

## Solid tumors after chronic lymphocytic leukemia

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Prior reports indicate that patients with chronic lymphocytic leukemia (CLL) may be at increased risk of subsequent neoplasms. This study quantified the risk of second cancers among 16 367 patients with CLL in the population-based Surveillance, Epidemiology and End Results Program. Overall, the observed/expected ratio (O/E) was 1.20 (95% confidence interval [CI], 1.15-1.26). Second cancer risks for

patients who received chemotherapy only as the first course of treatment (O/E = 1.21) were similar to risks for those who received no treatment initially (O/E = 1.19). Significant excesses were found for Kaposi sarcoma (O/E = 5.09), malignant melanoma (O/E = 3.18), and cancers of the larynx (O/E = 1.72) and the lung (O/E = 1.66). Increased risks were also found for brain cancer among men (O/E =

1.91) and for cancers of the stomach (O/E = 1.76) and bladder (O/E = 1.52) among women. Additional investigations of cancers after CLL are needed to explore the role of immunologic impairment and/or other etiologic influences. (Blood. 2001;98:1979-1981)

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### Introduction

Chronic lymphocytic leukemia (CLL) is a malignancy of mature B lymphocytes of unknown etiology.<sup>1</sup> Prior studies have reported that site-specific excesses of second cancer may exist among patients with CLL.<sup>2,3</sup> Patterns of subsequent neoplasms in these individuals may provide insight into etiologic factors associated with both malignancies. In the present study, we describe the risk of second cancers among a large number of patients with CLL reported to the population-based cancer registries that comprise the Surveillance, Epidemiology and End Results (SEER) Program.

cytotoxic agents made it more likely that patients with CLL may have received them.<sup>5,6</sup> Diagnoses of secondary lymphopietic malignancies that may represent transformation of CLL<sup>7</sup> were excluded from the analyses.

### Results and discussion

Overall, 16 367 patients with CLL, including 5-year survivors (7024) and 10-year survivors (2479), were evaluated for second cancer risk, accumulating a total of 84 667 person-years of follow-up (Table 1). The mean age at diagnosis was 69.7 years, and the average follow-up was 5.2 years. Second cancers occurred in 1820 patients (O/E = 1.20; 95% CI, 1.15-1.26). Risks of subsequent neoplasms in the < 1 year, 1-4 year, 5-9 year, and  $\geq$  10 year intervals following CLL diagnosis were 1.25, 1.25, 1.14, and 1.16, respectively (P for trend = .14). Second cancer risks for patients who received chemotherapy only as the first course of treatment (O/E = 1.21) were similar to risks for those who received no treatment initially (O/E = 1.19). No significant difference in risk of all solid tumors combined was found for patients diagnosed with CLL between 1973-1989 (O/E = 1.19) and 1990-1996 (O/E = 1.29).

Significantly increased risks were observed for Kaposi sarcoma (KS) (O/E = 5.09), malignant melanoma (O/E = 3.18), and cancers of the larynx (O/E = 1.72) and the lung (O/E = 1.66). Men with CLL, but not women, experienced significantly increased risks of brain cancer (O/E = 1.91). In addition, significant excesses of cancers of the stomach (O/E = 1.76) and bladder (O/E = 1.52) were restricted to women.

Prior studies of patients with CLL have documented increased risks of various forms of skin cancer, including malignant melanoma,<sup>2,8-11</sup> probably resulting from the immune perturbations.<sup>12</sup> Risk of malignant melanoma is elevated in patients with therapeutic immune suppression associated with organ transplantation, and

### Study design

#### Patients and methods

Included in the present analysis are 16 367 patients with CLL registered in the SEER Program between 1973 and 1996. Data describing 9456 of these patients, diagnosed through 1988, were reported in a previous publication.<sup>3</sup> Follow-up for this subgroup is now updated from 1989 to 1996. Person-years of observation began from 2 months after the date of CLL diagnosis to the date of last follow-up, death, diagnosis of a second cancer, or the end of the study (December 31, 1996), whichever occurred first. Expected numbers of cancers were estimated from the multiplication of the SEER incidence rates specific for 5-year age, sex, race, and 5-year calendar year intervals by the accumulated person-years at risk. Risk of second cancers was estimated as the ratio of observed to expected number of cases (O/E) with 95% confidence intervals (CI), assuming a Poisson distribution. Cancer sites were classified according to the World Health Organization's *International Classification of Diseases for Oncology, Second Edition*.<sup>4</sup> For our analysis, we compared the 2 largest treatment groups, ie, those who received chemotherapy only as initial therapy and those who did not receive treatment. Neither information on subsequent courses of therapy nor information regarding the specific chemotherapeutic agents with which patients were initially treated was available in the SEER Program. As a surrogate, the study period was divided into 1973-1989 and 1990-1996; the former represents an era before the widespread use of nucleoside analogs for CLL, whereas in the latter period the greater availability of those

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**Table 1. Observed numbers and observed/expected ratios of solid tumors among 16 367 of the 2-month survivors of chronic lymphocytic leukemia reported to the SEER Program between 1973 and 1996**

	All patients (n = 16 367)		Men (n = 9517)		Women (n = 6850)	
	Obs	O/E	Obs	O/E	Obs	O/E
All solid tumors*	1820	1.20	1210	1.22†	610	1.18†
Specific sites						
All buccal	42	1.02	35	1.13	7	0.71
Esophagus	14	0.80	14	1.02	0	[E] = 3.8
Stomach	47	1.10	24	0.81	23‡	1.76†
Colon	206	1.13	110	1.01	96	1.23
Rectum	72	1.09	40	0.93	32	1.38
Liver, bile duct, gall bladder	19	0.73	11	0.68	8	0.80
Pancreas	45	0.96	32	1.19	13	0.65
Larynx	31	1.72†	27	1.68†	4	1.98
Lung	421	1.66†	318	1.68†	103	1.62†
Female breast	141	0.97	—	—	141	0.97
Uterine cervix	4	0.56	—	—	4	0.56
Uterine corpus	23	0.68	—	—	23	0.69
Ovary	18	0.92	—	—	18	0.92
Prostate	338	1.01	338	1.01	—	—
Testis	2	2.44	2	2.44	—	—
Bladder	91	0.98	64	0.85	27	1.52†
Kidney, renal pelvis, ureter	42	1.16	29	1.12	13	1.24
Melanoma	90	3.18†	62	3.14†	28	3.28†
Eye	5	2.26	3	2.10	2	2.56
Brain, central nervous system	22§	1.49	18	1.91†	4	0.76
Thyroid	4	0.60	3	0.98	1	0.28
Kaposi sarcoma	9	5.09†	3	2.06	6	19.13†
Other¶	134	1.44†	77	1.45†	57	1.44†

Person-years of observation were 84 667 for all patients, 46 997 for men, and 37 670 for women.

SEER indicates Surveillance, Epidemiology, and End Results; Obs, observed; O/E, observed/expected; [E], expected number of cases.

\*Excludes nonmelanoma skin cancers and lymphohematopoietic malignancies.

† $P < .05$ .

‡Includes cancers of antrum (4), cardia (4), greater and lesser curvatures (2), pylorus (2), fundus (1), overlapping lesion (3), and not otherwise specified (7). Histologic types include adenocarcinoma (21), signet cell carcinoma (1), and carcinoid tumor (1).

§Includes glioblastoma (16), meningioma (3), astrocytoma (2), and glioma (1).

||Absolute excesses of Kaposi sarcoma per 100 000 patients with CLL per year were 15 and 3 for women and men respectively.

¶Includes 80 cancers of ill-defined or unknown primary site.

this risk is further enhanced by increases in sunlight exposure.<sup>13</sup> However, the apparent excess of skin cancers in CLL may be partly due to the increased medical surveillance of these patients.

Clinical features of patients with CLL with subsequent KS (6 women, 3 men) are presented in Table 2. To our knowledge, we are the first to report an increased risk of KS among patients with CLL. Two-fold to 7-fold increased risks of KS have been observed among patients with all types of lymphoid malignancies combined (Hodgkin disease, non-Hodgkin lymphoma, and all leukemia),<sup>14,15</sup> but risk estimates for CLL were not provided separately. In one

registry-based study that reported a 3-fold risk of sarcoma after CLL,<sup>16</sup> KS-specific risks were not estimated.

The increased risk of brain cancer among men with CLL is consistent with our earlier study,<sup>3</sup> although the basis for this association remains unclear. The majority of brain cancers were glioblastomas that, in contrast to lymphomas of the central nervous system, have not been linked to compromised immune function. The excess risk of bladder cancer that we observed among women may be related to chemotherapy, particularly cyclophosphamide,<sup>17</sup> although we did not have access to treatment information beyond

**Table 2. Characteristics of 9 patients with chronic lymphocytic leukemia who subsequently developed Kaposi sarcoma reported to the SEER Program, 1973-1996**

Case	Age*	Sex	Race	CLL (mo/y)	KS (mo/y)	Latency between CLL and KS (mo)	KS site	Survival after KS (mo)	Cause of death
1	78	M	White	2/1976	3/1983	85	R lower limb	1	CLL
2	80	M	White	9/1980	8/1981	11	Skin, NOS	8	Myocardial infarction
3	67	M	Black	9/1983	12/1989	75	Skin, NOS	28	CLL
4	73	F	White	2/1978	9/1982	55	L upper limb	5	CLL
5	66	F	White	6/1980	12/1988	102	B lower limbs	17	CLL
6	66	F	White	6/1986	10/1994	100	Skin, NOS	26	(Alive)
7	91	F	White	11/1988	8/1989	9	Skin, NOS	2	Myocardial infarction
8	70	F	White	12/1988	11/1990	23	Skin, NOS	27	CLL
9	85	F	White	3/1995	5/1995	2	B lower limb	5	KS

CLL indicates chronic lymphocytic leukemia; KS, Kaposi sarcoma; SEER, Surveillance, Epidemiology, and End Results; R, right; L, left; B, bilateral; NOS, not otherwise specified.

\*Age at CLL diagnosis.

the initial regimen. The increased risk of stomach cancer among women may be explained by an immune-related predisposition to *Helicobacter pylori* infection, an important risk factor for gastric carcinoma.<sup>18</sup> However, these associations were limited to one sex, and they may have resulted from multiple statistical comparisons. Although increased medical surveillance may be involved also, the excess risks extended throughout the period of observation. The elevated risk of lung and laryngeal cancers in both sexes suggests the role of cigarette smoking, which may contribute to the increase of bladder<sup>19</sup> and gastric cancers.<sup>20</sup> Data on tobacco smoking were not available in our study, but it seems plausible that the carcinogenic effects of smoking are heightened by radiotherapy, chemotherapy, and/or immune deficiency.<sup>21,22</sup>

Our data indicate that the overall risk of developing a second cancer is modestly but significantly elevated, independent of initial treatment, in persons with CLL compared with those in the general population. In terms of absolute risk, an excess of 366 solid tumors, including approximately 9 KSS, might be observed among 100 000 patients with CLL during each year of follow-up. Although the role of shared etiologic factors remains unclear, the pattern of excess

cancers in CLL survivors suggests an influence of immunodeficiency associated with CLL.<sup>23</sup> Given the prolonged survival of patients with CLL, it is important for physicians to be alert to the occurrence of second cancers, particularly when new symptoms or physical findings arise. It would also seem prudent to urge patients with CLL to avoid exposures to carcinogens such as tobacco smoke and excessive sunlight. Further studies of second cancers in CLL should address the role of shared risk factors, immunologic impairment, and/or other determinants. Where feasible, molecular probes should be included to elucidate the mechanisms underlying the constellation of tumors associated with CLL.

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