Second Primary Malignancies in Hepatocellular Cancer – A US Population-based Study

BINAY K. SHAH[1], PUJAN KANDEL[2] and AMIT KHANAL[3]

[1]*North Puget Cancer Center, Sedro-Woolley, WA, U.S.A.;*
[2]*Mayo Clinic School of Medicine, Jacksonville, FL, U.S.A.;*
[3]*Section of Hematology and Oncology, Department of Medicine, University of Illinois at Chicago, Chicago, IL, U.S.A.*

Abstract. *Background/Aim: A second primary malignancy is a serious long-term complication in cancer survivors. The aim of this study was to evaluate the risk of second primary malignancies in patients with hepatocellular carcinoma (HCC). Materials and Methods: We selected adult patients (≥18 years) diagnosed with HCC from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) 13 database. We calculated the risk of second primary malignancies in these patients using multiple primary standardized incidence ratio (MP-SIR) session of SEER* stat software. Second primary malignancy was defined as a metachronous malignancy diagnosed 6 months or more after an index HCC. Results: A total of 15,296 patients with a diagnosis of primary HCC were reported in the SEER 13 registry during January 1992 to December 2011. A total of 446 (2.83%) developed 466 second primary malignancies with an observed/expected ratio of 10.07 (95% confidence interval=0.97-1.17, p=0.16) and absolute risk of 7.17 per 10,000 population. Risk of stomach and of thyroid cancer were significantly increased among older patients. Risk of lung cancer and of hepatobiliary cancer were significantly higher compared to that of the general population after two years of latency. Conclusion: Risk of specific second primary malignancies in adult patients with HCC depends on age of the patient and latency.*

This study was presented as a poster at 2015 ASCO annual meeting, 15-17, 2015 at Chicago

Correspondence to: Dr. Binay Kumar Shah, North Puget Cancer Center, 2000 Hospital Drive, Sedro-Woolley, WA 98284, U.S.A. Tel: +1 3608567588, Fax: +1 3608567252, e-mail: binay.shah@gmail.com

Key Words: Hepatocellular cancer, second primary malignancy, SEER, latency.

Improvement in diagnostic modalities and treatment of cancer has led to an increase in the number of cancer survivors. Approximately 18 million cancer survivors are expected by 2022 (1). It is important to learn about the long-term effects of cancer and its treatment among cancer survivors. Second primary malignancy (SPM) is a serious long-term complication in cancer survivors. SPMs are significantly increased in patients with various solid and hematological malignancies (2-5). Hepatocellular carcinoma (HCC) is the sixth most common cancer and third most common cause of cancer-related death worldwide (6, 7). HCC accounts for 2.2% of all new cancer diagnoses in the United States, with an estimated 35,660 new cases and 24,550 deaths in 2015 (8). There were an estimated 50,734 people living with liver cancer in the United States. Several factors, including diagnosis of HCC at early stage and advances in therapy, have led to improved prognosis for patients with HCC. A recent study showed improvement in survival of patients with advanced HCC after the introduction of sorafenib (9).

In this study, we evaluated the risk of SPMs in adults with HCC in the United States using the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database.

Patients and Methods

The SEER is a population-based cancer database run by the National Cancer Institute. The SEER 13 represents approximately 14% of the population of the USA and includes 13 cancer registries: San Francisco-Oakland, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle (Puget Sound region), Utah, Atlanta, San Jose-Monterey, Los Angles, Alaska Natives, and rural Georgia. High-quality data are collected from hospitals and cancer treatment centers. The database includes primary tumor site, staging, patient demographics, treatment modality, and survival statistics (10). We selected adult patients (≥18 years) diagnosed with first primary HCC between January 1992 and December 2011. We excluded cases diagnosed at autopsy and those lost to follow-up. The patients were followed up from the date of diagnosis to the date of last

Table I. *Demographics of patients from the SEER 13 included in the study.*

Variables	Value
Total number of patients, n	15,296
Gender n	
Male	11,391
Female	3,905
Race, n	
White	8,959
Black	1,726
Other	4,611
Median age (range)	66.16 (42.33-95.5) years
Median follow-up (range)	28 months (6 months-18.5 years)
Total no. of SPMs	427
Total no. of patients with one SPM	408
Total no. of patients with one or more SPM	19
Age at the time of diagnosis of SPM	66.16 (42.33-95.5) years
Latency to developing SPM	27 months (6 months-18.25 years)

SPM: Second primary malignancy.

known vital status, death, or the last point of data collection. SPM was defined as a metachronous malignancy diagnosed 6 months or more after an index HCC (11).

We calculated the standardized incidence ratio, absolute excess risk (AER) and confidence interval (CI) in patients with HCC using the multiple primary standardized incidence ratio session of SEER* stat software, version 8.1.5 (National Cancer Institute, Bethesda, MD, USA). A value of $p<0.05$ was considered statistically significant. The standardized incidence ratio measures the relative risk between two cancer events and is calculated by dividing the observed incidence by the expected incidence of SPM (O/E ratio) in the general population (8). AER measures the excess events normalized to the number of person years (PY) observed [AER=(O–E) PY] (12).

Results

A total of 15,296 patients diagnosed with primary HCC met the study criteria. The majority of the patients were men (74.47%) and belonged to the Caucasian race (58.57%). The median age at the time of diagnosis was 66.16 years (range=42.33-95.5 years). Detailed patient demographics are presented in Table I. The median follow-up duration was 28 months (range=6-18.5 years). A total of 446 (2.83%) patients developed 466 SPM with an O/E ratio of 10.07 (95% CI=0.97-1.17) and AER of 7.17 per 10,000 population ($p=0.16$). These patients had significant excess risk of non-Hodgkin's lymphoma and several types of solid tumors, including cancer of the head and neck, lung, thyroid, adrenal glands, stomach, anus and hepatobiliary region (Table II). Interestingly, there was significantly reduced risk of prostate cancer among patients with HCC compared to the general population.

Younger patients (aged <60 years) had increased risk of malignancies of oropharynx (O/E=4.18, 95% CI=2.23-7.15, $p=0.01$; AER=7.15), lung and bronchus (O/E=30.03, CI=1.9-4.58, $p=0.01$; AER=11.6), hepatobiliary system (O/E=4.35, 95% CI=2.32-7.44, $p=0.01$; AER=7.8), small intestine (O/E=8.11, 95% CI=1.67-23.1, $p=0.01$; AER=20.07) and non-Hodgkin's lymphoma (O/E=4.44, 95% CI=2.43-7.44, $p=0.01$; AER=8.53.) Among older patients (Age ≥60 years), there was increased risk of cancer of the oropharynx (O/E=1.7, 95% CI=1.12-3.2, $p=0.01$; AER=40.01), stomach (O/E=1.93, 95% CI=1.16-30.02, $p=0.02$; AER=4.67), hepatobiliary system (O/E=2.63, 95% CI=1.7-3.88, $p=0.01$; AER=7.88), lung and bronchus (O/E=1.1, 95% CI=0.4-1.41, $p=0.01$; AER=2.76), thyroid (O/E=2.83, 95% CI=1.29-5.3, $p=0.01$; AER=2.6) and non- Hodgkin's lymphoma (O/E=1.65, 95% CI=10.06-2.45, $p=0.01$; AER=4.8).

Similarly, the median time for development of first SPM from the time of diagnosis of HCC was 27 months (range=6-18.25 years) for the whole cohort. The risk of head and neck cancer, Kaposi Sarcoma, and hematological malignancies were increased within the first two years of latency. Risks of lung cancer and hepatobiliary cancer were significantly higher compared to general population after two years of latency.

Discussion

The number of deaths due to cancer is declining (13). SPMs are common and have an overall cumulative incidence of 14% at 25 years of follow-up (14). Several factors, including cancer type, anticancer therapy, pre-existing conditions and patients' habits, lead to increased risk of long-term

Table II. *Second primary malignancies in hepatocellular cancer.*

Site	Observed	O/E	*p*-Value	95% CI		AER
				Lower	Upper	
All	466	10.07	0.16	0.97	1.17	9.17
All excluding non-melanoma skin	461	10.06	0.2	0.97	1.16	8.1
All solid tumors	393	10.01	0.92	0.91	1.11	0.63
Brain tumor	4	0.98	0.61	0.27	2.5	–0.03
Head and neck	38	2.31	0.01	1.64	3.17	6.66
Thyroid	13	2.69	0.01	1.43	4.6	2.52
Lung and bronchus	82	1.33	0.01	10.05	1.65	6.23
Soft tissue including heart	5	2.2	0.16	0.72	5.14	0.84
Esophagus	4	0.74	0.74	0.2	1.89	-0.44
Stomach	20	1.78	0.02	10.09	2.75	2.71
Hepato biliary	43	2.71	0.01	1.96	3.66	8.39
Pancreas	9	0.72	0.40	0.33	1.37	–10.06
Colon and rectum	35	0.74	0.06	0.52	10.03	–3.79
Anus, anal canal and anorectum	4	3.74	0.04	10.02	9.57	0.91
Bones and joints	1	2.56	0.66	0.06	14.25	0.19
Skin excluding basal and squamous	15	10.02	0.50	0.57	1.68	0.08
Melanoma of the skin	10	0.76	0.46	0.36	1.39	-0.99
Breast	22	0.79	0.88	0.5	1.2	–1.79
Uterus	1	0.18	0.99	0	0.99	–1.44
Ovary	5	1.76	0.30	0.57	4.1	0.67
Prostate	52	0.47	0.01	0.35	0.61	–18.44
Kidney and renal pelvis	14	1	0.56	0.55	1.68	0
Adrenal gland	2	15.64	0.01	1.89	56.5	0.58
Urinary bladder	20	0.87	0.62	0.53	1.34	–0.92
Myeloma	5	0.8	0.80	0.26	1.87	–0.38
Non-Hodgkin lymphoma	38	20.03	0.01	1.44	2.79	5.96
Acute myeloid leukemia	8	1.44	0.20	0.62	2.84	0.76
Chronic lymphocytic leukemia	3	0.7	0.79	0.15	20.06	–0.39
Chronic myeloid leukemia	3	2.17	0.10	0.45	6.35	0.5

AER: Absolute excess risk; O/E: observed to expected incidence ratio; CI: confidence interval.

complications and premature mortality in patients with a previous history of cancer (15, 16). Data on SPMs is critical in developing the framework for pilot intervention studies and the development of evidence-based guidelines for follow up of these patients. The Institute of Medicine report in 2006 recommended that evidence-based guidelines be used to identify and manage the long-term complications of cancer, such as surveillance for and prevention of recurrences and SPMs (17). Research on survivors with recurrent disease or second cancer is limited. That is why studies on SPMs provide important information that may be used to guide follow-up and management of cancer survivors.

In our study, 2.83% of patients with HCC developed SPMs. In contrast, the rates of SPMs in previous studies from USA were 3.5-8% (18, 19). Similarly, studies from Spain (20) and Japan (21, 22) showed 2.4% and 0.7-1.9% respectively developed SPMs. Differences in etiologies and treatment strategies employed in different parts of the world may be responsible for differences in the rates of SPM in survivors of HCC. Clearly, long-term follow-up of HCC survivors should be different depending on these factors.

Cirrhosis is common among patients with HCC. Cirrhosis is known to have a role in carcinogenesis (23). Depending on geographic region, a common cause of cirrhosis may be viral hepatitis or alcoholism. This may lead to a different pattern of SPM among patients with HCC. For example, a study from Taiwan did not show any alcohol-related SPMs (24). The authors hypothesized that chronic hepatitis, not alcoholism is the major cause of cirrhosis in Taiwan, and that is why alcohol-related SPMs were not found in the study. These findings suggest the need for studies on SPMs in HCC in different geographic areas.

This study has several strengths, including its large sample size, long-term follow-up and high-quality data maintained through quality control studies. The limitations are related to the use of population–based databases. The SEER database does not collect information on factors such as smoking, alcohol use, exposure to environmental factors, co-

morbidities, family history, or chemotherapy used. There is a possibility that a small number of cancer recurrences in certain anatomic locations may be classified as SPM. Migration of patients out of the SEER area may underestimate the risk of SPM.

In conclusion, our study showed that risks of non-Hodgkin's lymphoma and several solid tumor types are increased in the patients with HCC depending on patient age and tumor latency.

References

1 Cowens-Alvarado R, Sharpe K, Pratt-Chapman M, Willis A, Gansler T, Ganz PA, Edge SB, McCabe MS and Stein K: Advancing survivorship care through the National Cancer Survivorship Resource Center: developing American Cancer Society guidelines for primary care providers. CA Cancer J Clin *63(3):* 147-150, 2013.

2 Rubino C, de Vathaire F, Dottorini ME, Hall P, Schvartz C, Couette JE, Dondon MG, Abbas MT, Langlois C and Schlumberger M: Second primary malignancies in thyroid cancer patients. Br J Cancer *89(9)*: 1638-144, 2003.

3 Ghimire KB and Shah BK: Second primary malignancies in adult acute lymphoblastic leukemia: a US population–based study. Blood *124(12)*: 2000-2001, 2014.

4 Ghimire KB and Shah BK: Second primary malignancies in adult acute myeloid leukemia – a US population-based study. Anticancer Res *34(7)*: 3855-3859, 2014.

5 Shah BK and Budhathoki N: Second primary malignancy in anal carcinoma–a US population-based study. Anticancer Res *35(7)*: 4131-4134, 2015.

6 Omata M, Lesmana LA, Tateishi R, Chen PJ, Lin SM, Yoshida H, Kudo M, Lee JM, Choi BI, Poon RT, Shiina S, Cheng AL, Jia JD, Obi S, Han KH, Jafri W, Chow P, Lim SG, Chawla YK, Budihusodo U, Gani RA, Lesmana CR, Putranto TA, Liaw YF and Sarin SK: Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. Hepatol Int *4(2)*: 439-474, 2010.

7 Hung HH, Chiou YY, Hsia CY, Su CW, Chou YH, Chiang JH, Kao WY, Huo TI, Huang YH, Su YH, Lin HC, Lee SD and Wu JC: Survival rates are comparable after radiofrequency ablation or surgery in patients with small hepatocellular carcinomas. Clin Gastroenterol Hepatol *9(1)*: 79-86, 2011.

8 http://seer.cancer.gov/statfacts/html/livibd.html. Accessed 20 April 2016

9 Shah BK, Bhandari A, Ghimire KB and Manandhar S: Improvement in survival of advanced hepatocellular carcinoma patients: Results of an updated period analysis of SEER database. InASCO Annu Meet Proc *33(3) suppl*: 383, 2015.

10 http://seer.cancer.gov/data/metadata.html. (Accessed 19 November 2015).

11 Warrens S. and O Gates: Multiple primary malignant tumors: a survey of the literature and a statistical study. Am J Cancer *16*: 1358-1414, 1932.

12 Schoenberg BS and Myers MH: Statistical methods for studying multiple primary malignant neoplasms. Cancer *40(S4)*: 1892-1898, 1977.

13 Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe Nur U, Tracey E, Coory M, Hatcher J, McGahan CE, Turner D, Marrett L, Gjerstorff ML, Johannesen TB, Adolfsson J, Lambe M, Lawrence G, Meechan D, Morris EJ, Middleton R,Steward J and Richards MA: Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. Lancet *37(9760)*: 127-138, 2011.

14 Yang J, Terebelo H and Zonder J: Secondary primary malignancies in multiple myeloma: an old nemesis revisited. Adv Hematol *2012*: 801495, 2012.

15 Berrington de Gonzalez A, Curtis RE, Kry SF, Gilbert E, Laman S, Berg CD, Stovall M and Ron E: Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. Lancet Oncol *12(4)*: 353-360, 2011.

16 Aisenberg AC: Problems in Hodgkin's disease management. Blood *93(3)*: 761-779, 1999.

17 Hewitt M, Greenfield S and Stoval E: From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, DC: National Academies Press, 2006.

18 Wong LL, Lurie F and Takanishi DM Jr.: Other primary neoplasms in patients with hepatocellular cancer: prognostic implications? Hawaii Med J *66*: 204, 206-208, 2007.

19 Nzeako UC, Goodman ZD and Ishak KG. Association of hepatocellular carcinoma in North American patients with extrahepatic primary malignancies. Cancer *74*: 2765-2771, 1994.

20 Fernández-Ruiz M, Guerra-Vales JM, Castelbón-Fernández FJ, Llenas-García J, Caurcel-Díaz L and Colina-Ruizdelgado F: Multiple primary malignancies in Spanish patients with hepatocellular carcinoma: analysis of a hospital-based tumor registry. J Gastroenterol Hepatol *24*: 1424-1430, 2009.

21 Takayasu K, Kasugai H, Ikeya S, Muramatsu Y, Moriyama N, Makuuchi M, Yamazaki S and Hirohashi S. A clinical and radiologic study of primary liver cancer associated with extrahepatic primary cancer. Cancer *69*: 45-51, 1992.

22 Shimada M, Takenaka K, Fujiwara Y, Gion T, Shirabe K, Nishizaki T, Yanaga K and Sugimachi K. Characteristics of hepatocellular carcinoma associated with extrahepatic primary malignancies in Southern Japan. Am J Gastroenterol *91(4)*: 754-758, 1996.

23 Sorensen HT, Friis S, Olsen JH, Thulstrup AM, Mellemkjaer L, Linet M, Trichopoulos D, Vilstrup H and Olsen J. Risk of liver and other types of cancer in patients with cirrhosis: a nationwide cohort study in Denmark. Hepatology *28*: 921-925, 1998.

24 Wu WC, Chen YT, Hwang CY, Su CW, Li SY, Chen TJ, Liu CJ, Kao WY, Chao Y, Lin HC, Wu JC. Second primary cancers in patients with hepatocellular carcinoma: a nationwide cohort study in Taiwan. Liver Int *33(4)*: 616-623, 2013.

Received April 28, 2016
Revised May 27, 2016
Accepted May 31, 2016