

Second primary cancers in patients with acute lymphoblastic, chronic lymphocytic and hairy cell leukemia

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Key Words:	second cancers, immune suppression, bi-directional risk, mechanistic implication, B cell leukemia

SUPPLEMENTARY TABLES SI-SVI

Table SI. Risk of cancer after CLL diagnosed in three time periods

Cancer site	Diagnosed in 1971-1985 Followed until 1985				Diagnosed in 1986-2000 Followed until 2000				Diagnosed in 2001-2015 Followed until 2015			
	N	RR	Lower	Upper	N	RR	Lower	Upper	N	RR	Lower	Upper
UAT	7	1.57	0.75	3.29	14	<u>2.48</u>	1.47	4.2	15	<u>1.96</u>	1.18	3.25
Stomach	21	<u>1.83</u>	1.2	2.81	11	1.19	0.66	2.16	12	1.53	0.87	2.69
Small intestine	0	-	-	-	1	0.86	0.12	6.09	73	<u>1.41</u>	1.12	1.77
Colorectum	35	<u>1.52</u>	1.09	2.12	53	<u>1.52</u>	1.16	1.99	11	1.35	0.75	2.44
Liver	11	1.44	0.8	2.6	15	<u>1.92</u>	1.16	3.18	1	2.06	0.29	14.68
Pancreas	10	1.39	0.75	2.58	16	<u>2.24</u>	1.37	3.66	58	<u>1.82</u>	1.41	2.35
Nose	2	<u>6.27</u>	1.56	25.13	1	2.57	0.36	18.27	37	0.82	0.6	1.13
Lung	46	<u>3.36</u>	2.51	4.48	54	<u>2.85</u>	2.18	3.72	4	<u>2.71</u>	1.02	7.22
Breast	15	0.89	0.53	1.47	19	0.7	0.44	1.09	12	1.3	0.74	2.29
Cervix	1	0.79	0.11	5.61	3	2.11	0.68	6.54	15	<u>1.96</u>	1.18	3.25
Prostate	63	<u>1.95</u>	1.52	2.49	82	<u>1.32</u>	1.06	1.64	120	1.04	0.87	1.24
Kidney	13	<u>2.13</u>	1.24	3.67	19	<u>2.75</u>	1.76	4.32	23	<u>2.67</u>	1.77	4.02
Bladder	20	<u>2.36</u>	1.52	3.65	32	<u>2.16</u>	1.53	3.05	42	<u>1.9</u>	1.4	2.57
Melanoma	7	<u>2.5</u>	1.19	5.24	26	<u>3.86</u>	2.63	5.67	58	<u>3.58</u>	2.76	4.63
Skin	57	<u>9.12</u>	7.03	11.84	104	<u>6.73</u>	5.55	8.15	262	<u>7.77</u>	6.88	8.78
Nervous System	15	<u>3.87</u>	2.33	6.42	10	<u>1.95</u>	1.05	3.63	15	<u>2.11</u>	1.27	3.5
Thyroid	1	0.84	0.12	5.98	2	1.68	0.42	6.71	5	<u>3.12</u>	1.3	7.5
Connective tissue	4	<u>4.06</u>	1.52	10.83	4	2.64	0.99	7.04	5	<u>2.56</u>	1.06	6.15
NHL	16	<u>3.7</u>	2.26	6.04	26	<u>3.01</u>	2.05	4.42	26	<u>1.97</u>	1.34	2.9
Hodgkin lymphoma	2	2.55	0.64	10.22	6	<u>10.87</u>	4.87	24.27	9	<u>15.13</u>	7.84	29.2
Myeloma	3	1.04	0.33	3.22	3	0.72	0.23	2.24	11	<u>1.94</u>	1.07	3.5
Myeloid malignancies	4	1.48	0.56	3.95	11	<u>2.29</u>	1.27	4.13	23	<u>2.82</u>	1.88	4.25
CUP	11	<u>1.86</u>	1.03	3.35	22	<u>2.06</u>	1.36	3.13	17	1.36	0.84	2.19
All ^a	377	<u>2.28</u>	2.06	2.52	544	<u>2.05</u>	1.89	2.23	849	<u>1.99</u>	1.86	2.13

N, frequency; RR, relative risk; CLL, chronic lymphoblastic leukemia, UAT, upper aerodigestive tract; SCC, squamous cell carcinoma; NHL, non-Hodgkin lymphoma; CUP, cancer of unknown primary;

Bold, italicized and underlined indicate statistical significance at 5%, 1% and 0.1% level respectively

a, Leukemia has been excluded from "All cancers".

Table SII. Risk of CLL after cancer diagnosed in three time periods

Cancer site	Diagnosed in 1971-1985 Followed until 1985				Diagnosed in 1986-2000 Followed until 2000				Diagnosed in 2001-2015 Followed until 2015			
	N	RR	Lower	Upper	N	RR	Lower	Upper	N	RR	Lower	Upper
UAT	5	0.85	0.35	2.05	7	1.24	0.59	2.61	10	1.47	0.79	2.73
Stomach	12	2.24	1.27	3.95	4	0.87	0.33	2.33	5	1.5	0.63	3.62
Colorectum	23	1.05	0.69	1.58	29	0.91	0.63	1.31	70	1.57	1.24	1.99
Liver	1	0.77	0.11	5.45	5	2.97	1.24	7.14	3	1.38	0.45	4.29
Lung	7	1.56	0.74	3.27	14	2.25	1.33	3.81	8	0.75	0.37	1.49
Breast	23	0.79	0.52	1.19	25	0.6	0.4	0.89	45	0.74	0.55	0.99
Endometrium	2	0.29	0.07	1.15	7	0.68	0.32	1.42	16	1.04	0.64	1.7
Prostate	47	1.52	1.14	2.03	93	1.69	1.38	2.08	178	1.43	1.23	1.67
Kidney	4	0.86	0.32	2.3	7	1.15	0.55	2.42	14	1.94	1.15	3.28
Bladder	15	1.43	0.86	2.38	24	1.51	1.01	2.26	25	1.28	0.86	1.9
Melanoma	4	0.99	0.37	2.64	15	1.62	0.97	2.69	41	2.3	1.69	3.13
Skin	24	3.07	2.05	4.59	57	4.55	3.5	5.92	71	3.05	2.41	3.85
Nervous System	2	0.84	0.21	3.34	3	0.66	0.21	2.05	10	1.51	0.81	2.81
NHL	17	5.12	3.18	8.24	22	3.04	2	4.62	14	1.24	0.74	2.1
Hodgkin lymphoma	1	1.63	0.23	11.57	1	2.18	0.31	15.47	4	6.41	2.4	17.08
Myeloid malignancies	5	2.71	1.13	6.53	4	1.64	0.62	4.37	15	3.32	2.00	5.51
All ^a	212	1.31	1.14	1.5	343	1.42	1.27	1.58	545	1.41	1.29	1.54

N, frequency; RR, relative risk; CLL, chronic lymphoblastic leukemia, UAT, upper aerodigestive tract; SCC, squamous cell carcinoma; NHL, non-Hodgkin lymphoma; CUP, cancer of unknown primary;

Bold, italicized and underlined indicate statistical significance at 5%, 1% and 0.1% level respectively

a, Leukemia has been excluded from "All cancers".

Table SIII. Risk of cancer after ALL diagnosed in three time periods

Cancer site	Diagnosed in 1971-1985 Followed until 1985				Diagnosed in 1986-2000 Followed until 2000				Diagnosed 2001-2015 Followed until 2015			
	N	RR	Lower	Upper	N	RR	Lower	Upper	N	RR	Lower	Upper
Stomach	4	4.02	1.51	10.72	0	-	-	-	0	-	-	-
Colorectum	3	1.32	0.42	4.08	3	4.26	1.37	13.2	2	1.68	0.42	6.73
Lung	6	4.97	2.23	11.06	0	-	-	-	0	-	-	-
Cervix	1	5.26	0.74	37.34	0	-	-	-	1	9.48	1.34	67.31
Kidney	3	5.51	1.78	17.08	1	5.71	0.8	40.55	0	-	-	-
Bladder	1	1.07	0.15	7.61	2	6.68	1.67	26.69	2	4.1	1.03	16.4
Skin	3	4.56	1.47	14.14	3	13.13	4.24	40.73	2	3.59	0.9	14.35
Nervous System	3	8.41	2.71	26.07	0	-	-	-	1	3.29	0.46	23.37
Endocrine	1	4.56	0.64	32.34	1	8.55	1.2	60.68	3	17.32	5.59	53.71
Connective tissue	0	-	-	-	0	-	-	-	1	16.54	1.26	217.4
NHL	3	7.37	2.38	22.85	1	4.64	0.65	32.94	0	0	0	.
Hodgkin lymphoma	1	11.98	1.69	85.09	0	-	-	-	0	-	-	-
Myeloid malignancies	1	3.91	0.55	27.76	2	17.58	4.40	70.29	1	4.80	0.68	34.11
All ^a	38	2.43	1.77	3.34	16	2.7	1.65	4.41	16	1.49	0.92	2.44

N, frequency; RR, relative risk; ALL, acute lymphoblastic leukemia, UAT, upper aerodigestive tract; SCC, squamous cell carcinoma; NHL, non-Hodgkin lymphoma; CUP, cancer of unknown primary;

Bold, italicized and underlined indicate statistical significance at 5%, 1% and 0.1% level respectively

a, Leukemia has been excluded from "All cancers".

Table SIV. Risk of ALL after cancer diagnosed in three time periods

Cancer site	Diagnosed in 1971-1985 Followed until 1985				Diagnosed in 1986-2000 Followed until 2000				Diagnosed in 2001-2015 Followed until 2015			
	N	RR	Lower	Upper	N	RR	Lower	Upper	N	RR	Lower	Upper
Colorectum	3	1.39	0.45	4.32	1	0.57	0.08	4.09	5	2.79	1.15	6.76
Breast	2	0.66	0.17	2.66	8	2.95	1.46	5.96	6	1.99	0.89	4.47
Kidney	2	4.2	1.05	16.84	0	-	-	-	0	-	-	-
Endocrine	0	-	-	-	0	-	-	-	3	8.66	2.78	26.98
Connective tissue	1	9.21	1.29	65.51	0	-	-	-	0	-	-	-
NHL	2	5.91	1.47	23.71	2	4.34	1.08	17.43	5	9.5	3.92	23
Hodgkin lymphoma	1	12.83	1.8	91.23	0	-	-	-	0	-	-	-
Myeloid malignancies	0				7	45.79	21.66	96.81	9	40.54	20.91	78.62
CUP	0	-	-	-	0	-	-	-	1	7.54	1.06	53.73
All ^a	24	1.45	0.96	2.19	21	1.46	0.94	2.27	38	2.17	1.54	3.05

N, frequency; RR, relative risk; ALL, acute lymphoblastic leukemia, UAT, upper aerodigestive tract; SCC, squamous cell carcinoma; NHL, non-Hodgkin lymphoma; CUP, cancer of unknown primary;

Bold, italicized and underlined indicate statistical significance at 5%, 1% and 0.1% level respectively

^a, Leukemia has been excluded from "All cancers".

Table SV. Risk of cancer after HCL diagnosed in three time periods

Cancer site	Diagnosed 1986-2000 Followed until 2000				Diagnosed 2001-2015 Followed until 2015			
	N	RR	Lower	Upper	N	RR	Lower	Upper
UAT	2	4.48	1.12	17.91	0	-	-	-
Ovary	0	-	-	-	1	7.36	1.04	52.27
Testis	1	19.99	2.81	142.04	0	-	-	-
Kidney	0	-	-	-	3	4.9	1.58	15.19
Skin	6	<u>6.38</u>	2.87	14.21	5	2.91	1.21	6.99
Nervous System	3	6.28	2.03	19.48	0	-	-	-
Thyroid	1	9.84	1.38	69.86	0	-	-	-
Connective tissue	0	-	-	-	1	7.15	1.01	50.81
NHL	1	1.53	0.21	10.83	8	<u>9.11</u>	4.55	18.22
Hodgkin lymphoma	0	-	-	-	1	<u>18.4</u>	2.59	130.77
Myeloid malignancies	2	5.56	1.39	22.23	1	1.91	0.27	13.53
CUP	1	1.36	0.19	9.64	2	2.64	0.66	10.57
All ^a	33	1.55	1.1	2.18	52	<u>1.79</u>	1.36	2.35

N, frequency; RR, relative risk; HCL, hairy cell leukemia, UAT, upper aerodigestive tract; SCC, squamous cell carcinoma; NHL, non-Hodgkin lymphoma; CUP, cancer of unknown primary;

Bold, italicized and underlined indicate statistical significance at 5%, 1% and 0.1% level respectively

^a, Leukemia has been excluded from "All cancers".

Table SVI. Risk of HCL after cancer diagnosed in three time periods

Cancer site	Diagnosed in 1986-2000 Followed until 2000				Diagnosed in 2001-2015 Followed until 2015			
	N	RR	Lower	Upper	N	RR	Lower	Upper
Prostate	8	2.42	1.19	4.93	13	1.81	1.03	3.18
Male genital	0	-	-	-	1	21.14	2.97	150.59
Kidney	2	5.25	1.31	21.1	0	-	-	-
Bladder	3	3.17	1.01	9.91	1	1.04	0.15	7.44
Melanoma	3	4.49	1.44	13.99	4	3.8	1.42	10.17
Connective tissue	0	-	-	-	1	10.08	1.42	71.77
NHL	5	<u>11.22</u>	4.63	27.16	1	1.73	0.24	12.35
All ^a	29	<u>2.12</u>	1.44	3.12	27	1.38	0.93	2.05

N, frequency; RR, relative risk; HCL, hairy cell leukemia, UAT, upper aerodigestive tract; SCC, squamous cell carcinoma; NHL, non-Hodgkin lymphoma; CUP, cancer of unknown primary;

Bold, italicized and underlined indicate statistical significance at 5%, 1% and 0.1% level respectively

a, Leukemia has been excluded from "All cancers".

Second primary cancers in patients with acute lymphoblastic, chronic lymphocytic and hairy cell leukaemia

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SUMMARY

Improvement of survival in lymphocytic leukaemia has been accompanied by the occurrence of second primary cancer (SPCs). Based on Swedish Family Cancer Database, we applied bi-directional analyses in which relative risks (RRs) were calculated for any SPCs in patients with chronic lymphocytic leukaemia (CLL), acute lymphoblastic leukaemia (ALL) and hairy cell leukaemia (HCL) and the risks of these leukaemias as SPCs. After CLL, RRs for were significant for 20 SPCs, and high for skin squamous cell cancer (24.58 for *in situ* and 7.63 for invasive), Merkel cell carcinoma (14.36), Hodgkin lymphoma (7.16) and Kaposi sarcoma (6.76). Conversely, 15 CLL cancer pairs were reciprocally increased. The increased risks were reciprocal for ALL and four cancers, RR for ALL was 15.35 after myeloid neoplasia. HCL showed reciprocally increased RRs with non-Hodgkin lymphoma and melanoma. The concordance between RRs for bi-directional associations between CLL and different cancers, and HCL and different cancers was highly significant. For CLL, the bi-directional risks with skin cancers and other immune-related cancers (also for HCL) suggest the probable involvement of immune dysfunction. For ALL, treatment may contribute to risks of multiple SPCs. Increased risk of ALL after haematological neoplasms may indicate bone marrow dysfunction. These findings may help guide treatment decisions and prognostic assessment.

INTRODUCTION

Chronic lymphocytic leukaemia (CLL), which is the most common type of leukaemia, is characterized by a progressive clonal accumulation of phenotypically mature malignant B lymphocytes in the blood, bone marrow and lymph nodes (Nabhan and Rosen, 2014, Kipps et al., 2017). Established risk factors for CLL include monoclonal B-cell lymphocytosis, family history, mutations in shelterin complex genes, over 40 low-risk gene variants and exposure to

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3 some pesticides (Speedy et al., 2014, Speedy et al., 2016, Kipps et al., 2017, Law et al., 2017,
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5 Leonard et al., 2017). Autoimmune conditions, such as autoimmune haemolytic anaemia and
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7 immune thrombocytopenic purpura, are both risk factors and therapy-related comorbidities
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9 (Hemminki et al., 2013, Kipps et al., 2017). CLL can be divided into two main subtypes,
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11 according to whether CLL cells express an unmutated or mutated immunoglobulin heavy-
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13 chain variable region gene (Kipps et al., 2017). Numerous genetic changes take place during
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15 the evolution of CLL, including somatic mutations and chromosomal aberrations (Kipps et
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17 al., 2017, Burns et al., 2018). Many patients are diagnosed at an asymptomatic stage with
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19 monoclonal B-cell lymphocytosis and may not initially require treatment, but once entering
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21 the symptomatic stage management strategies include chemotherapy with alkylating agents
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23 and purine analogues, combination of chemotherapy and immunotherapy, and recently, drugs
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25 that target key signalling pathways (Kristinsson et al., 2009, Nabhan and Rosen, 2014, Kipps
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27 et al., 2017). Many second primary cancers (SPCs) have been found to be increased in
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29 patients with CLL, including non-melanoma skin cancer, melanoma, sarcoma and lung, renal
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31 and prostate cancers (Morton et al., 2010, Royle et al., 2011, Beiggi et al., 2013). Between 2
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33 and 5% of CLL cases transform to an aggressive non-Hodgkin lymphoma (NHL) or Hodgkin
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35 lymphoma (HL) (Richter syndrome) (Kipps et al., 2017). Small lymphocytic lymphoma can
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37 be diagnosed in 5% of patients with CLL (Nabhan and Rosen, 2014, Kipps et al., 2017).
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47 Adult (diagnosed at 20 years or older) acute lymphoblastic leukaemia (ALL) constitutes
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49 about 40% of ALL cases, 75% of which are B-cell lineage and 25% are T-cell lineage (Al
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51 Ustwani et al., 2016). Recurrent cytogenetic abnormalities are found in 70% of adults and
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53 90% of children with ALL while the Philadelphia chromosome (*BCR-ABL1* fusion) is far
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55 more common in adults (15–30%) than in children (2%) (Al Ustwani et al., 2016, Inaba et al.,
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57 2013, Jabbour et al., 2018). Other fusion genes are common in adult as well as childhood
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3 ALL (Inaba et al., 2013, Jabbour et al., 2018). Cytotoxic therapies, which are effective in
4 childhood ALL, have generally been ineffective for management of adult ALL, where long
5 term survival remains generally poor (Rowe, 2010). Risk factors for SPC after ALL are
6 largely unknown and data on SPCs are limited, although one trial observed an increase for
7 lymphoproliferative neoplasms (Tavernier et al., 2007).

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17 Hairy cell leukaemia (HCL) is a rare B-cell disease typified by somatic *BRAF* mutations
18 (Grever et al., 2014, Leonard et al., 2017). Clinical features at presentation generally include
19 splenomegaly, lymphocytosis and monocytopenia with an underlying immunocompromised
20 state (Getta et al., 2015). Infectious complications have been a hallmark of the clinical course
21 in HCL patients but to what extent the immunocompromised state is the result of the
22 underlying disease or following immunosuppressive chemotherapy remains unclear (Grever
23 et al., 2014). Many patients have an indolent course and no therapies are initially required
24 (Dinmohamed et al., 2018). Therapies based on purine analogues were developed in 1990,
25 which achieve good response rates, and, more recently, targeted treatments have become
26 available, including inhibition of the mutated BRAF kinase (Grever et al., 2014, Getta et al.,
27 2015). Since 1990, relative survival has been similar to that of the background population
28 among patients diagnosed before the age of 60 years, and has now improved to some 90%,
29 even among elderly people (Dinmohamed et al., 2018). An increased risk of SPCs in HCL
30 patients has been reported for HL, NHL and thyroid cancer, for which HCL-related
31 immunological impairment was suggested to contribute (Hisada et al., 2007, Cornet et al.,
32 2014, Dasanu et al., 2015).

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56 In this study, we analysed individual data from the Swedish Cancer Registry to assess the
57 risks of SPCs following diagnosis of CLL, ALL and HCL, and also the risk of these
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3 leukaemias after the diagnosis of another cancer. Even though many studies have published
4 the risks of SPC after CLL and some have been published after HCL, no previous studies
5 have analysed the risks of leukaemias as SPC. The bi-directional analysis was recently
6 applied for myeloid neoplasms and NHL in providing evidence for reciprocal relationships
7 between cancer risks (Chattopadhyay et al., 2018a, Chattopadhyay et al., 2018b). The
8 findings from bi-directional analyses may give insight concerning the mechanisms of SPC,
9 particularly on the contribution of the adverse consequence of therapy, as therapies are rarely
10 identical for two cancers. These findings may provide evidence that an immune-suppressed
11 state may be the key mechanism if bi-directional risks are found.
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26 **PATIENTS AND METHODS**

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28 The Swedish Family Cancer Database includes the Swedish population organized in family
29 data and is linked to the Swedish Cancer Registry, which was founded in 1958; it covers the
30 entire population and includes more than two million cancers registered since 1958
31 (Hemminki et al., 2010). Six regional registries were created in the mid-1980s, which are
32 associated with the oncological centres in each medical region of Sweden, and where the
33 registration, coding and major check-up and correction work is performed. The
34 regionalization implies a high-quality service through close contact between the Swedish
35 Cancer Registry at the regional level and the reporting clinician, thus simplifying the
36 undertaking of correcting and checking the data.
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49 The registry is based on compulsory cancer notifications from clinicians and
50 pathologists/cytologists (Pukkala et al., 2017).
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56 Adult (>20 years) CLL, ALL and HCL patients were identified from the database. Over 95%
57 of all registered lymphocytic leukaemia cases were histologically verified. While the cancer
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3 registry does not publish specific statistics on histological verification of SPCs, these are
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5 included with primary cancers, for which histological verification has been approximately
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7 98% since the 1970s (Centre for Epidemiology, 2013). An *ad hoc* study on the diagnostic
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9 accuracy of second neoplasms found that 98% were correctly classified (Frödin et al., 1997).
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11 Cancer types were identified through revisions 7 and 10 of the International Classification of
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13 Diseases (ICD) in combination with SNOMED (ICD-O2) codes that were introduced in
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15 1993. Subtypes of invasive skin cancers, including squamous cell carcinoma (SCC), Merkel
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17 cell cancer and Kaposi sarcoma, as well as *in situ* skin cancer were included. Myeloid
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19 malignancies included acute (AML) and chronic myeloid leukaemia (CML), myelodysplastic
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21 syndromes (MDS) and myeloproliferative neoplasms (MPN). The follow-up was started from
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23 the year of diagnosis and terminated at death, detection of a SPC, emigration or 31 December
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25 2015, whichever came first.
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33 A Poisson regression model was used to estimate relative risks (RRs) for SPCs by comparing
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35 incidence rates for each SPC in patients with lymphocytic leukaemia to the respective
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37 incidence of this cancer as first primary cancer in the reference population aged 20 years or
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39 older. In the reverse analysis, RRs for lymphocytic leukaemia were considered as SPCs
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41 following any primary cancer in patients aged 20 years or older. The patients with CLL, ALL
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43 and HCL diagnosed between 1971-1985, 1986-2000 and 2001-2015 (HCL data were
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45 available only for the last two periods) were followed for 15 years from the time of diagnosis
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47 to estimate the periodic risks for a SPC. Sex, age group (5-year bands), calendar period (5-
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49 year bands), residential area (large cities, South Sweden, North Sweden or unspecified) and
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51 socioeconomic status (blue-collar worker, white-collar worker, farmer, private, professional
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53 or other/unspecified) were adjusted in the regression model. Confidence intervals (CIs) were
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55 calculated for 5%, 1% and 0.1% level of significance. The concordance between RRs of
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3 cancer sites that were both significant in the bi-directional analyses was assessed by
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5 Spearman rank-order correlation. All analyses were performed in SAS (v9.4) (SAS Institute,
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7 Cary, NC).
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12 The study was approved by the Ethical Committee of Lund University without a requirement
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14 for informed consent. Through advertisements in major newspapers people could choose to
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16 opt out of the study before the research register was constructed. The project database is
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18 located at Centre for Primary Health Care in Malmö, Sweden. The study was conducted in
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20 accordance with the approved guidelines.
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24 25 26 **RESULTS**

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28 Basic demographic data on the study population are provided in Table I. CLL was by far the
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30 largest diagnostic category, with 18,407 patients diagnosed at a median age of 71 years; 2773
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32 SPCs (15.1%) were diagnosed with a median follow-up time of four years. For ALL, the
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34 patient number was 2,474 and for HCL it was 823, followed by 168 (7.0%) and 150 (18.2%)
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36 SPCs, respectively. The respective median diagnostic ages were 63 and 62 years. CLL was
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38 diagnosed as a SPC in 2010 cancer patients, ALL in 179 patients and HCL in 97 patients.
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44 Risks for SPCs following diagnosis of CLL and risks of CLL following diagnosis of non-
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46 CLL cancers are shown in Table II. Only cancer sites with at least 10 cases or significant
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48 results are shown, which is same for the following tables. Overall, the risk of SPC was
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50 increased to 1.96. RRs were significant for 20 cancers with the largest RRs being shown after
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52 skin squamous cell cancer (24.58 *in situ* and 7.63 invasive), Merkel cell carcinoma (14.36),
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54 HL (7.16) and Kaposi sarcoma (6.76). In the reverse analysis, for CLL as a SPC, the overall
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56 risk was significantly increased to 1.30 (Table II, right set of columns). RRs were
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3 significantly increased for second CLL after 16 cancers with the largest RRs being shown
4 after Merkel cell carcinoma (7.39), Kaposi sarcoma (5.26), invasive skin cancer (3.02), NHL
5 (2.96) and myeloid neoplasia (2.32). A total of 15 CLL cancer pairs were reciprocally
6 increased. The concordance between the RR for each non-CLL cancer following a diagnosis
7 of CLL and the RR for CLL following diagnosis of a non-CLL cancer was highly statistically
8 significant ($r=0.67$, $P=0.006$).
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19 Table III shows the RRs for SPC after ALL and for ALL as a SPC. The overall RR was
20 increased to 2.13 for SPC after ALL. The risks for 14 cancers were increased, with the
21 highest RRs recorded for HL (14.65), *in situ* skin cancer (7.81), endocrine tumours (5.61),
22 invasive skin cancer (5.20), kidney cancer (5.02) and NHL (4.92). In the reverse analysis, the
23 overall RR was 1.51. Risks for ALL after six cancers were increased, most after myeloid
24 neoplasia (15.35), HL (8.14) and NHL (6.78); for six cancers the increased risks were
25 reciprocal. The primary myeloid neoplasias preceding ALL included AML (n=4), CML
26 (n=9), MDS (n=2) and MPN (n=5); the median follow-up time from myeloid neoplasm to
27 ALL was 25 months. The concordance between RR for each non-ALL cancer following a
28 diagnosis of ALL and RR for ALL following diagnosis of a non-ALL cancer was not
29 significant ($r=0.60$, $P=0.3$). No cases of Merkel cell cancer or Kaposi sarcoma were found in
30 these analyses.
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49 Table IV shows the RRs for SPC after HCL and for HCL as a SPC. The overall RR was
50 increased to 1.65 for SPC after HCL, contributed by eight cancers with increased RRs. The
51 highest RR was found for nasal cancer, but this was based on one case only; the RRs for
52 NHL was 4.70, for *in situ* skin cancer it was 4.17 and for invasive skin cancer it was 3.62,
53 barely higher than the RR for kidney cancer (3.60). In the reverse analysis, the overall RR
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3 was 1.62, with HCL risk increased after three cancers, most after NHL (5.99). NHL and
4 melanoma showed reciprocally increased RRs. The concordance between RR for each non-
5 HCL cancer following a diagnosis of HCL and RR for HCL following diagnosis of a non-
6 HCL cancer was highly statistically significant ($r=1.00$).
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14 Periodic analyses of SPC risks related to the three types of leukaemia are reported in Tables
15 SI to SVI. Each follow-up period was about 15 years, which allows comparison between the
16 periods. Risk of SPC after CLL is shown in Table SI, with a stable overall risk of about 2.0.
17 Skin SCC was increased through all periods (RRs between 6.73 and 9.12) but the high risk of
18 HL was noted only in the last two periods. In the reverse order (Table SII), i.e., CLL as a
19 SPC, the overall RRs were stable at around 1.4, and CLL was increased after skin SCC
20 through all periods (RRs between 3.05 and 4.55). The results for ALL and HCL were
21 inconclusive because of small case numbers. However, the risk of ALL was extremely high
22 (RR over 40) as a SPC after myeloid malignancies in the last two follow-up periods.
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40 DISCUSSION

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42 The novel aspect of the present study was the bi-directional analysis of SPCs, which will
43 allow mechanistic insight into the formation of SPCs. The risk of NHL was increased as a
44 SPC after CLL, ALL and HCL, and the risk for each leukaemia was increased as a SPC after
45 NHL. The correlations of the bi-directional associations were highly significant for CLL and
46 HCL but not for ALL. Invasive and *in situ* skin cancers, HL, melanoma and kidney cancer
47 were most systematically associated as first cancer and SPC with the three leukaemias. The
48 pattern of associated cancers provides strong epidemiological evidence that immune
49 dysfunction plays a role. Immunosuppressed organ transplant patients have an increased risk
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3 of skin SCC and NHL (20-fold) but also kidney cancer (15-fold), melanoma, leukaemia and
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5 anogenital cancers (5-fold) and other cancers (Rama and Grinyo, 2010, Birkeland et al., 1995,
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7 Wimmer et al., 2007). The bidirectional spectrum of cancer risk seen in the present analysis is
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9 reminiscent of immunosuppressed patients. This is in contrast to the conclusions of a recent
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11 review on CLL, which stated that ‘...malignancies observed do not mirror those in patients
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13 with other immunodeficiency diseases’ (Kipps et al., 2017). For CLL, very high reciprocal
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15 risks of Merkel cell cancer were noted, as has been previously reported as SPC after CLL
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17 (Tadmor et al., 2011, Tadmor et al., 2012). We also found novel reciprocal associations of
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19 CLL with Kaposi sarcoma, which was not significant in a previous study (Morton et al.,
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21 2010). As both Kaposi sarcoma and Merkel cell carcinoma are virally induced and associated
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23 with immunodeficiency conditions, including autoimmune diseases, the strong associations
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25 of these cancers with CLL provide further evidence on underlying immunological
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27 mechanisms (Hemminki et al., 2012, Zur Hausen, 2009).
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36 The strengths of this study were the nationwide coverage of cancers from a cancer registry
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38 where virtually all cancers have been histologically verified. The obligation to report cancers
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40 to the cancer registry has included SPCs, and international pooling studies have shown that
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42 the Swedish rates of SPCs are among the highest of all cancer registries (Brennan et al.,
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44 2005). In agreement, the present study found the proportion of SPCs after CLL to be 15.1%,
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46 higher than 9.1% in the US study based on the statistics in the Surveillance, Epidemiology,
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48 and End Results (SEER) database (Morton et al., 2010). Similarly, the present proportion of
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50 SPCs after HCL of 18.2% was higher than that of 11.5% reported in the SEER database
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52 (Hisada et al., 2007). The present proportion for ALL was lowest (7.0%) among the three
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54 leukaemias, which most likely indicates that these proportions are related to survival in the
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56 particular cancers. Accordingly, the median follow-up times decreased from HCL (8 years) to
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3 CLL (4 years) and ALL (3 years). A limitation of the study was that we did not have the
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5 opportunity to incorporate information on treatment.
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10 Previous studies have not considered myeloid neoplasia as SPC after CLL or other
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12 leukaemias. The present results showed that myeloid neoplasia were bi-directionally
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14 associated with CLL and ALL. The risk of ALL was very high (15.35) as a SPC, which was
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16 observed in the period 1986 to 2015. The related myeloid neoplasia included all main types
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18 of this disease and ALL diagnosis followed after a median of only 25 months, suggesting
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20 generalized bone marrow dysfunction as a possible mechanism. However, this was not
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22 reflected in a general immune dysfunction since ALL risk after skin cancer was not
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24 increased. Risk of ALL was increased bi-directionally with NHL and HL. The risks of many
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26 cancers were increased after ALL, to which chemotherapy may have contributed. As an
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28 example, ALL risk was increased after testicular cancer, for which the normal treatment
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30 includes radiotherapy and a combination of DNA-damaging drugs (Hanna and Einhorn,
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32 2014). In a clinical trial of adult ALL patients, 40% of 23 SPCs were myeloid neoplasia and
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34 the remaining cases were equally divided between skin and internal tumours and lymphoma
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36 (Tavernier et al., 2007).
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45 Richter syndrome is estimated to account for 2 to 5% of CLL patients whose disease
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47 transforms to NHL or HL, thus some of the observed risks may be contributed by this
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49 mechanism (Kipps et al., 2017). However, this mechanism is unlikely to operate in the
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51 reverse order and the risk of CLL was almost equally high (2.96) as a SPC after NHL as was
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53 the risk of NHL after CLL (3.11).
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3 Factors influencing malignant transformation of CLL include genetic alterations, aberrant
4 immune signalling and growth stimulation by the cellular environment (Kipps et al., 2017).
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6 Immune signalling is thought to be triggered by surface immunoglobulin acting as an
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8 autoantigen and leading to a constitutively active B-cell receptor (Kipps et al., 2017). The
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10 steps leading to clinical hypogammaglobulinaemia remain unclear, but may involve systemic
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12 increases of interleukin 10 levels with ensuing immunosuppression. CLL cells express high
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14 levels of the programmed cell death ligands PD-L1 and PD-L2 (also termed CD274 and
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16 PDCD1LG2), which suppress T-cell effector functions leading to clonal expansion of
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18 malignant cells (Kipps et al., 2017). Tumours can interfere with T-cell orchestrated immune
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20 function, which mirrors the impact of iatrogenic immune suppression, resulting in the
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22 immunological escape of dormant tumours (which were in immunological equilibrium) and,
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24 finally, a diagnosis of an SPC (Friman et al., 2016).
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33 In conclusion, we have provided a comprehensive bi-directional analysis of cancer risks
34 associated with CLL, ALL and HCL. For CLL, the bi-directional risks with NHL, skin SCC,
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36 Merkel cell carcinoma and Kaposi sarcoma suggest that not only immune dysfunction in CLL
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38 predisposes to multiple SPCs but cancer-related immune dysfunction is able to trigger
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40 formation of CLL as a SPC. For ALL, treatment may be an important contributor to the risks
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42 of multiple SPCs. ALL risk was increased as a SPC after myeloid neoplasms and lymphoma,
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44 which may indicate bone marrow dysfunction. For the rare HCL, the results were in-line with
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46 known immune dysfunction. As a clinical take-home message, the study quantified risks for
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48 SPC, guiding treatment decisions and prognostic assessment. Benefit-risk ratios of therapies
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50 need to be constantly evaluated, which may suggest less cytotoxic treatment options or
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52 reduction of treatment intensity in certain individuals, as in HL. Research needs to be
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54 intensified on the management of patients on targeted agents, including inhibitors of BRAF,
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3 BCL2, BTK and PI3K, many of which influence the function of the immune system. In a
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5 broader context, target and off-target effects of immunotherapy reagents, such as anti-PD1,
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7 anti-PDL1 and anti-CTLA4, are a continued challenge.
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28 29 **AUTHOR CONTRIBUTIONS**

30
31 KH, GZ, AS, SC designed the study. JS, KS acquired the data. GZ, SC, KH, AS, AH
32
33 performed the statistical analysis and interpretation. KH, AF, RSH, GZ, SC, AS, AH, KS, JS
34
35 wrote the manuscript. All authors approved the final text.
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40 41 **CONFLICTS OF INTEREST**

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43 A.H. is a shareholder in Targovax ASA. A.H. is an employee and shareholder in TILT
44
45 Biotherapeutics Ltd. All other authors declared no conflict of interest.
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Table I. Distribution of patients with leukaemia

Leukaemia as first primary cancer				
Leukaemia	N	Age at diagnosis (years); median (range)	Follow-up time to SPC (years); median (range)	SPC, n (%) ^a
CLL	18,407	71 (63 - 79)	4 (1 - 8)	2773 (15.1)
ALL	2,474	63 (46 - 74)	3 (0 - 8.5)	168 (7.0)
HCL	823	62 (51 - 71)	8 (3 - 12)	150 (18.2)
Leukaemia as second primary cancer, after around 1.63 million first primary cancers^a				
Leukaemia	N	Age at diagnosis (years); median (range)	Follow-up time to SPC (years); median (range)	
CLL	2010	76 (70 - 82)	5 (1 - 12)	
ALL	179	72 (63 - 78)	5 (2 - 11)	
HCL	97	72 (66 - 79)	5 (2 - 10)	

^a, not including leukaemia

ALL: acute lymphoblastic leukaemia; CLL: chronic lymphocytic leukaemia; HCL: hairy cell leukaemia; SPC: second primary cancer.

Table II. Risk of cancer after diagnosis of CLL and that of CLL after diagnosis of cancer

Cancer site	Risk of cancer after CLL				Risk of CLL after cancer			
	N	RR	Lower	Upper	N	RR	Lower	Upper
UAT	60	<u>2.02</u>	1.57	2.60	42	1.03	0.76	1.39
Oesophagus	12	0.90	0.51	1.59	7	1.56	0.74	3.26
Stomach	82	<u>1.50</u>	1.21	1.86	38	1.01	0.74	1.39
Small intestine	11	1.78	0.99	3.22	5	0.93	0.39	2.23
Colorectum	247	<u>1.36</u>	1.20	1.54	215	1.16	1.02	1.33
Liver	53	1.29	0.98	1.68	15	1.59	0.96	2.63
Pancreas	45	1.11	0.83	1.49	2	0.22	0.06	0.89
Nose	5	2.41	1.00	5.80	2	0.72	0.18	2.89
Lung	246	<u>2.38</u>	2.10	2.70	48	1.33	1.00	1.76
Breast	115	0.79	0.66	0.95	239	0.81	0.72	0.93
Cervix	9	1.26	0.66	2.42	21	0.56	0.36	0.86
Endometrium	32	1.14	0.81	1.61	70	0.83	0.66	1.05
Ovary	20	1.08	0.70	1.68	32	0.86	0.61	1.22
Prostate	403	<u>1.20</u>	1.09	1.33	465	<u>1.57</u>	1.43	1.73
Kidney	74	<u>2.06</u>	1.64	2.59	56	1.48	1.14	1.93
Bladder	134	<u>1.84</u>	1.55	2.18	126	<u>1.47</u>	1.24	1.76
Melanoma	127	<u>3.22</u>	2.71	3.83	97	<u>1.47</u>	1.20	1.8
SCC, invasive	639	<u>7.63</u>	7.06	8.25	183	<u>3.02</u>	2.61	3.50
Merkel	11	<u>14.36</u>	7.90	26.09	3	<u>7.39</u>	2.38	22.92
Kaposi	5	<u>6.76</u>	2.80	16.29	4	<u>5.26</u>	1.98	14.02
Skin SCC, <i>in situ</i>	235	<u>24.58</u>	21.58	28.00	231	<u>2.60</u>	2.28	2.96
Nervous System	66	<u>2.54</u>	2.00	3.24	47	1.24	0.93	1.65
Thyroid	11	1.58	0.88	2.86	31	<u>1.85</u>	1.30	2.63
Endocrine	25	1.57	1.06	2.32	53	1.32	1.01	1.73
Connective tissue	17	<u>2.32</u>	1.44	3.74	18	1.87	1.18	2.97
NHL	130	<u>3.11</u>	2.62	3.7	108	<u>2.96</u>	2.45	3.58
Hodgkin lymphoma	26	<u>7.16</u>	4.87	10.53	11	1.99	1.10	3.59
Myeloma	26	1.26	0.86	1.85	13	0.91	0.53	1.56
Myeloid malignancies	53	<u>2.12</u>	1.62	2.78	36	<u>2.32</u>	1.68	3.22
UPC	91	<u>1.88</u>	1.53	2.31	6	0.41	0.19	0.92
All cancers ^a	2773	<u>1.96</u>	1.89	2.04	2010	<u>1.30</u>	1.24	1.36

Bold, italicized and underlined indicate statistical significance at 5%, 1% and 0.1% level respectively

^a, Leukaemia has been excluded from "All cancers".

CLL: chronic lymphocytic leukaemia; N: frequency; NHL: non-Hodgkin lymphoma; RR: relative risk; SCC: squamous cell carcinoma; UAT: upper aerodigestive tract; UPC: unknown primary cancer.

Table III. Risk of cancer after diagnosis of ALL and that of ALL after diagnosis of cancer

Cancer site	Risk of cancer after ALL				Risk of ALL after cancer			
	N	RR	Lower	Upper	N	RR	Lower	Upper
Colorectum	17	1.6	1.00	2.58	23	1.64	1.08	2.47
Lung	20	<u>3.45</u>	2.23	5.35	4	1.34	0.50	3.59
Breast	11	1.07	0.59	1.94	38	1.64	1.19	2.26
Prostate	21	1.57	1.02	2.4	28	1.43	0.98	2.09
Testis	0	-	-	-	3	3.75	1.21	11.66
Kidney	12	<u>5.02</u>	2.85	8.84	3	0.99	0.32	3.06
Bladder	10	2.43	1.31	4.52	10	1.61	0.86	3.00
SCC, invasive	18	<u>5.20</u>	3.27	8.25	6	1.48	0.66	3.3
Skin SCC, <i>in situ</i>	3	<u>7.81</u>	2.52	24.22	6	1.05	0.47	2.35
Nervous System	5	2.58	1.07	6.2	1	0.31	0.04	2.19
Endocrine	6	<u>5.61</u>	2.52	12.49	4	1.35	0.51	3.61
Connective tissue	2	4.14	1.04	16.56	1	1.26	0.18	8.95
NHL	11	<u>4.92</u>	2.72	8.88	18	<u>6.78</u>	4.26	10.8
Hodgkin lymphoma	5	<u>14.65</u>	6.09	35.21	5	<u>8.14</u>	3.38	19.57
Myeloid malignancies	5	3.53	1.47	8.47	20	<u>15.35</u>	9.87	23.85
UPC	6	2.34	1.05	5.22	1	0.78	0.11	5.57
All ^a	168	<u>2.13</u>	1.83	2.48	179	<u>1.51</u>	1.29	1.76

Bold, italicized and underlined indicate statistical significance at 5%, 1% and 0.1% level respectively

^a, Leukaemia has been excluded from "All cancers".

ALL: acute lymphoblastic leukaemia; N: frequency; NHL: non-Hodgkin lymphoma; RR: relative risk; SCC: squamous cell carcinoma; UPC: unknown primary cancer.

Table IV. Risk of cancer after diagnosis of HCL and that of HCL after diagnosis of cancer

Cancer site	Risk of cancer after HCL				Risk of HCL after cancer			
	N	RR	Lower	Upper	N	RR	Lower	Upper
Colorectum	18	1.72	1.09	2.74	10	1.61	0.86	3.01
Nose	1	9.14	1.29	64.92	0	-	-	-
Prostate	39	1.15	0.84	1.57	31	<u>2.26</u>	1.56	3.26
Kidney	7	<u>3.60</u>	1.72	7.55	3	2.10	0.68	6.53
Melanoma	9	2.59	1.34	4.97	9	2.53	1.31	4.89
SCC, invasive	18	<u>3.62</u>	2.28	5.75	3	1.5	0.48	4.66
Skin SCC, <i>in situ</i>	3	<u>4.17</u>	1.35	12.95	6	1.88	0.84	4.2
NHL	13	<u>4.70</u>	2.73	8.10	10	<u>5.99</u>	3.21	11.2
UPC	6	2.34	1.05	5.21	0	-	-	-
All ^a	150	<u>1.65</u>	1.40	1.93	97	<u>1.62</u>	1.31	2.01

Bold, italicized and underlined indicate statistical significance at 5%, 1% and 0.1% level respectively

a, Leukaemia has been excluded from "All cancers".

HCL: hairy cell leukaemia; N: frequency; NHL: non-Hodgkin lymphoma; RR: relative risk; SCC: squamous cell carcinoma; UPC: unknown primary cancer

Second primary cancers in patients with acute lymphoblastic, chronic lymphocytic and hairy cell leukemikaemia

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For Peer Review

SUMMARY

Improvement of survival in lymphocytic leukemikaemia ~~is has been~~ accompanied by the occurrence of second primary cancer (SPCs). Based on Swedish Family- Cancer Database, we applied bi-directional analyses in which relative risks (RRs) were calculated for any SPCs in patients with chronic lymphocytic leukemikaemia (CLL), acute lymphoblastic leukemikaemia (ALL) and hairy cell leukemikaemia (HCL) and ~~the~~ risks of these leukemikaemias as SPCs. After CLL, RRs for were significant for 20 SPCs, and high for skin squamous cell cancer (24.58 for *in situ* and 7.63 for invasive), Merkel cell carcinoma (14.36), Hodgkin lymphoma (7.16) and Kaposi sarcoma (6.76). ~~ReverseelyConversely~~, 15 CLL- cancer pairs were reciprocally increased. ~~The increased risks were reciprocal~~ for ALL and four cancers, ~~the increased risks were reciprocal~~. RR for ALL was 15.35 after myeloid neoplasia. HCL showed reciprocally increased RRs with non-Hodgkin lymphoma and melanoma. The concordance between RRs for bi-directional associations between CLL and different cancers, and HCL and different cancers was highly significant. For CLL, the bi-directional risks with skin cancers and other immune-related cancers (also for HCL) suggest ~~likely the probable~~ involvement of immune dysfunction. For ALL, treatment may contribute to risks of multiple SPCs. Increased risk of ALL after ~~hemhaematological~~ neoplasms may indicate bone marrow dysfunction. ~~These~~ findings ~~may~~ help guide treatment decisions and prognostic assessment.

INTRODUCTION

Chronic lymphocytic leukemia (CLL), which is the most common type of leukemia, is characterized by a progressive clonal accumulation of phenotypically mature malignant B lymphocytes in the blood, bone marrow and lymph nodes (Nabhan and Rosen, 2014, Kipps et al., 2017). Established risk factors for CLL include monoclonal B-cell lymphocytosis, family history, mutations in shelterin complex genes, over 40 low-risk gene variants and exposure to some pesticides (Speedy et al., 2014, Speedy et al., 2016, Kipps et al., 2017, Law et al., 2017, Leonard et al., 2017). Autoimmune conditions, such as autoimmune hemolytic anemia and immune thrombocytopenic purpura, are both risk factors and therapy-related comorbidities (Hemminki et al., 2013, Kipps et al., 2017).

CLL can be divided into two main subtypes, which are distinguished by whether CLL cells express an unmutated or mutated immunoglobulin heavy-chain variable region gene (Kipps et al., 2017). Numerous genetic changes take place during the evolution of CLL, including somatic mutations and chromosomal aberrations (Kipps et al., 2017, Burns et al., 2018). Many patients are diagnosed at an asymptomatic stage with monoclonal B-cell lymphocytosis and may not initially require treatment, but once entering the symptomatic stage management strategies include chemotherapy with alkylating agents and purine analogues, combination of chemotherapy and immunotherapy, and recently, drugs that target key signaling pathways (Kristinsson et al., 2009, Nabhan and Rosen, 2014, Kipps et al., 2017). Many second primary cancers (SPCs) have been found to be increased in patients with CLL, including non-melanoma skin cancer, melanoma, sarcoma, and lung, renal and prostate cancers (Morton et al., 2010, Royle et al., 2011, Beiggi et al., 2013). Between 2 to and 5% of CLL cases transform to an aggressive non-Hodgkin lymphoma (NHL) or Hodgkin lymphoma (HL) may take place (Richter syndrome)

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3 (Kipps et al., 2017). Small lymphocytic lymphoma ~~may-can~~ be diagnosed in 5% of patients
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5 with CLL (Nabhan and Rosen, 2014, Kipps et al., 2017).
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10 Adult (diagnosed at 20 years or older) acute lymphoblastic leukemikaemia (ALL) constitutes
11 about 40% of ALL ~~cases, with~~ 75% ~~having-of which are~~ B-cell lineage and 25% ~~having-are~~
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13 T-cell lineage (Al Ustwani et al., 2016). Recurrent cytogenetic abnormalities are found in
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15 70% of adults and 90% of children with ALL while the Philadelphia chromosome (*BCR-*
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17 *ABL1* fusion) is far more common in adults (15–30%) than in children (2%) (Al Ustwani et
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19 al., 2016, Inaba et al., 2013, Jabbour et al., 2018). ~~Even~~ Other fusion genes are common in
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21 adult as well as childhood ALL (Inaba et al., 2013, Jabbour et al., 2018). Cytotoxic therapies,
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23 which are effective in childhood ALL, have generally been ineffective for management of
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25 adult ALL, ~~whose-where~~ long term survival remains generally poor (Rowe, 2010). Risk
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27 factors for SPC after ALL are largely unknown and data on SPCs are limited, although ~~but in~~
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29 one trial observed an increase ~~was-observed~~ for lymphoproliferative neoplasms (Tavernier et
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31 al., 2007).
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40 Hairy cell leukemikaemia (HCL) is a rare B-cell disease typified by somatic *BRAF* mutations
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42 (Grever et al., 2014, Leonard et al., 2017). Clinical features at presentation generally include
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44 splenomegaly, lymphocytosis and monocytopenia with an underlying immunocompromised
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46 state (Getta et al., 2015). Infectious complications have been a hallmark of the clinical course
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48 in HCL patients but to what extent the immunocompromised state is the result of the
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50 underlying disease or following immunosuppressive chemotherapy remains unclear (Grever
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52 et al., 2014). Many patients have an indolent course and no therapies are initially required
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54 (Dinmohamed et al., 2018). Therapies based on purine analogues were developed in 1990
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56 ~~based-on-purine-analogues~~, which achieve good response rates, and, more recently, targeted
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3 treatments have become available, including inhibition of the mutated BRAF kinase (Grever
4 et al., 2014, Getta et al., 2015). ~~Relative-Since 1990, relative~~ survival has been ~~close-similar~~
5 to ~~that of~~ the background population among patients diagnosed before ~~the age of~~ 60 years
6 ~~since 1990~~, and has now improved to some 90%, even among elderly people (Dinmohamed
7 et al., 2018). An increased risk of SPCs in HCL patients has been reported for ~~Hodgkin-HL,~~
8 ~~and non-Hodgkin-lymphoma (NHL)~~ and ~~for~~ thyroid cancer, for which HCL-related
9 immunological impairment was suggested to contribute (Hisada et al., 2007, Cornet et al.,
10 2014, Dasanu et al., 2015).

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24 In this study, we ~~analyzed~~analysed individual data from the Swedish Cancer Registry to
25 assess ~~the~~ risks of SPCs following diagnosis of ~~the-CLL, ALL and HCL~~three types of
26 ~~leukemia~~, and also the risk of these leukemias after the diagnosis of another cancer.
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Even though many studies have published ~~the~~ risks of SPC after CLL and some ~~have been~~
~~published~~ after HCL, ~~there are~~ no previous studies ~~analyzing~~have analysed the risks of
leukemias as SPC. The bi-directional analysis was recently applied for myeloid
neoplasms and ~~non-Hodgkin-lymphoma~~NHL in providing evidence for reciprocal
relationships between cancer risks (Chattopadhyay et al., ~~2018b~~2018a, Chattopadhyay et al.,
~~2018a~~2018b). The findings from bi-directional analyses may give insight concerning ~~the~~
mechanisms of SPC, particularly on the contribution of ~~the~~ adverse consequence of therapy,
as therapies are rarely identical for two cancers. These findings may provide evidence that ~~an~~
~~immune-immune~~-suppressed state may be the key mechanism if bi-directional risks are
found.

PATIENTS AND METHODS

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3 The Swedish Family-Cancer Database includes the Swedish population organized in family
4 data and is linked to the Swedish Cancer Registry, which was founded in 1958; it covers the
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6 entire population ~~and including~~ includes more than two million cancers registered since 1958
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8 (Hemminki et al., 2010). ~~Six regional Since registries were created in~~ the mid-1980s, ~~which~~
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10 ~~are there are six regional registries~~ associated with the oncological ~~center~~ centres in each
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12 medical region of Sweden, ~~and~~ where the registration, coding and major check-up and
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14 correction work is performed. ~~The regionalization implies a high-quality service through a~~
15
16 close contact between the Swedish Cancer Registry at the regional level and the reporting
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18 clinician, thus simplifying the undertaking of correcting and checking the data.
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24 The registry is based on compulsory cancer notifications from clinicians and
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26 pathologists/cytologists (Pukkala et al., 2017).
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31 Adult (>20 years) CLL, ALL and HCL patients were identified from the database. Over 95%
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33 of all registered lymphocytic leukemikaemia cases were histologically verified. While the
34
35 cancer registry does not publish specific statistics on histological verification of SPCs, these
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37 are included with primary cancers, for which histological verification has been approximately
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39 98% ~~from since~~ the 1970s (Centre for Epidemiology, 2013). An *ad hoc* study on the
40
41 diagnostic accuracy of second neoplasms found ~~that~~ 98% ~~to be were~~ correctly classified.
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43 (Frödin et al., 1997). Cancer types were identified through revisions 7 and 10 of ~~the~~
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45 International Classification of Diseases (ICD) in combination with SNOMED (ICD-O2)
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47 codes that were introduced in 1993. Subtypes of invasive skin cancers, including squamous
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49 cell carcinoma (SCC), Merkel cell cancer and Kaposi sarcoma, as well as *in situ* skin cancer
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51 were included. Myeloid malignancies included acute (AML) and chronic myeloid
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53 leukemikaemia (CML), myelodysplastic syndromes (MDS) and myeloproliferative
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3 neoplasms ([MPN](#)). The follow-up was started from the year of diagnosis and terminated at
4 death, detection of a SPC, emigration or [31 December 31, 2015](#), whichever came first.
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10 [A](#) Poisson regression model was used to estimate relative risks (RRs) for SPCs by comparing
11 incidence rates for each SPC in patients with lymphocytic leukemikaemia to the respective
12 incidence of this cancer as first primary [cancer](#) in the reference population aged 20 years or
13 older. In the reverse analysis, RRs for lymphocytic leukemikaemia were considered as SPCs
14 following any primary cancer in patients aged 20 years or older. The patients with [CLL, ALL](#)
15 [and HCL the three leukemias](#) diagnosed between 1971-1985, 1986-2000 and 2001-2015
16 (HCL data were available only for the last two periods) were followed for 15 years [since](#)
17 [from](#) the time of diagnosis to estimate the periodic risks for a SPC. Sex, age group (5-year
18 bands), calendar period (5-year bands), residential area (large cities, South Sweden, North
19 Sweden, or unspecified) and socioeconomic status (blue-collar worker, white-collar worker,
20 farmer, private, professional, or other/unspecified) were adjusted in the regression model.
21 Confidence intervals (CIs) were calculated for 5%, 1% and 0.1% level of significance. The
22 concordance between RRs of cancer sites that were both significant in the bi-directional
23 analyses was assessed by Spearman rank-order correlation. All analyses were performed in
24 SAS (v9.4) ([SAS Institute, Cary, NC](#)).
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47 The study was approved by the Ethical Committee of Lund University without a requirement
48 for informed consent. Through advertisements in major newspapers people could choose to
49 opt out of the study before the research register was constructed. The project database is
50 located at [CenterCentre](#) for Primary Health Care in Malmö, Sweden. The study was
51 conducted in accordance with the approved guidelines.
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RESULTS

Basic demographic data on the study population are provided in Table 4I. CLL was by far the largest diagnostic category, with 18,407 patients, diagnosed at a median age of 71 years; 2773 SPCs (15.1%) were diagnosed with a median follow-up time of four years. For ALL, the patient number was 2,474 and for HCL it was 823, followed by 168 (7.0%) and 150 (18.2%) SPCs, respectively. The respective median diagnostic ages were 63 and 62 years. CLL was diagnosed as a SPC in 2010 cancer patients, ALL in 179 patients and HCL in 97 patients.

Risks for SPCs following diagnosis of CLL and risks of CLL following diagnosis of non-CLL cancers are shown in Table 2II. Only cancer sites with at least 10 cases or significant results are shown, which is same for the following tables. Overall, the risk of SPC was increased to 1.96. RRs were significant for 20 cancers with the largest RRs being shown after skin squamous cell cancer (24.58 *in situ* and 7.63 invasive), Merkel cell carcinoma (14.36), ~~Hodgkin lymphoma~~HL (7.16), ~~and~~ Kaposi sarcoma (6.76) ~~and Hodgkin lymphoma (7.16)~~. In the reverse analysis, for CLL as a SPC, the overall risk was significantly increased to 1.30 (Table 2II, right set of columns). RRs were significantly increased for second CLL after 16 cancers with the largest RRs being shown after Merkel cell carcinoma (7.39), Kaposi sarcoma (5.26), invasive skin cancer (3.02), ~~and~~ NHL (2.96) and myeloid neoplasia (2.32). A total of 15 CLL-cancer pairs were reciprocally increased. The concordance between the RR for each non-CLL cancer following a diagnosis of CLL and the RR for CLL following diagnosis of a non-CLL cancer was highly statistically significant ($r=0.67$, $P=0.006$).

Table 3III shows the RRs for SPC after ALL and for ALL as a SPC. The overall RR was increased to 2.13 for SPC after ALL. The risks for 14 cancers were increased, ~~and~~ with the

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3 highest RRs ~~were~~ recorded for ~~Hodgkin-lymphoma~~HL (14.65), *in situ* skin cancer (7.81),
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5 endocrine tumours (5.61), invasive skin cancer (5.20), kidney cancer (5.02) and NHL (4.92).

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8 In the reverse analysis, the overall RR was 1.51. Risks for ALL after six cancers were
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10 increased, most after myeloid neoplasia (15.35), ~~Hodgkin-lymphoma~~HL (8.14) and NHL
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12 (6.78); for six cancers the increased risks were reciprocal. The primary myeloid neoplasias
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14 preceding ALL ~~constituted~~ included ~~four acute myeloid leukemia~~AML (n=4), ~~nine chronic~~
15
16 ~~myeloid leukemia~~CML (n=9), ~~two myelodysplastic syndrome~~MDS (n=2) and ~~five~~
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18 ~~myeloproliferative neoplasms~~MPN (n=5); the median follow-up time from myeloid neoplasm
19
20 to ALL was 25 months. The concordance between RR for each non-ALL cancer following a
21
22 diagnosis of ALL and RR for ALL following diagnosis of a non-ALL cancer was not
23
24 significant ($r=0.60$, $P=0.3$). No cases of Merkel cell cancer or Kaposi sarcoma were found in
25
26 these analyses.
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34 Table 4-IV shows the RRs for SPC after HCL and for HCL as a SPC. The overall RR was
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36 increased to 1.65 for SPC after HCL, contributed by eight cancers with increased RRs. The
37
38 highest RR was found for nasal cancer, but this was based on one case only; the RRs for
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40 NHL was 4.70, for *in situ* skin cancer it was 4.17 and for invasive skin cancer it was 3.62,
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42 barely higher than the RR for kidney cancer (3.60). In the reverse analysis, the overall RR
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44 was 1.62, with HCL risk increased after three cancers, most after NHL (5.99). NHL and
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46 melanoma showed reciprocally increased RRs. The concordance between RR for each non-
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48 HCL cancer following a diagnosis of HCL and RR for HCL following diagnosis of a non-
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50 HCL cancer was highly statistically significant ($r=1.00$).
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57 Periodic analyses of SPC risks related to the three types of leukemikaemia ~~were~~ are reported
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59 in ~~Supplementary~~ Tables 1-SI to 6SVI. Each follow-up period was about 15 years, which
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3 allows comparison between the periods. Risk of SPC after CLL is shown in [Supplementary](#)
4 Table [1-SI](#), with a stable overall risk of about 2.0. Skin SCC was increased through all
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6 periods (RRs between 6.73 and 9.12) but the high risk of [Hodgkin lymphomaHL](#) was noted
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8 only in the last two periods. In the reverse order ([Supplementary-Table 2SII](#)), *i.e.*, CLL as a
9
10 SPC, the overall RRs were stable at around 1.4, and CLL was increased after skin SCC
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12 through all periods (RRs between 3.05 and 4.55). The results for ALL and HCL were
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14 inconclusive because of small case numbers. However, the risk of ALL was extremely high
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16 (RR over 40) as a SPC after myeloid malignancies in the last two follow-up periods.
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26 DISCUSSION

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28 The novel aspect of the present study was the bi-directional analysis of SPCs, which will
29
30 allow mechanistic insight into [the](#) formation of SPCs. The risk of NHL was increased as a
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32 SPC after ~~each of CLL, ALL and HCL, the three leukemias~~ and the risk for each
33
34 leukemikaemia was increased as a SPC after NHL. The correlations of the bi-directional
35
36 associations were highly significant for CLL and HCL but not for ALL. Invasive and *in situ*
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38 skin cancers, [Hodgkin lymphomaHL](#), melanoma and kidney cancer were most systematically
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40 associated as first cancer and SPC with the three leukemikaemias. The pattern of associated
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42 cancers provides strong epidemiological evidence that immune dysfunction plays a role.
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44
45 Immunosuppressed organ transplant patients have an increased risk of skin SCC and NHL
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47 (20-fold) but also kidney cancer (15-fold), melanoma, leukemikaemia and anogenital cancers
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49 (5-fold) and other cancers (Rama and Grinyo, 2010, Birkeland et al., 1995, Wimmer et al.,
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51 2007). The bidirectional spectrum of cancer risk seen in the present analysis is reminiscent of
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53 immunosuppressed patients. This is in contrast to the conclusions ~~in-of~~ a recent review on
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55 CLL, ~~which stating-stated~~ that ‘...malignancies observed do not mirror those in patients with
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3 other immunodeficiency diseases' (Kipps et al., 2017). For CLL, very high reciprocal risks of
4 Merkel cell cancer were noted, as has been previously reported as SPC after CLL (Tadmor et
5 al., 2011, Tadmor et al., 2012). We also ~~showed~~ found novel reciprocal associations of CLL
6 with Kaposi sarcoma, which was not significant in a previous study (Morton et al., 2010). As
7 both Kaposi sarcoma and Merkel cell carcinoma are virally induced and associated with
8 immunodeficiency conditions, including autoimmune diseases, the strong associations of
9 these cancers with CLL provide further evidence on underlying immunological mechanisms
10 (Hemminki et al., 2012, Zur Hausen, 2009).
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24 The strengths of this study were the nationwide coverage of cancers from a cancer registry
25 where ~~practically-virtually~~ all cancers have been histologically verified. The obligation to
26 report cancers to the cancer registry has included SPCs, and international pooling studies
27 have shown that the Swedish rates of SPCs are among the highest of all cancer registries
28 (Brennan et al., 2005). In agreement, ~~in~~ the present study found the proportion of SPCs after
29 CLL ~~was to be~~ 15.1%, higher than 9.1% in the US study based on the statistics in the
30 Surveillance, Epidemiology, and End Results (SEER) database (Morton et al., 2010).
31 Similarly, the present proportion of SPCs after HCL of 18.2% was higher than that of 11.5%
32 reported in the SEER database (Hisada et al., 2007). ~~For ALL~~ The present proportion for
33 ALL was lowest (7.0%) among the three leukemias, which most likely indicates that
34 these proportions are related to survival in the particular cancers. Accordingly, the median
35 follow-up times decreased from HCL (8 years) to CLL (4 years) and ALL (3 years). A
36 limitation of the study was that we did not have the opportunity to incorporate information on
37 treatment.
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3 Previous studies have not considered myeloid neoplasia as SPC after CLL or other
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5 leukemias. The present results showed that myeloid neoplasia were bi-directionally
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7 associated with CLL and ALL. The risk of ALL was very high (15.35) as a SPC, ~~which and~~
8
9 ~~the high risk~~ was observed in the period 1986 to 2015. The related myeloid neoplasia
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11 included all main types of this disease and ALL diagnosis followed after a median of only 25
12
13 months, suggesting generalized bone marrow dysfunction as a possible mechanism.
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15 However, this was not reflected in a general immune dysfunction since ALL risk after skin
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17 cancer was not increased. Risk of ALL was increased bi-directionally with NHL and ~~Hodgkin~~
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19 ~~lymphoma~~HL. ~~Risks~~ ~~The risks~~ of many cancers were increased after ALL, ~~for to~~ which
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21 chemotherapy may have contributed. As an example, ALL risk was increased after testicular
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23 cancer, for which the normal treatment includes radiotherapy and a combination of ~~DNA~~
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25 ~~DNA~~-damaging drugs (Hanna and Einhorn, 2014). In a clinical trial ~~on of~~ adult ALL patients,
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27 40% of 23 SPCs were myeloid neoplasia and the remaining cases were equally divided
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29 between skin and internal tumours and lymphoma (Tavernier et al., 2007).
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38 Richter syndrome is estimated to account for 2 to 5% of CLL patients whose disease ~~is~~
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40 ~~transformed~~ ~~transforms~~ to NHL or ~~Hodgkin lymphoma~~HL, thus some of the observed risks
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42 may be contributed by this mechanism (Kipps et al., 2017). However, this mechanism is
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44 unlikely to operate in the reverse order and the risk of CLL was almost equally high (2.96) as
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46 ~~a~~ SPC after NHL as was the risk of NHL after CLL (3.11).
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51 Factors influencing malignant transformation of CLL include genetic alterations, aberrant
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53 immune ~~signalingsignalling~~ and growth stimulation by the cellular environment (Kipps et al.,
54
55 2017). Immune ~~signalingsignalling~~ is thought to be triggered by surface immunoglobulin
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57 acting as an autoantigen and leading to a constitutively active B-cell receptor (Kipps et al.,
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2017). The steps leading to clinical hypogammaglobulinemia remain unclear, but may involve systemic increases of IL-interleukin 10 levels with ensuing immunosuppression. CLL cells express high levels of the programmed cell death ligands PD-L1 and PD-L2 (also termed CD274 and PDCD1LG2~~programmed cell death ligands~~), which suppress T-cell effector functions leading to clonal expansion of malignant cells (Kipps et al., 2017).

Tumours can interfere with T-cell orchestrated immune function, which mirrors the impact of iatrogenic immune suppression, resulting in the immunological escape of dormant tumours (which were in immunological equilibrium); and, finally, a diagnosis of an SPC (Friman et al., 2016).

In conclusion, we have provided a comprehensive bi-directional analysis of cancer risks associated with CLL, ALL and HCL. For CLL, the bi-directional risks with NHL, skin SCC, Merkel cell carcinoma and Kaposi sarcoma suggest that not only immune dysfunction in CLL predisposes to multiple SPCs but ~~cancer-cancer~~-related immune dysfunction is able to trigger formation of CLL as a SPC. For ALL, treatment may be an important contributor to the risks of multiple SPCs. ALL risk was increased as a SPC after myeloid neoplasms and lymphoma, which may indicate bone marrow dysfunction. For the rare HCL, the results were in-line with known immune dysfunction. As a clinical take-home message, the study quantified risks for SPC, guiding treatment decisions and prognostic assessment. Benefit-risk ratios of therapies need to be constantly evaluated, which may suggest, ~~as in Hodgkin lymphoma~~, less cytotoxic treatment options or reduction of treatment intensity in certain individuals, as in HL.

Research needs to be intensified on the management of patients on targeted agents, including inhibitors of BRAF, BCL2, BTK, and PI3K, many of which influence the function of the immune system. In a broader context, target and off-target effects of immunotherapy reagents, such as anti-PD1, anti-PDL1, and anti-CTLA4, are a continued challenge.

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AUTHOR CONTRIBUTIONS

KH, GZ, AS, SC designed the study. JS, KS acquired the data. GZ, SC, KH, AS, AH performed the statistical analysis and interpretation. KH, AF, RSH, GZ, SC, AS, AH, KS, JS wrote the manuscript. All authors approved the final text.

CONFLICTS OF INTEREST

A.H. is a shareholder in Targovax ASA. A.H. is an employee and shareholder in TILT Biotherapeutics Ltd. ~~Other~~ All other authors declared no conflict of interest.

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Table 1. Distribution of patients with leukaemia

Leukaemia as first primary cancer				
Type Leukaemia	N	Median age at diagnosis (range); median (years)	Follow-up time (range) to second primary SPC (years); median (range)	No. of SPC, n (%) ^a
CLL	18,407	71 (63 - 79)	4 (1 - 8)	2773 (15.1)
ALL	2,474	63 (46 - 74)	3 (0 - 8.5)	168 (7.0)
HCL	823	62 (51 - 71)	8 (3 - 12)	150 (18.2)
Leukaemia as second primary cancer, after around 1.63 million first primary cancers ^a				
Leukaemia Type	N	Age at diagnosis (years); median (range); Median age at diagnosis (years)	Follow-up time to SPC (years); median (range); Follow-up time from first primary (years)	
CLL	2010	76 (70 - 82)	5 (1 - 12)	
ALL	179	72 (63 - 78)	5 (2 - 11)	
HCL	97	72 (66 - 79)	5 (2 - 10)	

^a, leukemia is not included including leukaemia

ALL: acute lymphoblastic leukaemia; CLL: chronic lymphocytic leukaemia; HCL: hairy cell leukaemia; SPC: second primary cancer. CLL, chronic lymphoblastic leukemia, ALL, acute lymphoblastic leukemia, HCL, Hairy-cell leukemia, SPC, second primary cancer

Table 2-II. Risk of cancer after diagnosis of CLL and that of CLL after diagnosis of cancer

Cancer site	Risk of cancer after CLL				Risk of CLL after cancer			
	N	RR	Lower	Upper	N	RR	Lower	Upper
UAT	60	<u>2.02</u>	1.57	2.60	42	1.03	0.76	1.39
EsophagusOesophagus	12	0.90	0.51	1.59	7	1.56	0.74	3.26
Stomach	82	<u>1.50</u>	1.21	1.86	38	1.01	0.74	1.39
Small intestine	11	1.78	0.99	3.22	5	0.93	0.39	2.23
Colorectum	247	<u>1.36</u>	1.20	1.54	215	1.16	1.02	1.33
Liver	53	1.29	0.98	1.68	15	1.59	0.96	2.63
Pancreas	45	1.11	0.83	1.49	2	0.22	0.06	0.89
Nose	5	2.41	1.00	5.80	2	0.72	0.18	2.89
Lung	246	<u>2.38</u>	2.10	2.70	48	1.33	1.00	1.76
Breast	115	0.79	0.66	0.95	239	0.81	0.72	0.93
Cervix	9	1.26	0.66	2.42	21	0.56	0.36	0.86
Endometrium	32	1.14	0.81	1.61	70	0.83	0.66	1.05
Ovary	20	1.08	0.70	1.68	32	0.86	0.61	1.22
Prostate	403	<u>1.20</u>	1.09	1.33	465	<u>1.57</u>	1.43	1.73
Kidney	74	<u>2.06</u>	1.64	2.59	56	1.48	1.14	1.93
Bladder	134	<u>1.84</u>	1.55	2.18	126	<u>1.47</u>	1.24	1.76
Melanoma	127	<u>3.22</u>	2.71	3.83	97	<u>1.47</u>	1.20	1.8

SCC, invasive	639	<u>7.63</u>	7.06	8.25	183	<u>3.02</u>	2.61	3.50
Merkel	11	<u>14.36</u>	7.90	26.09	3	<u>7.39</u>	2.38	22.92
Kaposi	5	<u>6.76</u>	2.80	16.29	4	<u>5.26</u>	1.98	14.02
Skin SCC, <i>in situ</i>	235	<u>24.58</u>	21.58	28.00	231	<u>2.60</u>	2.28	2.96
Nervous System	66	<u>2.54</u>	2.00	3.24	47	1.24	0.93	1.65
Thyroid	11	1.58	0.88	2.86	31	<u>1.85</u>	1.30	2.63
Endocrine	25	<u>1.57</u>	1.06	2.32	53	<u>1.32</u>	1.01	1.73
Connective tissue	17	<u>2.32</u>	1.44	3.74	18	<u>1.87</u>	1.18	2.97
NHL	130	<u>3.11</u>	2.62	3.7	108	<u>2.96</u>	2.45	3.58
Hodgkin lymphoma	26	<u>7.16</u>	4.87	10.53	11	<u>1.99</u>	1.10	3.59
Myeloma	26	1.26	0.86	1.85	13	0.91	0.53	1.56
Myeloid malignancies	53	<u>2.12</u>	1.62	2.78	36	<u>2.32</u>	1.68	3.22
CUPUPC	91	<u>1.88</u>	1.53	2.31	6	<u>0.41</u>	0.19	0.92
All cancers ^a	2773	<u>1.96</u>	1.89	2.04	2010	<u>1.30</u>	1.24	1.36

N, frequency; RR, relative risk; CLL, chronic lymphoblastic leukemia, UAT, upper aerodigestive tract; SCC, squamous cell carcinoma; NHL, non-Hodgkin lymphoma; CUP, cancer of unknown primary;

Bold, italicized and underlined indicate statistical significance at 5%, 1% and 0.1% level respectively

^a, Leukemia has been excluded from "All cancers".

CLL: chronic lymphocytic leukaemia; N: frequency; NHL: non-Hodgkin lymphoma; RR: relative risk; SCC: squamous cell carcinoma; UAT: upper aerodigestive tract; UPC: unknown primary cancer.

Table 3-III. Risk of cancer after diagnosis of ALL and that of ALL after diagnosis of cancer

Cancer site	Risk of cancer after ALL				Risk of ALL after cancer			
	N	RR	Lower	Upper	N	RR	Lower	Upper
Colorectum	17	1.6	1.00	2.58	23	1.64	1.08	2.47
Lung	20	<u>3.45</u>	2.23	5.35	4	1.34	0.50	3.59
Breast	11	1.07	0.59	1.94	38	1.64	1.19	2.26
Prostate	21	1.57	1.02	2.4	28	1.43	0.98	2.09
Testis	0	-	-	-	3	3.75	1.21	11.66
Kidney	12	<u>5.02</u>	2.85	8.84	3	0.99	0.32	3.06
Bladder	10	2.43	1.31	4.52	10	1.61	0.86	3.00
SCC, invasive	18	<u>5.20</u>	3.27	8.25	6	1.48	0.66	3.3
Skin SCC, <i>in situ</i>	3	<u>7.81</u>	2.52	24.22	6	1.05	0.47	2.35
Nervous System	5	2.58	1.07	6.2	1	0.31	0.04	2.19
Endocrine	6	<u>5.61</u>	2.52	12.49	4	1.35	0.51	3.61
Connective tissue	2	4.14	1.04	16.56	1	1.26	0.18	8.95
NHL	11	<u>4.92</u>	2.72	8.88	18	<u>6.78</u>	4.26	10.8
Hodgkin lymphoma	5	<u>14.65</u>	6.09	35.21	5	<u>8.14</u>	3.38	19.57
Myeloid malignancies	5	3.53	1.47	8.47	20	<u>15.35</u>	9.87	23.85
CUPUPC	6	2.34	1.05	5.22	1	0.78	0.11	5.57
All ^a	168	<u>2.13</u>	1.83	2.48	179	<u>1.51</u>	1.29	1.76

N, frequency; RR, relative risk; ALL, acute lymphoblastic leukemia, UAT, upper aerodigestive tract; SCC, squamous cell carcinoma; NHL, non-Hodgkin lymphoma; CUP, cancer of unknown primary;

Bold, italicized and underlined indicate statistical significance at 5%, 1% and 0.1% level respectively

^a, Leukemia has been excluded from "All cancers".

ALL: acute lymphoblastic leukaemia; N: frequency; NHL: non-Hodgkin lymphoma; RR: relative risk; SCC: squamous cell carcinoma; UPC: unknown primary cancer.

Table 4-IV. Risk of cancer after diagnosis of HCL and that of HCL after diagnosis of cancer

Cancer site	Risk of cancer after HCL				Risk of HCL after cancer			
	N	RR	Lower	Upper	N	RR	Lower	Upper
Colorectum	18	1.72	1.09	2.74	10	1.61	0.86	3.01
Nose	1	9.14	1.29	64.92	0	-	-	-
Prostate	39	1.15	0.84	1.57	31	<u>2.26</u>	1.56	3.26
Kidney	7	<u>3.60</u>	1.72	7.55	3	2.10	0.68	6.53
Melanoma	9	2.59	1.34	4.97	9	2.53	1.31	4.89
SCC, invasive	18	<u>3.62</u>	2.28	5.75	3	1.5	0.48	4.66
Skin SCC, <i>in situ</i>	3	<u>4.17</u>	1.35	12.95	6	1.88	0.84	4.2
NHL	13	<u>4.70</u>	2.73	8.10	10	<u>5.99</u>	3.21	11.2
CUPUPC	6	2.34	1.05	5.21	0	-	-	-
All ^a	150	<u>1.65</u>	1.40	1.93	97	<u>1.62</u>	1.31	2.01

N, frequency; RR, relative risk; HCL, hairy cell leukemia, UAT, upper aerodigestive tract; SCC, squamous cell carcinoma; NHL, non-Hodgkin lymphoma; CUP, cancer of unknown primary;

Bold, italicized and underlined indicate statistical significance at 5%, 1% and 0.1% level respectively

a, Leukemia has been excluded from "All cancers".

HCL: hairy cell leukaemia; N: frequency; NHL: non-Hodgkin lymphoma; RR: relative risk; SCC: squamous cell carcinoma; UPC: unknown primary cancer