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LETTER TO THE EDITOR

Second primary malignancy in Burkitt's lymphoma

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To the Editor,

Burkitt's lymphoma is an uncommon form of non-Hodgkin's lymphoma. In the US, the incidence of Burkitt's lymphoma during 2001–2009 period was 0.4 cases per 100 000 population [1]. Burkitt's lymphoma constitutes 0.4% of all the lymphoid malignancies and accounting for between 40% and 50% of childhood non-Hodgkin's lymphomas (NHLs) in non-endemic areas [2,3]. The sporadic form in adults accounts for 1–2% of all adult lymphomas in western Europe and the US [4].

Burkitt's lymphoma is treated with of high-intensity, short-duration combination chemotherapy. Treatment is effective with approximately 90% of pediatric patients and up to 50–60% of adults with long-term disease-free survival [5–8]. The rate of second primary malignancies (SPM) in Burkitt's lymphoma patients is unknown. In this study, we analyzed the risk of SPMs in adult patients with Burkitt's lymphoma from National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database.

The SEER 13 is a population based cancer database sponsored by National Cancer Institute. SEER 13 represents 13.8% of the US population and covers the following geographical areas – San Francisco-Oakland SMSA, Connecticut, Detroit (Metropolitan), Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, Atlanta (Metropolitan), San Jose-Monterey, Los Angeles, Alaska Natives, and Rural Georgia. The SEER program collects comprehensive cancer data from hospitals and cancer treatment centers and maintains high quality data from defined geographical areas. It is a mature database with 98% case completeness [9].

We selected Burkitt's lymphoma patients diagnosed during January 1992 to December 2011 from SEER 13 Regs Research Data, Nov 2013 Sub (1992–2011) database [1]. We excluded cases diagnosed at autopsy and those who were lost to follow-up. Patients were followed up from the time of diagnosis of Burkitt's lymphoma to the date of last known vital status, death or the last point of data collection. SPM was defined as metachronous malignancy developing six months or more after an index Burkitt's lymphoma based on Warren and Gates criteria [10] as modified by the NCI [11].

We used the multiple primary standardized incidence ratio (MP-SIR) session of the SEER stat software version 8.1.5 March 26, 2014 for statistical analysis. We calculated the SIR, absolute excess risk (AER) and confidence interval for SPM in patients with Burkitt's lymphoma by age (0–59 years vs. 60 + years) and latency (6–23 months vs. 24 + months). The SIR is also known as the relative risk. It is a measure of the strength of association between two cancers. It is calculated by dividing the observed incidence of SPM by the expected incidence of SPM (O/E ratio) in the general population [12]. AER is an absolute measure of the clinical burden of additional cancer occurrence in a given population. It measures the actual number of excess events normalized to the numbers of person years observed [AER = (O/E)/PY].

A total of 1757 patients with a diagnosis of primary Burkitt's lymphoma were reported in the

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SEER 13 registry during January 1992 to December 2011. The median age at diagnosis of Burkitt's lymphoma was 59 years (13–95 years) and median follow-up duration of patients was 16 months (0–147 months).

A total of 80 patients (4.55%) developed 86 second primary malignancies, with an observed/expected (O/E) ratio of 2.02 (95% confidence interval = 1.62–2.5, $p < 0.05$), and an AER 45.82/10 000 populations. Median age at the time of diagnosis of SPM was 63 years (13–95 years). There was significantly higher risk of anal carcinoma, thyroid malignancies, head and neck tumor, pancreatico-hepatobiliary malignancies and Kaposi sarcoma compared to the general population (Table I). Among hematological malignancies, non-Hodgkin's lymphoma and acute myeloid leukemia were significantly increased with O/E ratio of 5.11 and 22.59, respectively.

Median latency for development of all SPM in Burkitt's lymphoma patient was 58.5 months (6–194 months). There was significantly higher risk of Kaposi sarcoma (N = 4, O/E = 125.59, p-value = < 0.05, AER = 19.33) and thyroid cancer (N = 2, O/E = 12.57, p-value = 0.02, AER = 8.97) within the first two years of latency. Excess risk was observed for anal carcinoma (N = 3, O/E = 27.20, p-value = < 0.05, AER = 3.89), breast cancer (N = 7, O/E = 2.84, p-value = 0.03, AER = 6.11), Hodgkin's lymphoma (N = 2, O/E = 8.32, p-value = 0.05, AER = 2.37), non-Hodgkin's lymphoma (N = 8, O/E = 5.22, p-value = < 0.05, AER = 8.71), acute myeloid leukemia (N = 7, O/E = 25.06, p-value = < 0.05, AER = 9.05), Kaposi Sarcoma (N = 3, O/E = 36.82, p-value = < 0.05, AER = 3.93) and pancreatico-hepatobiliary carcinoma (N = 6, O/E = 3.5, p-value = 0.01, AER = 5.77) after two years of latency.

With improvement in diagnostics and therapy, the number of cancer survivors is increasing [13]. It is expected that by 2022, approximately 18 million cancer survivors will be present in the US [14]. Factors related to cancer, pre-existing conditions and therapeutic interventions lead to increased risk of second primary malignancies in cancer survivors [15]. Improved understanding of long-term complications of cancer and its treatment is necessary to guide post-treatment surveillance of cancer patients. The 2005 IOM report recommends use of evidence-based clinical practice guidelines to identify and manage long-term effects of cancer and its treatment. Unfortunately, due to lack of high-quality evidence, there are no standardized practice guidelines for management of adult cancer survivors.

In this population-based study, we report significantly higher risk of SPMs in Burkitt's lymphoma patients. This is the first study to document the risk of SPMs in Burkitt's lymphoma patients. The risk of specific SPM depends on latency.

Strengths of our study include large sample size, high level of quality control of the SEER program,

Table I. Second primary malignancies in patients with Burkitt's lymphoma.

	Total population; person's risk = 175, person years at risk = 9481.70						
	Observed	Expected	O/E	p-Value	CI lower	CI upper	Absolute excess risk
All sites	86	42.55	2.02	< 0.05	1.62	2.5	45.82
All sites excluding non-melanoma skin	86	42.35	2.03	< 0.05	1.62	2.51	46.03
All solid tumors	64	37.49	1.71	< 0.05	1.31	2.18	27.96
Skin excluding basal and squamous	5	2.25	2.22	0.14	0.72	5.19	2.9
Head and neck	5	1.54	3.26	0.04	1.06	7.6	3.65
Pancreatico-hepatobiliary	6	2.17	2.76	0.04	1.01	6.01	4.03
Esophagus	2	0.5	4.01	0.18	0.49	14.49	1.58
Colorectum	7	4.17	1.68	0.24	0.67	3.46	2.98
Anus, anal canal and anorectum	3	0.14	21.18	< 0.05	4.37	61.9	3.01
Lung and bronchus	3	5.28	0.57	0.44	0.12	1.66	−2.41
Breast	7	3.31	2.12	0.1	0.85	4.36	3.89
Corpus and uterus, NOS	1	0.66	1.52	0.96	0.04	8.45	0.36
Male genital system	7	9.93	0.7	0.44	0.28	1.45	−3.09
Urinary system	6	3.74	1.6	0.34	0.59	3.49	2.38
Brain and other nervous system	1	0.64	1.57	0.98	0.04	8.73	0.38
Thyroid	4	0.76	5.27	0.02	1.44	13.5	3.42
Hodgkin lymphoma	2	0.3	6.68	0.07	0.81	24.12	1.79
Non-Hodgkin lymphoma	10	1.96	5.11	< 0.05	2.45	9.39	8.48
Acute lymphocytic leukemia	1	0.15	6.77	0.26	0.17	37.75	0.9
Chronic lymphocytic leukemia	0	0.47	0		0	7.79	−0.5
Acute myeloid leukemia	8	0.35	22.59	< 0.05	9.75	44.52	8.06
Chronic myeloid leukemia	1	0.17	6.05	0.3	0.15	33.68	0.88
Kaposi sarcoma	7	0.11	61.77	< 0.05	24.84	127.27	7.26

98% case completeness. Limitations of our study are specific to population-based registry. The SEER program does not collect data on co-morbidities including HIV status, risk factors and chemotherapy used for the treatment of cancer. Similarly, a small number of recurrences in certain anatomic locations may be misclassified as SPM. Migration of patients out of a SEER geographic registry may lead to underestimation of SPM risk.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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