ACTA ONCOLOGICA, 2018
VOL. 57, NO. 2, 239–243
https://doi.org/10.1080/0284186X.2017.1390250

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

The risk of second primary malignancy in patients with stage Ia non-small cell lung cancer: a U.S. population-based study

Amit Khanal[a], Bilal Haider Lashari[b], Sreechandralekha Kruthiventi[c], Lubina Arjyal[d], Amir Bista[e], Priya Rimal[f] and Dipesh Uprety[g]

[a]Department of Hematology and Oncology, University of Illinois at Chicago, Chicago, IL, USA; [b]Abington Memorial Hospital, Abington, PA, USA; [c]P.S.I. Medical College, Chinoutpalli, India; [d]Gundersen Health System, La Crosse, WI, USA; [e]Gundersen Health System, La Crosse, WI, USA; [f]Nepal Medical College Teaching Hospital, Kathmandu, Nepal; [g]Gundersen Health System, La Crosse, WI, USA

ABSTRACT

Background: Lung cancer is one of the most common cancers worldwide. Patients with early stage lung cancer have improved long-term survival. With the introduction of low-dose CT scan, more patients are going to be diagnosed at an early stage. However, there is limited data on the risk of second primary malignancies (SPMs) in these subsets of patients in the United States.

Methods: We utilized SEER-13 (Surveillance, Epidemiology and End Results) registry to obtain Multiple Primary- Standardized Incidence Ratio and an Absolute Excess Risk between January 2004 and December 2010 for patients with Stage Ia non-small cell lung cancer.

Results: The database comprised of 12,246 patients. A total of 1431 (11.68%) patients developed 1563 SPMs with an observed to expected (O/E) ratio of 2.07 (95% CI = 1.92–2.23, $p < .001$) in patients with adenocarcinoma and 2.05 (95% CI = 1.92–2.19, $p < .001$) in squamous cell carcinoma group.

Conclusions: This study showed an excess risk of SPMs in patients with early stage non-small cell lung cancer. We recommend a close follow-up, paying attention to concerning symptoms or examination findings and judicious use of age-appropriate cancer screening.

ARTICLE HISTORY
Received 6 August 2017
Accepted 2 October 2017

Introduction

Lung cancer is an increasing area of concern in global health. Posing a disease incidence of over 1.8 million patients in 2012 and causing 1.6 million deaths worldwide. In the United States alone, lung cancer occurs in about 225,000 patients each year and causes over 160,000 deaths annually [1]. In the UK about 46,000 new cases of lung cancer were diagnosed in 2014, making it the third most common cancer diagnosis [2]. The mean five-year survival rate of lung cancer is about 17%. The survival rate improves to 55% when the cases are detected at early localized stage. However, only 16% of lung cancer cases are diagnosed at an early stage [3].

The risk of second primary malignancy (SPM) in lung cancer survivors is not well reported in the literature. With the introduction of low dose CT scan for screening, its importance is emerging as early diagnosis of lung cancer through screening, increases survival by up to 20% [4].

In this study, we aimed to identify the risk of SPM in patients with early stage non-small cell lung cancer (NSCLC) in the United States utilizing the SEER database and performed literature review to better understand how emerging screening and following tools would change the patterns of disease burden and survival.

Methods

Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute is a population-based database that assembles data related to incidence and survival on cancer patients in the United States. This is one of the largest cancer registries in the world and covers approximately 28% of the US population [5]. SEER 13 registries consist of patients from Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia and the Alaska Native Tumor Registry.

We utilized SEER-13 registry to select adult patients (18 years of age and above) diagnosed with stage Ia non-small cell lung cancer as their first malignancy between January 2004 and December 2010.

Second Primary Malignancy is defined as a metachronous cancer which develops six months after an index NSCLC based on Warren and Gates criteria. Multiple primary standardized incidence ratio (MP-SIR) and an absolute excess risk (AER) for an occurrence of SPM were obtained utilizing SEER stat application. SIR is a ratio of observed to expect incidence ratio (O/E) of SPM and AER is an actual number of excess SPMs in patient with NSCLC per 10,000 person-years at risk. Statistical significance was defined for a p-value $\leq .05$.

CONTACT Dipesh Uprety duprety@gundersenhealth.org Department of Medical Oncology, Gundersen Health System, 1900 South Avenue (mail stop EB2-001), La Crosse, WI 54601, USA

Results

The database identified a cohort of 12,246 patients. Five-thousand two-hundred and eighty patients had adenocarcinoma and 6966 patients had squamous cell carcinoma. A total of 1431 patients had a second primary malignancy. We identified 623 patients with a second primary malignancy in adenocarcinoma survivors (11.8%) and 808 patients with squamous cell carcinoma patients (11.6%). A latency period between the diagnosis of the primary and second primary malignancy was about 34 months in both the groups (Table 1).

Fifty-seven patients in the adenocarcinoma group had a second primary malignancy before the age of 60 years (O/E 3.85; $p < .0001$) while 626 developed it after age 60 years (O/E 1.99; $p < .0001$). Solid tumors made up for the bulk of disease, in both age groups with the respiratory system affected in almost half of all the patients.

In patients with squamous cell cancer, 94 patients aged less than 60 years developed a SPM (O/E 3.90 $p < .00001$) and 786 patients were aged greater than 60 (O/E 1.94 $p < .00001$). Solid tumors comprised of an overwhelming majority of SPM in this group, comprising 93% of disease burden and an excess risk of 178.87. The respiratory system was the most frequently affected in this group as well.

A significant excess risk was observed for varying malignancies in both groups. Patients with adenocarcinoma had statistically significant excess risk for the development of gastrointestinal (ER 6.64 $p = .001$), pancreatic (ER 6.64 $p = .001$), thyroid (ER 5.51 $p = .0001$) and female breast cancer (4.99 $p = .1$). The risk of GI, breast, and pancreatic cancer was significant after 24 months of the index diagnosis, while respiratory, genitourinary, and thyroid malignancy risk was independent of latency.

Patients with squamous cell carcinoma had significant excess risk for the development of urogenital (ER 16.78, $p < .00001$), thyroid (5.4, $p < .00001$), pancreas (5.55, $p < .001$) and GI tract malignancies ($p < .001$). Similar risk trends were observed, where the risk of GI, breast, pancreatic and oral cavity cancers was significantly increased 24 months or more after the index diagnosis. While respiratory, genitourinary, and other malignancies increased marginally in a temporal fashion and largely remained independent. The risk of second primary malignancy in patients with adenocarcinoma and squamous cell carcinoma are summarized in Tables 2 and 3 respectively.

An increased risk of all solid tumors was observed in both sub sets. An excess risk of 185 ($p < .00001$) in adenocarcinoma patients versus 178 ($p < .00001$) in squamous cell patients. This risk was independent of radiation exposure. Patients not exposed to radiation had a higher excess risk when compared to patients exposed to radiation in both the groups.

Table 1. Demographics of the study population.

	Demography			
	Adenocarcinoma		Squamous carcinoma	
	Number/Median	%/Range	Number/Median	%/Range
Total patient with Stage early lung cancer	5280		6966	
Gender				
Male	2347	44.45	2853	40.96
Female	2933	55.55	4113	59.04
Race				
White	4445	84.19	5713	82.01
Black	584	11.06	584	8.38
Other	409	7.75	640	9.19
Total SPM	683		880	
Total patient with SPM	623	11.80	808	11.60
Gender				
Male	308	49.44	384	47.52
Female	315	50.56	424	52.48
Race				
White	533	85.55	674	83.42
Black	47	7.54	67	8.29
Other	43	6.90	67	8.29
Total number of patient with 1 SPM	566	90.85	739	91.46
Gender				
Male	282	49.82	353	47.77
Female	284	50.18	386	52.23
Race				
White	481	84.98	616	83.36
Black	46	8.13	62	8.39
Other	39	6.89	61	8.25
Total number of patient with 2 or more SPM	57	9.15	69	8.54
Gender				
Male	26	45.61	31	44.93
Female	31	54.39	38	55.07
Race				
White	52	91.23	58	84.06
Black	1	1.75	5	7.25
Other	4	7.02	6	8.70
Age for SPM (median)	76.25 years	50.75–92.83 years	72.75 years	39.08–97.08 years
Latency (median)	2.75 years	6 months–8.92 years	2.83 years	6 months–8.58 years
Follow-up (median)	4.67 years	7 months–8.92 years	5 years	6 months–8.92 years

Discussion

1.8 million Patients were diagnosed with lung cancer in 2012. It resulted in 1.6 million deaths worldwide. 225,000 new lung cancer patients are diagnosed in the United States each year and over 160,000 deaths annually are attributed to it, making it the second leading cause of cancer in both sexes and the leading cause of cancer related mortality over recent years [1]. In the United Kingdom, it comprised 46,000 new cases and was the third leading cancer diagnosis [2].

Cigarette smoking is the leading cause of disease followed by other less common risk factors, including radiation exposure, environmental toxins, pulmonary fibrosis, familial history and dietary factors.

The results of the National Lung screening trial showed the efficacy of employing Low dose CT scanning as a screening tool in high-risk individuals [6], and prompted the subsequent incorporation of this entity as the recommended standard of care for high-risk individuals by the United States Preventive Service Task Force [7].

There is split opinion currently regarding the cost-value and economic burden of CT screening. Data suggest that a large number of false-positive results and the potential for over diagnosis may occur leading to increasing follow up scans, nodule resections and surgery [7]. However, in a recent analysis of a hypothetical cohort of 18 million people, the lung cancer screening yielded significant quality adjusted life years gains [8]. In contrast to previous opinion, this makes a case for the economic feasibility of screening.

With the institution of lung cancer screening, the early of diagnosis of lung cancer will become more effective, and the incidence of disease in early stage is expected to rise. A Canadian simulation estimates lung cancer incidence to increase by 7% with stage IA diagnoses increasing by 15% and stage IV decreasing by 7.5% with use of screening [9]. Higher smoking rates and faster population growth in Europe and the US assumes a trend towards increasing Stage I disease diagnosis, comprising 55–85% of the cancers diagnosed with screening in multiple small studies [10].

Table 2. Second primary malignancy in patients with adenocarcinoma.

Adenocarcinoma	*N*	Expected	O/E	Two tail *p*	CI	Excess risk
All sites	683	329.73	2.07	<.001	1.92–2.23	194.22
All sites excluding non-melanoma skin	682	328.05	2.08	<.001	1.93–2.24	194.59
All solid tumors	628	290.5	2.16	<.001	2–2.34	185.55
Pharynx	4	0.93	4.28	.0300	1.17–10.96	1.69
Digestive system	95	66.62	1.43	.0012	1.15–1.74	15.6
Pancreas	23	10.93	2.11	.0019	1.33–3.16	6.64
Respiratory system	316	53.75	5.88	<.001	5.25–6.56	144.18
Nose, nasal cavity and middle ear	3	0.44	6.81	.0205	1.4–19.89	1.41
Larynx	8	2.28	3.51	.0049	1.52–6.92	3.15
Lung and bronchus	303	50.93	5.95	<.001	5.3–6.66	138.58
Trachea	2	0.04	47.77	.0016	5.79–172.56	1.08
Skin excluding basal and squamous	5	14.89	0.34	.0060	0.11–0.78	−5.44
Melanoma of the skin	4	13.21	0.3	.0064	0.08–0.78	−5.07
Female breast	50	40.91	1.22	.1852	0.91–1.61	4.99
Urinary bladder	46	19.49	2.36	<.001	1.73–3.15	14.57
Thyroid	14	3.98	3.52	.0001	1.93–5.91	5.51
All lymphatic and hematopoietic diseases	43	30.59	1.41	.7558	1.02–1.89	6.82
Acute myeloid leukemia	9	2.91	3.09	.0063	1.41–5.87	3.35

Table 3. Risk of second primary malignancy in squamous cell carcinoma.

	Total					
Squamous carcinoma	Observed	Expected	O/E	Two tail *p*	CI	Excess risk
All sites	880	428.9	2.05	<.001	1.92–2.19	181.54
All sites excluding non-melanoma skin	877	426.79	2.05	<.001	1.92–2.2	181.18
All solid tumors	823	378.52	2.17	<.001	2.03–2.33	178.87
Oral cavity and pharynx	21	8.59	2.44	.0005	1.51–3.74	4.99
Tonsil	4	1	4.01	.0380	1.09–10.26	1.21
Digestive system	120	86.62	1.39	.0008	1.15–1.66	13.43
Pancreas	28	14.21	1.97	.0016	1.31–2.85	5.55
Respiratory system	409	69.09	5.92	<.001	5.36–6.52	136.79
Larynx	10	2.85	3.5	.0015	1.68–6.44	2.88
Lung, bronchus, trachea, mediastinum and other respiratory organ	397	65.62	6.05	<.001	5.47–6.67	133.36
Lung and bronchus	396	65.53	6.04	<.001	5.46–6.67	132.99
Skin excluding basal and squamous	9	18.85	0.48	.0193	0.22–0.91	−3.96
Melanoma of the skin	6	16.74	0.36	.0049	0.13–0.78	−4.32
Male genital system	81	62.75	1.29	.0303	1.03–1.6	7.35
Prostate	81	62.12	1.3	.0245	1.04–1.62	7.6
Urinary system	80	38.29	2.09	<.001	1.66–2.6	16.78
Urinary bladder	56	24	2.33	<.001	1.76–3.03	12.88
Kidney and renal pelvis	23	13.19	1.74	.0179	1.1–2.62	3.95
Kidney	21	12.05	1.74	.0242	1.08–2.66	3.6
Endocrine system	21	6	3.5	<.001	2.17–5.35	6.04
Thyroid	19	5.58	3.4	<.001	2.05–5.31	5.4

Currently, however, only 16% of lung cancer is diagnosed at an early stage, conferring a 55% five-year survival as opposed to 17.7% for advanced disease [3]. Localized disease without lymph node involvement is managed surgically, while mediastinal involvement requires ablative radiotherapy and/or adjuvant chemotherapy depending on final staging.

Lung cancer survivors are offered oncologic surveillance primarily to detect recurrence of disease, and second primary lung cancer at early stages to offer definitive treatment and improve survival and quality of life. The incidence of second primary malignancy in lung cancer survivors is not a well-established fact. Our results identified around 11% cancer survivors had a second primary malignancy. The respiratory system was the most frequently affected in this group. SPM risk was markedly elevated beyond two years with some malignancy risk only becoming significant after the initial period of surveillance.

While our study is limited by such factors as it does not account for details of toxin exposure such as smoking after the primary diagnosis, and does not include other risk factors such as individual risk factors, family history of malignancy, socioeconomic status, and comorbidities. Also, although we have utilized Warren and Gates criteria to define SPM, one may argue that some of these malignancies are either recurrent or metastatic disease of the index non-small cell lung cancer. The major strengths include a largely representative population sample, long follow-up period and huge sample size that lead to important conclusions which can be used to suggest further areas of study.

With the implementation of low dose CT screening in high-risk individuals and expected rise in the incidence of early stage lung cancer as described previously, the incidence of second primary malignancy may also increase. This is suggested by the improved survival of individual patients with more time available for a second malignancy to develop. This increase may reflect the systemic effect of carcinogen exposure, tumor-related genetic predisposition, and exposure to chemotherapeutic agents or radiation [11]. Whatever the etiologic factors may be, the development of a metachronous SPM heralds a grim prognosis with median time to death reported to be 14.3 months in a recent study [12].

Lung involvement as a second primary malignancy as described by our study supports the results of Lou et al. in an analysis of 1640 patients, describing CT scan surveillance as being superior to symptoms in leading to the diagnosis of a recurrence in 157 Stage I-II lung cancer, as opposed to advanced stage disease, where recurrence was identified by symptoms more commonly [13]. Distant second primaries, however, have not been studied in sufficient detail, and an ever-growing need exists for standardized trials delineating the modality of choice in detecting these at an early stage so that mortality can be sufficiently decreased with the institution of early therapy.

The risk of a second primary is also augmented by continued tobacco exposure, as evident from our results which showed an overwhelming number of second primaries from tumors which have directly been linked to tobacco exposure. Attention should be paid towards smoking cessation as a crucial intervention in lung cancer survivors [14]. As highlighted in a recent meta-analysis, continued smoking after a diagnosis of early stage lung tumor was associated with increased risk of all-cause mortality and recurrence [15], highlighting the importance of smoking cessation in routine care of lung cancer survivors.

A combined approach of routine follow-up, close communication between primary healthcare provider and oncologist, paying attention to subtle symptoms and physical examinations, judicious age-appropriate cancer screening, counseling and pharmacologic support in an attempt at smoking cessation with the use of surveillance imaging up to 4–5 years [16] after the primary diagnosis may aide in detection of second primaries, and ultimately improve survival.

An important aspect to be considered is the economic feasibility of low-dose CT scan when considering not only lung cancer, but also the second primary malignancies that are found indirectly through this process. It may be worth investing in further prospective studies as we continue to move forward.

Disclosure statement

We declare that we do not have any conflict of interest.

ORCID

Bilal Haider Lashari http://orcid.org/0000-0001-8257-7740

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65:5–29.
[2] Lung cancer incidence statistics. Cancer Research UK Web site. Updated 2015 [cited 2017 Sep 12]. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence.
[3] SEER cancer statistics review (CSR) 1975–2013. 2016 [cited 2017 Sep 12]. Available at: http://seer.cancer.gov/csr/1975_2013/.
[4] Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395–409.
[5] National Cancer Institute Surveillance, Epidemiology, and End Results Program. 2017 [cited 2017 Sep 14]. Available at: https://seer.cancer.gov/about/overview.html.
[6] Team, The National Lung Screening Trial Research. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395–409.
[7] Tanoue LT, Tanner NT, Gould MK, et al. Lung cancer screening. Am J Respir Crit Care Med. 2015;191:19–33.
[8] Villanti AC, Jiang Y, Abrams DB, et al. A cost-utility analysis of lung cancer screening and the additional benefits of incorporating smoking cessation interventions. PLoS One. 2013;8:e71379.
[9] Edwards JP, Datta I, Hunt JD, et al. The impact of computed tomographic screening for lung cancer on the thoracic surgery workforce. Ann Thorac Surg. 2014;98:447–452.
[10] Mulshine JL, Sullivan DC. Clinical practice. Lung cancer screening. N Engl J Med. 2005;352:2714–2720.
[11] Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst. 2002;94:182–192.
[12] Kono M, Allen PK, Lin SH, et al. Incidence of and survival outcomes after metachronous second primary malignancy after the

treatment of limited-stage small cell lung cancer. Int J Radiat Oncol Biol Phys. 2016;96:E430.

[13] Lou F, Sima CS, Rusch VW, et al. Differences in patterns of recurrence in early-stage versus locally advanced non-small cell lung cancer. Ann Thorac Surg. 2014;98:1761.

[14] Shiels MS, Gibson T, Sampson J, et al. Cigarette smoking prior to first cancer and risk of second smoking-associated cancers among survivors of bladder, kidney, head and neck, and stage I lung cancers. J Clin Oncol. 2014;32:3989–3995.

[15] Parsons A, Daley A, Begh R, et al. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. BMJ. 2010;340:b5569.

[16] Jaklitsch MT, Jacobson FL, Austin JHM, et al. The American association for thoracic surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. J Thorac Cardiovasc Surg. 2012;144:33–38.