis was re-assessed as benign hyperplasia.

The observed numbers of cancer cases among probands and relatives were compared with the expected numbers calculated on the basis of sex and 5-year age- and calendar time-specific incidence rates of cancer to yield the standardized incidence ratio

(SIR). Danish cancer incidence rates were used for the analyses including Danish probands and their relatives, and Swedish cancer incidence rates were used in the analyses including Swedish probands and their relatives. Associated 95% confidence intervals (CIs) were calculated under the assumption that the observed number of cancer cases followed a Poisson distribution, by use of exact Poisson limits or of Byar's approximation [7]. Significantly increased SIRs have lower confidence limits that are above or equal to 1·0, and significantly decreased SIRs have upper confidence limits that are below or equal to 1·0. This means that the *P*-value for obtaining the SIR estimate is less than 0·05 under the null hypothesis that the observed number of cancer in the study population is not different from the expected number in the general population.

RESULTS

Patients

When Danish and Swedish patients were merged into one cohort, the largest group consisted of those with IgA deficiency ($n = 386$), while the group of patients with CVID was somewhat smaller ($n = 176$) (Table 1). The proportions of men and women with these conditions were quite similar. Most of the patients had the debut or diagnosis of the immunodeficiency during the 1980s. For the total cohort of Danish and Swedish patients, 6639 person-years were accumulated, and the average length of follow-up was 11·8 years.

There were 28 cases of cancer in the combined cohort of Danish and Swedish patients with IgA deficiency or CVID, with 21·3 expected, yielding a SIR of 1·3 (95% CI = 0·9–1·9) (Table 2). A 7·5-fold significantly increased risk was observed for stomach cancer on the basis of five cases, of which four were seen among the Swedish patients. The risk for non-Hodgkin's lymphoma was significantly increased by approximately six times, with four cases observed, while the risk of Hodgkin's disease was non-significantly elevated on the basis of one case. The excess of non-Hodgkin's lymphoma was based on only two Danish and two Swedish cases, which resulted in SIRs of 40·0 and 3·2, respectively. The case of Hodgkin's disease occurred in a Swedish patient.

When the combined cohort was stratified on the type of immunodeficiency (Table 3), the overall cancer risk was significantly increased among patients with CVID (SIR = 1·8; 95% CI = 1·0–2·9), but not among patients with IgA deficiency (SIR = 1·0; 95% CI = 0·5–1·7). The increased risk among patients with CVID was due mainly to significantly increased SIRs of 10·3 (95% CI = 2·1–30·2) and 12·1 (95% CI = 3·3–31·0) for stomach cancer and malignant lymphoma, respectively. Among patients with IgA deficiency, the risk was nonsignificantly increased for stomach cancer (SIR = 5·4; 95% CI = 0·7–19·5) and lymphomas (SIR = 2·6; 95% CI = 0·1–14·3), however, the latter result was based on only one observed case.

Of the five cases of stomach cancer, four occurred in men (Table 4). IgA deficiency was probably present at birth for the two patients with stomach cancer, although it was diagnosed many years later when they were 64 and 78 years. The CVID patients were relatively old at the debut of their immunodeficiency, except for one man who was 22 years at debut. Two patients had the debut of CVID many years prior to the stomach cancers, while the third patient had the debut of CVID close to the diagnosis of stomach cancer. None of the lymphomas was diagnosed in childhood or adolescence. Four of the five cases of lymphomas were in women. The IgA-deficient patient had non-Hodgkin's lymphoma

Table 2. Observed (Obs) and expected (Exp) numbers and standardized incidence ratios (SIRs) of cancer among patients with IgA deficiency or CVID in Denmark and Sweden

	Combined cohort ($n = 562$)				Danish patients ($n = 64$)				Swedish patients ($n = 498$)			
Cancer site	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI
All malignant neoplasms	28	21·3	1·3	0·9–1·9	5	2·0	2·5	0·8–5·9	23	19·2	1·2	0·8–1·8
Buccal cavity and pharynx	1	0·4	2·4	0·1–13·3	0	0·0	–	0·0–92·2	1	0·4	2·7	0·0–14·8
Digestive system	9	4·3	2·1	1·0–4·0	1	0·3	3·4	0·0–19·1	8[1]	4·0	2·0	0·9–4·0
Stomach	5	0·7	7·5	2·4–17·4	1	0·0	26·3	0·3–147	4	0·6	6·3	1·7–16·1
Lung	0	1·5	–	0·0–2·4	0	0·2	–	0·0–17·6	0	1·3	–	0·0–2·8
Breast	0	3·5	–	0·0–1·1	0	0·4	–	0·0–10·9	0	3·1	–	0·0–1·2
Female genital organs	3	2·0	1·5	0·3–4·4	0	0·2	–	0·0–16·8	3[2]	1·8	1·7	0·3–4·9
Male genital organs	2	2·0	1·0	0·1–3·6	0	0·1	–	0·0–46·1	2	1·9	1·0	0·1–3·8
Urinary system	2	1·6	1·3	0·2–4·6	0	0·1	–	0·0–30·7	2	1·5	1·4	0·2–5·0
Skin	1	1·8	0·6	0·0–3·2	0	0·3	–	0·0–11·2	1	1·4	0·7	0·0–3·9
Brain and nervous system	2	0·9	2·3	0·3–8·3	1	0·1	9·8	0·1–54·3	1	0·8	1·3	0·0–7·3
Endocrine glands[3]	1	0·4	2·3	0·1–12·7	0	0·0	–	1·7–51·6	1[4]	0·4	2·3	0·0–12·6
Hematopoietic and lymphatic system	5	1·6	3·2	1·0–7·5	2	0·2	13·3	1·6–48·2	3	1·4	2·2	0·4–6·3
Non-Hodgkin's lymphoma	4	0·7	6·0	1·6–15·3	2	0·1	40·0	4·8–144	2	0·6	3·2	0·4–11·7
Hodgkin's disease	1	0·1	7·1	0·2–39·8	0	0·0	–	0·0–184	1	0·1	8·1	0·1–45·3
Leukaemia	0	0·5	–	0·0–7·7	0	0·1	–	0·0–61·5	0	0·4	–	0·0–8·8
Other specified sites	0	0·8	–	0·0–4·8	0	0·1	–	0·0–46·1	0	0·7	–	0·0–5·3
Metastases and unspecified sites	2	0·6	3·2	0·4–11·5	1	0·0	24·8	0·3–138	1	0·6	1·7	0·0–9·5

[1]Cancer of the large intestine ($n = 2$) and pancreas ($n = 2$) in addition to the stomach cancers. [2]Cancer of the corpus uteri ($n = 2$) and ovary ($n = 1$). [3]Not including thymomas. [4]Cancer of the parathyroid gland significantly elevated SIRs are marked bold ($P < 0·05$).

Table 3. Observed (Obs) and expected (Exp) numbers and standardized incidence ratios (SIRs) of all malignant neoplasms and cancers at selected sites by type of immunodeficiency among Danish and Swedish patients combined

Immunodeficiency	Cancer site	No.	Obs	Exp	SIR	95% CI
IgA deficiency		386				
	All malignant neoplasms		12	12·2	1·0	0·5–1·7
	Stomach		2	0·4	5·4	0·7–19·5
	Lymphomas		1	0·5	2·1	0·1–11·6
	Non-Hodgkin's lymphoma		1	0·4	2·6	0·1–14·3
	Hodgkin's disease		0	0·1	–	0·0–41·0
CVID		176				
	All malignant neoplasms		16	9·2	1·8	1·0–2·9
	Stomach		3	0·3	10·3	2·1–30·2
	Lymphomas		4	0·3	12·1	3·3–31·0
	Non-Hodgkin's lymphoma		3	0·3	11·1	2·3–32·5
	Hodgkin's disease		1	0·1	16·7	0·4–92·9

Significantly elevated SIRs are marked with bold ($P < 0·05$).

Table 4. Detailed information on cases of stomach cancer and lymphoma among Danish and Swedish patients with IgA deficiency or CVID

Cancer type	Sex	Type of immuno-deficiency	Age at debut of immuno-deficiency (years)	Year of debut of immuno-deficiency	Year of diagnosis of immuno-deficiency	Age at cancer diagnosis (years)	Year of cancer diagnosis	Years between debut and cancer
Stomach cancer								
	M	IgAD	0	1903 (at birth)[1]	1981	82	1986	82
	F	IgAD	0	1925 (at birth)[1]	1989	68	1993	68
	M	CVID	22	1945	1973	65	1988	43
	M	CVID	67	1978	1980	69	1981	2
	M	CVID	50	1965	1971	72	1987	22
Lymphoma								
Non-Hodgkin's lymphoma	M	IgAD	0	1946 (at birth)[1]	1985	38	1985	38
Non-Hodgkin's lymphoma	F	CVID	<46	Before 1971	1971	52	1977	>6
Non-Hodgkin's lymphoma	F	CVID	58	1975	1976	59	1976	1
Non-Hodgkin's lymphoma	F	CVID	37	1950	1978	76	1990	40
Hodgkin's disease	F	CVID	31	1969	1981	49	1987	18
Metastasis; malignant lym-phoma suspected at autopsy	M	CVID	–	Unknown	1962	30	1987	>25

IgAD, immunoglobulin A deficiency; CVID, common variable immunodeficiency. [1]IgAD was probably present from birth.

at the age of 38 years. The three CVID patients had the debut of their immunodeficiency at the age of 37 or later, with very different intervals between the debut of CVID and non-Hodgkin's lymphoma (1, >6 and 40 years). The patient with Hodgkin's disease had the debut of CVID at a young age and developed the malignancy several years later. A case recorded as a metastasis of unknown primary site in the cancer registry file was suspected to be a malignant lymphoma at autopsy, but no definite diagnosis was possible according to the autopsy report. CVID had been diagnosed and the patient treated with gammaglobulin from the age of 6, and death with the suspected lymphoma occurred at the age of 30 years.

Relatives

A total of 2071 relatives of Danish and Swedish patients with IgA deficiency or CVID were followed for 59 014 person-years, i.e. a mean follow-up period of 28·4 years (21·2 years for Danish relatives and 30·9 years for Swedish relatives). In the combined group of relatives, 219 cases of cancer were observed, with 194·4 expected cases, yielding a SIR of 1·1 (95% CI = 1·0–1·3) (Table 5). The small overall excess of cancers was a result of slight excesses among grandparents and parents; the incidence among siblings and offspring was normal. When the type of immunodeficiency was considered, the excess of cancers was found to occur among relatives of patients with IgA deficiency. Male and female

Table 5. Observed (Obs) and expected (Exp) numbers and standardized incidence ratios (SIRs) of cancer among relatives of patients with IgA deficiency or CVID in Denmark and Sweden

		All malignant neoplasms				Stomach cancer				Lymphomas			
Subgroup of relatives	No.	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI
All	2071	219	194·4	1·1	1·0–1·3	5	8·0	0·6	0·2–1·5	8	6·9	1·2	0·5–2·3
Familial relationship													
Parents	920	134	127·5	1·1	0·9–1·3	0	5·2	–	0·0–0·7	3	4·3	0·7	0·1–2·0
Siblings	805	10	10·2	1·0	0·5–1·8	0	0·1	–	0·0–30·7	0	0·8	–	0·0–4·7
Offspring[1]	93	0	0·6	–	0·0–6·5	0	0·0	–	–	0	0·1	–	0·0–61·5
Grandparents[2]	253	75	56·2	1·3	1·0–1·7	5	2·7	1·9	0·6–4·4	5	1·8	2·8	0·9–6·6
Type of immunodeficiency													
IgA deficiency	1445	166	142·2	1·2	1·0–1·4	5	5·8	0·9	0·3–2·0	5	5·1	1·0	0·3–2·3
CVID	626	53	52·2	1·0	0·8–1·3	0	2·0	–	0·0–1·8	3	1·8	1·6	0·3–4·8
Country													
Denmark	505	13	17·8	0·7	0·4–1·3	0	0·3	–	0·0–11·5	1	0·7	1·4	0·0–8·0
Sweden	1566	206	176·6	1·2	1·0–1·3	5	7·6	0·7	0·2–1·5	7	6·2	1·1	0·5–2·3

CVID, common variable immunodeficiency. [1]Only identified in Denmark. [2]Only identified in Sweden.

relatives had cancer risks of approximately the same magnitude. The risk for stomach cancer was decreased, particularly among parents. Among all relatives combined, we observed eight lymphomas, which was 1·2 times the expected number (95% CI = 0·5–2·3). Among the female relatives, the SIR for breast cancer was 1·0 (95% CI = 0·6–1·4), while the risk for genital organ cancers was 1·4 (95% CI = 0·9–2·1) (data not shown). Thus, the slight overall excess of cancers among relatives was not due to an excess of any particular cancer type.

DISCUSSION

Our study shows that the overall risk for cancer was moderately elevated among patients with CVID and not elevated among patients with IgA deficiency. The risks for specific types of cancer, i.e. stomach cancer and lymphoma, were increased, the excess being confined mainly to patients with CVID. Relatives of patients with IgA deficiency had slightly elevated cancer rates, which were not explained by excesses of stomach cancer or lymphomas, but rather by small excesses of several types of cancer.

The study of cancer incidence among patients with immunodeficiency is hampered by the rarity of the disorders. In our study, we combined data from Denmark and Sweden and were thus able to investigate cancer incidence among a total of 562 patients with IgA deficiency and CVID and 2071 family relatives. The clinics in Stockholm and Göteborg received patients from all over Sweden and the Danish Immunodeficiency Register is nationwide [4]; however, we do not have complete coverage of patients with IgA deficiency nor CVID in either of the two countries. Nevertheless, our combined material is the largest for IgA deficiency and one of the largest for CVID. As the family members were traced through population registers, recall bias in regard to relatives with cancer was avoided. All subjects were followed for cancer in high quality Cancer Registries, and cancer diagnoses were recorded independently of the registration of the immunodeficiency.

A large sample of patients with primary immunodeficiency and cancer was collected in the Immunodeficiency Cancer Registry established in the early 1970s at the University of Minnesota, USA, based on reports of 195 patients with primary immunodeficiencies from the United States and other countries [8]. The data in the Registry cannot be used for computation of cancer incidence, but it can provide information on the pattern and characteristics of the cancers observed in patients with primary immunodeficiency. Among the 120 patients with CVID included in the Registry, 46% had non-Hodgkin's lymphoma, while Hodgkin's disease and stomach cancer constituted 7% and 16% of cases, respectively. The median age at diagnosis of non-Hodgkin's lymphoma was 23 years, and there were equal numbers of males and females. The Registry had reports on only 35 patients with IgA deficiency and cancer, of whom 16% had non-Hodgkin's lymphoma and 8% had Hodgkin's disease.

In two follow-up series of 50 and 240 patients with CVID [9,10] the predominant types of cancer also seemed to be lymphomas and stomach cancer, but the lack of a comparison group precluded calculation of a relative risk for cancer. Cancer incidence among patients with CVID has been compared to that in a reference group in two previous studies [1,2]. In a British study on 220 patients who survived the first 2 years after diagnosis and were followed for a mean of 11 years, a fivefold increase in the risk for all cancers was found, due mainly to a 47-fold increase in the risk for stomach cancer on the basis of seven cases and a 30-fold increase in the risk for lymphoma on the basis of three cases [1]. Even higher SIRs of 12 for all cancers combined and 259 for lymphomas were estimated on the basis of 13 observed cases of cancer and seven lymphomas among 98 patients with CVID from the Memorial Hospital in New York, USA, who were followed for an average of 6·5 years [2]. The risk estimates for the 176 CVID patients in the present study were much more moderate, with a 1·8-fold increase in the risk for overall cancer, a 10-fold increase in risk for stomach cancer and a 12-fold increase in the risk for lymphomas. Even if we include the lymphoma suspected at autopsy to be an observed case, the risk estimate for lymphoma would increase only slightly to 15·2.

Selective IgA deficiency has a frequency of one in 700 among whites, although many of these individuals have no apparent

disease [11]. The cancer risk in people with IgA deficiency has not been assessed previously. In a 20-year follow-up study in Finland of 204 blood donors with severe deficiency of serum IgA or decreased serum IgA, one patient died from testicular cancer and one from hepatic carcinoma [12]. A higher frequency of IgA deficiency was seen among cancer patients at the Memorial Sloan-Kettering Cancer Center in New York, USA, than in other patient groups studied in the United States, particularly among those with gastrointestinal cancer and lymphoproliferative malignancies [13], but the number of IgA-deficient patients was very small, and deficiency of IgA may be caused by the cancer itself or by treatment for cancer. The results obtained for this group of patients in our study show no excess of all cancers or of lymphomas but do provide some evidence for an increased risk for stomach cancer, although the risk estimate was not significantly elevated.

There is evidence that CVID and IgA deficiency are related diseases or even different expressions of the same disease. IgA deficiency may develop into CVID, and many patients with CVID have first-degree relatives with selective IgA deficiency [14]. A common susceptibility gene located in the MHC class III region on chromosome 6 has been implicated for both CVID and IgA deficiency [15]. This suggests that phenotypic characteristics, e.g. infections, may be an underlying cause for the excess of lymphomas seen only among CVID patients. This could be investigated further by looking at the cancer incidence among unaffected relatives of such patients. To our knowledge, the cancer risk among family members of patients with IgA deficiency has been not been examined before, but one previous study included 1033 adult relatives of 25 CVID families in the United States who were followed for cancer incidence [3]. In comparison with background rates, the male relatives had a 0·5 times lower risk for cancer overall, and female relatives had a risk of unity, whereas a comparison with cancer among spouses showed a slightly reduced risk among male relatives and a significant twofold increase in risk among female relatives. The excess cases were female-specific cancers – cancers of the breast and female genital organs – which may explain why no excess was seen among males. Our findings resemble those obtained by comparison with background rates in the previous study. In particular, we did not see any increase in the risk for lymphoma similar to that seen in the patients with CVID or any excess of stomach cancers similar to that seen in the patients with CVID and IgA deficiency. Thus, genetic traits do not seem to be related to cancer development.

The factors that render immunodeficiency patients susceptible to infections may also underlie the development of specific cancers. Epstein–Barr virus is implicated in the pathogenesis of both non-Hodgkin's lymphoma and Hodgkin's disease [16] and has been suspected to cause lymphomas in primary immunodeficiencies, although the virus is not always detected in CVID-associated lymphomas. The suppression or lack of secretory IgA in CVID and IgA deficiency has been hypothesized to compromise the defence against infection with *Helicobacter pylori,* which is thought to cause stomach cancer. Although the role of secretory IgA in this defence has been questioned [17], a recent study on gastric lesions in patients with CVID confirmed a role for *H. pylori* in addition to p53 alterations in gastric carcinogenesis [18].

In conclusion, our data provide no evidence for a generalized effect of CVID or IgA deficiency on all types of cancer, but excesses of stomach cancer and lymphomas were found among patients with CVID, and stomach cancer was also found in excess among patients with IgA deficiency, although not significantly. In the combined cohort of Danish and Swedish patients with CVID, the extremely high risks for cancer reported earlier could not be confirmed, and the absolute excess number of cancers was small. There was no indication of a similar cancer risk among relatives of patients with IgA deficiency or CVID.

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