Received: 15 February 2021 | Accepted: 18 February 2021 | Published on: 24 June 2021

DOI: 10.1111/ajco.13582

ORIGINAL ARTICLE

WILEY

Survival and medical costs of melanoma patients with subsequent cancer diagnoses: A South Korean population-based retrospective cohort study

Hae-Young Park[1,*] | Hyun-Ju Yang[1,*] | Soo Min Jeon[1] | In Hee Lee[2] | Jin-Won Kwon[1]

[1] BK21 FOUR Community-Based Intelligent Novel Drug Discovery Education Unit, College of Pharmacy and Research Institute of Pharmaceutical Sciences, Kyungpook National University, Daegu, South Korea

[2] Division of Hematology/Oncology, Department of Internal Medicine, Daegu Catholic University School of Medicine, Daegu, South Korea

Correspondence
Jin-Won Kwon, MPH, PhD, College of Pharmacy and Research Institute of Pharmaceutical Sciences, Kyungpook National University, Daegu, South Korea.
Email: jwkwon@knu.ac.kr

[*] Hae-Young Park and Hyun-Ju Yang contributed equally to this work.

Funding information
Korea National Research Foundation, Grant/Award Number: NRF-2018R1D1A3B07047356

Abstract

Aim: Subsequent cancers (SCs) after melanoma diagnosis further increases the risks of mortality and medical costs. This population-based analysis aimed to evaluate risk factors for SC, mortality, and medical costs of melanoma patients with SC.

Methods: A retrospective cohort analysis was conducted using a nationwide claims database during 2002-2017 in South Korea. SC was defined as having other types of cancer diagnoses other than subsequent melanoma during-up to 5 years after melanoma diagnosis. Melanoma patients were divided into patients with and without SC, and the overall and subgroup survival rates, the risk of developing SC, and the total medical costs were analyzed using a Kaplan–Meier method and regressions.

Results: A total of 3740 melanoma patients were included in the analysis (mean age, 62.3 ± 15.4 y; 47.2% men), and 2273 patients (1157 within 2 months, 756 after 2 months of melanoma diagnosis) had SC. Higher Charlson comorbidity index score and male sex significantly increased the risk of developing SC. Five-year survival rate and cumulative medical costs were 62.3% (95% confidence interval [CI], 60.8-63.9) and $21,413, respectively, in all patients. Patients with SC diagnosed after 2 months showed the lowest survival rate of 47.8% (95% CI, 44.3-51.4) and the highest costs of $27,081, showing a mortality hazard ratio of 1.65 (range, 1.46-1.86) and a cost ratio of 1.189 (range, 1.112-1.271) compared with those without SC.

Conclusion: This study presented survival outcomes and medical costs in melanoma patients and confirmed that SC after the first diagnosis of melanoma significantly increased disease burden in terms of mortality and medical costs.

KEYWORDS
costs and cost analysis, melanoma, mortality, second primary cancer, survival analysis

1 | INTRODUCTION

The incidence and mortality rates of malignant melanoma in Asia and Korea are lower relative to Western countries but have increased in recent decades.[1] Malignant melanoma is the most fatal of the skin cancers,[2] and patients with melanoma have potential risks to develop subsequent cancers (SCs) owing to a second primary cancer (SPC),[3–5] which further increases patients' risk of mortality.

A meta-analysis has shown that compared to the general population, the risk of SPC among patients with melanoma was increased overall

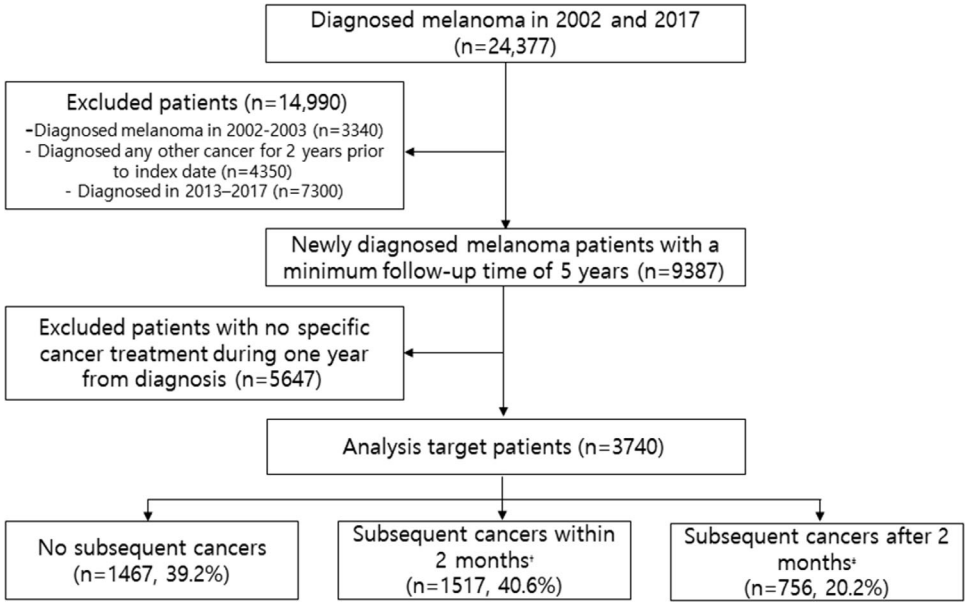

FIGURE 1 Patient inclusion flow. † Considered synchronous cancers; ‡ Considered second primary cancers

(relative risk: 1.57, 95% confidence interval [CI]: 1.29-1.90) and at several specific sites such as bone, skin, soft tissue, colon-rectum, breast of women, kidney, prostate, and lymphoid.[6] Melanoma survivors had a 1.32 times higher risk of developing SPCs compared with the general population in a study conducted in the United States.[7] According to Asian data, SPCs were observed in 9.3% of patients with cutaneous melanoma in Taiwan. The overall cancer incidence in melanoma patients was 2.54 times higher than that of the general population in Taiwan, with particularly higher risks for eye, connective tissue, and brain cancers.[8]

SPC was known as the most common cause of death in patients with SPC. In a recent study based on the Swedish Cancer Registry,[9] the hazard ratio (HR) was 1.82 in patients with SPC other than second primary melanoma compared to patients with no SPC. The risk of mortality for melanoma patients increased further if patients had both SPC and metastasis. The HR of nonmelanoma SPC patients with no metastasis was 2.59 with reference of no metastasis and no SPC, but the HR of nonmelanoma SPC patients with metastasis increased to 6.82.[9]

Primary melanoma and SCs can cause additional burden of disease for both the patients and public health interests, but data for Asian are not sufficient to assess and compare the risk of mortality based on the presence of SPC in patients with melanoma.[8,10] In a study by Bae et al., 5.9% (23 of 452 patients) of melanoma patients had metachronous primary cancers other than second primary melanoma or skin cancers. Although the study has attempted to assess the burden of SCs in melanoma patients in Korea, it has had small sample sizes and focused on a limited number of treatment centers.[10] Furthermore, while SPC could increase medical costs, no study has yet evaluated this for melanoma survivors with SPC. Therefore, this study is the first population-based study to investigate risk factors for developing SCs, mortality in absolute survival rate, and medical costs among melanoma patients with SCs in South Korea.

2 | MATERIALS AND METHODS

2.1 | Database and target subjects

A customized database provided by the National Health Insurance Cooperation was used for the analysis.[11] The database provided nationwide health insurance claims data for 24,377 patients with melanoma who had the diagnosis code C43 based on the International Codes of Disease 10th (ICD-10) revision from 2002 to 2017. The database included all the information within the range of national health insurance in the form of anonymity such as patient demographics, treatment information, death, costs, and etc. Newly diagnosed melanoma patients (n = 9387) with a minimum follow-up time of 5 years were identified after excluding patients who were diagnosed with melanoma in 2002-2003 (n = 3340) and in 2013-2017 (n = 7300) and who had any other cancer diagnosis in last 2 years before the melanoma diagnosis (n = 4350). Then patients without specific melanoma-related treatment during the first year after diagnosis (n = 5647) were excluded and finally, 3740 melanoma patients were included for analysis (Figure 1). The first diagnosis date of melanoma patients was set as the index date. The patients were divided into patients with (n = 2273) and without (n = 1467) SCs according to whether there had been any other types of cancer diagnoses, other than subsequent melanoma, within 5 years after the index date. The patients with SCs were again divided into two groups, namely those with SCs diagnosed within 2 months (n = 1517) and after 2 months (n = 756) from the index date. SCs that occur after 2 months are considered SPCs and the SCs within 2 months are considered synchronous cancers rather than SPCs.[8,12] As the database did not contain information on disease stage, we analyzed treatment pattern to assume disease stage. Treatment patterns were classified into three groups, operation only (OP), chemotherapy (CTx) or radiation therapy (RTx),

and combined therapy (OP + CTx/RTx), according to treatment records during the first year after diagnosis.

2.2 | Patient demographics and risk factors for developing other cancers

We noted the patient's sex, age, year of diagnosis, body mass index, and smoking status based on the index date. The Charlson comorbidity index (CCI) score was analyzed based on the diagnosis record for 1 year prior to the melanoma diagnosis. In the group of the patients with SCs, the period of occurrence of SCs was presented as mean ± standard deviation, and the incidence of SCs was summarized by the frequency of the region of occurrence according to ICD-10 code. Cox proportional hazard regression analysis was performed for the variables of sex, age, treatment modality, and CCI score to evaluate risk factors for the occurrence of SCs.

2.3 | Survival analysis by patient group

Survival rate was analyzed using the Kaplan–Meier method, and subgroup analysis was performed according to the occurrence of SCs. The analyzed results are presented as the mean follow-up period, the mean and median survival time, and 5- and 10-year survival rates. The HR for survival among subgroups was calculated using a Cox proportional hazard regression analysis.

2.4 | Medical cost analysis

The medical costs in this study were analyzed using the Kaplan–Meier Sample Average method.[13,14] The follow-up period after index data was divided into 1 month, and the average monthly cost incurred by survivors of each month was multiplied by the monthly survival probability determined using the Kaplan–Meier method, and then the cost was summed across a year and presented as an annual cost for each year.[13,14] The costs in this study included all-cause health care costs incurred in treating patients under the national health insurance scheme, including outpatient visits, treatment of comorbidity and medication costs, and these were inflated to 2019 Korean Won (KRW) and again converted to USD at a rate of 1200 KRW/USD based on exchange rates in the first half of 2020. The cost ratio between patients with SCs and patients without SCs was analyzed with and without survival time using a generalized linear regression model. Each result was presented as a cost ratio and 95% CIs. All the analyses were conducted with SAS enterprise guide (version 7.1; SAS Institute Inc., Cary, NC) and R Studio version 1.0.136 (R studio, Inc., Boston, MA).

3 | RESULTS

3.1 | Characteristics of the study population

The average age at the time of melanoma diagnosis was 62.3 (±15.4) years. Percentages of patients older than 60 years, men and CCI scores > 5 were higher in patients with SCs. When categorizing treatment modality, the majority of patients without SCs were found in the OP group (61.7%), whereas the proportion of patients treated with CTx or RTx only was higher in the group of patients with SCs diagnosed within 2 months (29.3%) and after 2 months (30.8%) than among patients without SCs (24.5%). In the group of patients with SCs, the mean time to the diagnosis of SCs was 23.5 (±17.6) months and was longer in OP group (27.6 ± 18.2 mo) than in the other two groups. The most prevalent cancer was other skin cancer, which was shown in 67.1% of patients with SCs diagnosed within 2 months and 34.7% of patients with SCs diagnosed after 2 months. In the group of patients with SCs diagnosed after 2 months, the most prevalent cancers were cancers of the respiratory system and intrathoracic organs (18.8%), digestive organs (10.4%), and connective and soft tissue (5.4%) (Table 1). In comparison with the general population, melanoma patients showed a much higher incidence of cancers of the skin, eye, connective and soft tissue, bone, and articular cartilage (Supporting information Table S1).

3.2 | Risk factors for developing SCs

Men and all patients with a CCI score of 5 compared to those with a CCI score of 3 demonstrated a higher risk of developing SCs. The patients in the treatment modality of OP + CTx/RTx and CTx/RTx only showed greater risk of developing SCs when compared with the OP group. There was no difference in risk depending on age at the time of diagnosis when using a reference age of 40 to 59 (Table 2).

3.3 | Survival

The median survival time was 116 months among all patients. By comparison, the median survival time was 115 months for patients with other cancers diagnosed within 2 months, 56 months for patients with other cancers diagnosed after 2 months, and not reached for the group of patients without SCs. The 5-year survival rates were 69.3% in the group of patients without SCs, 62.8% in the group of patients with SCs diagnosed within 2 months, and 47.8% in the group of patients with SCs diagnosed after 2 months. The 10-year survival rates were 57.0%, 48.5%, and 33.8%, respectively (Figure 2, Table 3). The HR for developing SCs in the group of patients with SCs was significantly increased compared with the group of patients without SCs (HR, 1.65; $P < .0001$) even after adjusting for sex, age at diagnosis, and CCI score (Table 3).

3.4 | Medical costs

The medical costs for the patients with SCs diagnosed after 2 months were estimated at $27,081 for the first 5 years after diagnosis, which was higher than the $19,469 estimated for patients without SCs. The medical costs for the first year were 42.3% of the cumulative 5-year cost in the group of patients without SCs, which was higher than that in the groups of patients with SCs. Based on the generalized linear

TABLE 1 Characteristics of the study population

	Without SCs	With SC		Total
		Diagnosed within 2 mo[a]	Diagnosed after 2 mo[b]	
No. of patients	1467	1517	756	3740
% of men	45.7%	47.0%	50.4%	47.2%
Age at diagnosis, y (%)				
Mean ± SD	60.6 ± 16.0	64.0 ± 15.0	62.3 ± 14.7	62.3 ± 15.4
<20	15 (1.0)	7 (0.5)	3 (0.4)	25 (0.7)
20-39	135 (9.2)	100 (6.6)	55 (7.3)	290 (7.8)
40-59	492 (33.5)	422 (27.8)	231 (30.6)	1145 (30.6)
60-79	672 (45.8)	780 (51.4)	394 (52.1)	1846 (49.4)
≥80	153 (10.4)	208 (13.7)	73 (9.7)	434 (11.6)
Year of diagnosis				
2004-2008	713 (48.6)	840 (55.4)	422 (55.8)	3740 (52.8)
2009-2012	754 (51.4)	677 (44.6)	334 (44.2)	1765 (47.2)
BMI				
Missing	641 (43.7)	722 (47.6)	334 (44.2)	1697 (45.4)
<18.5	23 (1.6)	41 (2.7)	10 (1.3)	74 (2.0)
18.5-22.9	293 (20.0)	294 (19.4)	137 (18.1)	724 (19.4)
23-24.9	210 (14.3)	197 (13.0)	114 (15.1)	521 (13.9)
25-29.9	276 (18.8)	239 (15.8)	146 (19.3)	661 (17. 7)
≥30.0	24 (1.6)	24 (1.6)	15 (2.0)	63 (1.7)
Smoking status				
Missing	658 (44.9)	732 (48.3)	337 (44.6)	1727 (46.2)
Never smoker	567 (38.7)	552 (36.4)	275 (36.4)	1394 (37.3)
Smoker	242 (16.5)	233 (15.4)	144 (19.1)	619 (16.6)
CCI score				
1	231 (15.8)	178 (11.7)	78 (10.3)	487 (13.0)
2	252 (17.2)	203 (13.4)	90 (11.9)	545 (14.6)
3	212 (14.5)	209 (13.8)	96 (12.7)	517 (13.8)
4	143 (9.8)	176 (11.6)	69 (9.1)	388 (10.4)
5	629 (42.9)	751 (49.5)	423 (56.0)	1803 (48.2)
Treatment modality during the year after diagnosis				
Operation only	905 (61.7)	900 (59.3)	375 (49.6)	2180 (58.3)
Operation + CTx/RTx	202 (13.8)	172 (11.3)	148 (19.6)	522 (14.0)
CTx/RTx only	360 (24.5)	445 (29.3)	233 (30.8)	1038 (27.8)
Time to SC diagnosis (median mo, mean mo ± SD).				
All			19.2, 23.5 ± 17.6	–
Operation only			26.2, 27.6 ± 18.2	–
Operation + CTx/RTx			13.6, 18.4 ± 15.2	–
CTx/RTx only			15.3, 20.3 ± 16.4	–
Cancer region				
(C44) Other skin		1018 (67.1)	262 (34.7)	
(C30-C39) Respiratory system and intrathoracic organs		104 (6.9)	142 (18.8)	
(C15-21, 25) Digestive organs		47 (3.1)	79 (10.4)	

(Continues)

TABLE 1 (Continued)

	Without SCs	With SC		Total
		Diagnosed within 2 mo[a]	Diagnosed after 2 mo[b]	
(C45-C49) Connective and soft tissue		97 (6.4)	41 (5.4)	
(C70-C72) Brain and central nervous system		18 (1.2)	37 (4.9)	
(C22-24) Liver, gallbladder, biliary tract		12 (0.8)	33 (4.4)	
(C00-C14) Lip, oral cavity, and pharynx		63 (4.2)	29 (3.8)	
Others		158 (10.4)	133 (17.6)	

BMI, body mass index; CCI, Charlson comorbidity index; CTx, chemotherapy; mo, months; RTx, radiation therapy; SD, Standard deviation; y, years.
[a]Considered synchronous cancers.
[b]Considered second primary cancers.

TABLE 2 Hazard ratio for diagnoses of SCs (adjusted for treatment, sex, age at diagnosis, and CCI score)

Parameter	Hazard ratio	95% CI		*P* value
		LCL	UCL	
Treatment modality (ref: operation only)				
Operation + CTx/RTx	1.851	1.525	2.247	<.0001
CTx/RTx only	1.759	1.486	2.081	<.0001
Sex (ref: male)				
Female	0.829	0.717	0.958	.0109
Age at diagnosis (ref: 40-59)				
<20	0.587	0.187	1.838	.3603
20-39	0.957	0.712	1.286	.7708
60-79	1.135	0.961	1.34	.135
≥80	1.112	0.85	1.455	.4389
CCI score (ref: 3)				
1	0.850	0.627	1.152	.2949
2	0.841	0.631	1.123	.2404
4	1.029	0.755	1.403	.8577
5	1.511	1.209	1.888	<.0001

CCI, Charlson comorbidity index; CI, confidence interval; CTx, chemotherapy; LCL, lower confidence limit; Ref, reference; RTx, radiation therapy; UCL, upper confidence limit.

regression model analysis, cost ratios between the group of patients with SCs diagnosed after 2 months and patients without SCs were 1.189 (95% CI, 1.112-1.271) during years 1 to 5 and 1.149 (95% CI, 1.090-1.212) per survival month (Table 4).

4 | DISCUSSION

This study found that 60.8% of patients who were newly diagnosed with melanoma without any other cancer developed SCs within 5 years after the first diagnosis of melanoma, and those diagnosed SCs after 2 months had significantly increased mortality (HR: 1.65, 95% CI: 1.46-1.86) and medical costs (cost ratio: 1.19, 95% CI: 1.11-1.27) compared to patients without SCs.

We assumed that most SCs diagnosed after 2 months from index date would be SPC, and that SCs diagnosed within 2 months are synchronous cancers owing to increased medical examination after the diagnosis of melanoma.[8,12] The survival and medical costs of patients with synchronous cancers were similar to the results of all patients. Therefore, this discussion was more focused on the results of SCs diagnosed after 2 months, which were regarded as SPC because the mortality and medical costs for those patients were significantly increased compared with the results of patients without SCs. Taiwanese data, which is in the same region in Asia as Korea, showed that melanoma patients had a more than 20 times higher incidence of SPC in connective tissue, eyes, brain, and the nasal cavity compared with the standardized incidence rates of the general population.[8] Based on data from the United States, SPC development excluding second

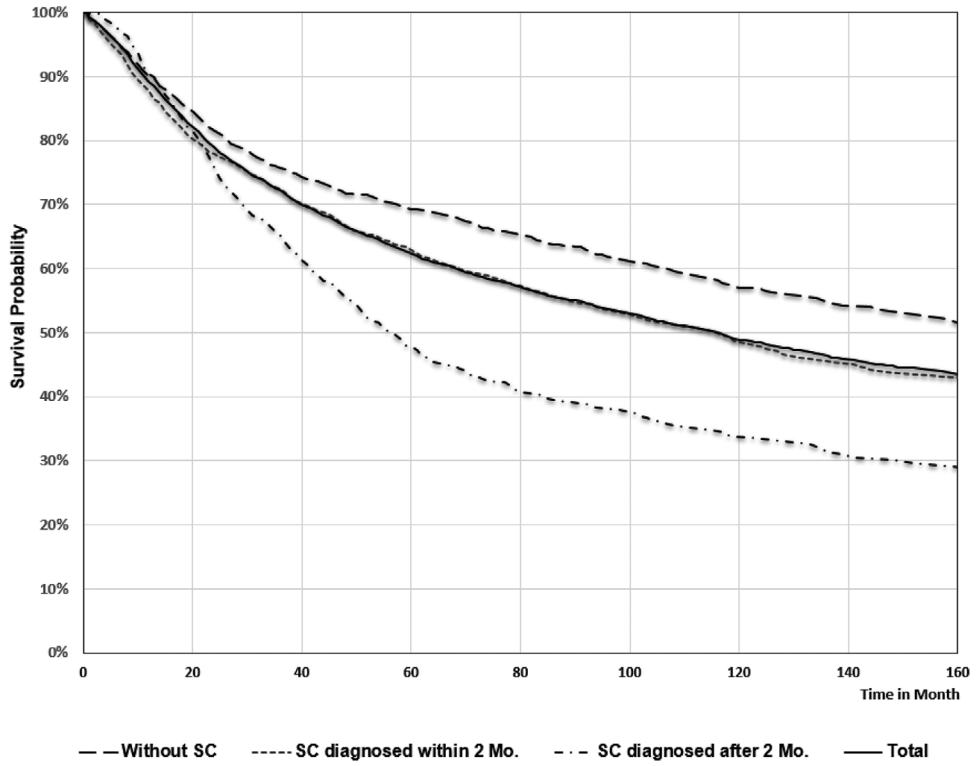

FIGURE 2 Survival of patients with melanoma over the follow-up period. MO, month; SC, subsequent cancer

TABLE 3 Survival data and Cox hazard analysis results

	Without SCs (n = 1467)	With SCs: Diagnosed within 2 mo[a] (n = 1517)	With SCs: Diagnosed after 2 mo[b] (n = 756)	Total patients (n = 3740)
Survival data				
Median follow-up, mo	89	82	58	82
Survival time (median mo, 95% CI)	Not reached	115 (101-126)	56 (50-61)	116 (106-124)
5-year survival (mean %, 95% CI)	69.3 (67.0-71.7)	62.8 (60.4-65.3)	47.8 (44.3-51.4)	62.3 (60.8-63.9)
10-year survival (mean %, 95% CI)	57.0 (54.4-60.0)	48.5 (45.9-51.3)	33.8 (30.4-37.5)	48.8 (57.2-50.6)
Survival hazard ratio[c]	1.00		1.65 (1.46-1.86)	

CI, confidence interval; mo, months.
[a]Considered synchronous cancers.
[b]Considered second primary cancers.
[c]Adjusted for sex, age at diagnosis, and CCI score.

primary melanoma was expected to occur in the region of salivary gland, retroperitoneum, trachea, eye, and thyroid in melanoma patients at a rate of 1.5 times higher. In this study, melanoma patients showed a more than five times higher incidence of SPCs in other skin, eye, connective and soft tissue, bone, and articular cartilage compared with the incidence probability of the Korean population of general patients in 2017 (Supporting information Table S1). These study results are more similar to the Taiwanese study compared to the present study. These cancers may occur with relatively higher incidence rates in Asian melanoma patients, even if their absolute incidence rate is low in the general population.

Incidence data for the development of SPC after primary melanoma diagnosis varied across countries with 12.1% or 18% in the United States,[5,15] 7.3% in Sweden,[9] and 9.3% in Taiwan.[8] We could not find population-level incidence of SPC in Korean melanoma patients, however, a study by Bae et al. involving 452 melanoma patients from a single-center found a 10.6% incidence of other primary systemic cancer.[10] In Bae et al.'s study, other primary systemic cancers

TABLE 4 Treatment costs for melanoma patients with and without SCs

		With SCs		
	Without SCs (A) (n = 1467)	Diagnosed within 2 mo[a] (n = 1517)	Diagnosed after 2 mo[b] (n = 756)	Total patients (n = 3740)
Cumulative treatment cost (USD[§])				
1st year	8227 (42.3%)	7912 (37.9%)	9973 (36.8%)	8379 (39.1%)
2nd year	11,871 (61.0%)	11,764 (56.3%)	15,902 (58.7%)	12 538 (58.6%)
3rd year	14,572 (74.8%)	15,042 (72.0%)	20,204 (74.6%)	15,773 (73.7%)
4th year	17,050 (87.6%)	18,095 (86.7%)	23,994 (88.6%)	18,729 (87.5%)
5th year	19,469 (100.0%)	20,882 (100.0%)	27,081 (100.0%)	21,413 (100.0%)
Cost ratio between A and B				
Year 1-5 total cost[c]	1.000		1.189 (1.112-1.271)	
Costs per survival mo[d]	1.000		1.149 (1.090-1.212)	

CI, confidence interval; mo, months, USD, United States dollar.
[a]Considered synchronous cancers.
[b]Considered second primary cancers.
[c]Effects are shown as adjusted for sex, age, and CCI score.
[d]Effects are shown as adjusted for sex, age, CCI score, and length of follow-up month.
[§]Korean Won (KRW) was converted to USD at a rate of 1200 KRW/USD based on exchange rates in the first half of 2020.

were evaluated and 51 (10.6%) other primary systemic cancer were detected among melanoma patients.

The incidence of SPC in melanoma patients may vary depending on the follow-up duration, proportion of censoring, inclusion criteria on SPC, race, etc. However, SPC incidence in this study, which was assumed by the proportion of SCs diagnosed after 2 months from the index date among all patients, was slightly higher compared with other study results. This might be the result of the inclusion of metastatic lesions originating from primary melanoma or other SPC. The source database in this study did not provide information about the cell type, so it was not possible to confirm whether the SC was a secondary primary cancer or metastatic recurrence. The metastatic recurrence rate in melanoma is reportedly quite high based on a Korean study that collected data from seven large medical centers.[16] Metastasis was diagnosed in 41.8% of stage 4 patients, and the regions reported were gastrointestine (30.3%), lung (28.4), distant lymph node (22.9%), and brain (18.3%). In our study, with the exception of other skin, the incidence of SCs was highest in the respiratory system, intrathoracic organs, and digestive organs. In addition, the incidence in the brain and central nervous system, lymphoid, hematopoietic, and related tissue was relatively high. When comparing the incidence between our study and the metastasis study in Korea, we cannot exclude the possibility that SCs in this study include some cases of metastatic recurrence.

In this study, we found that the disease severity, sex, and comorbidity status significantly affect the occurrence of SCs. SC risk was higher in men. Our study, as well as the national cancer statistics in the United States and Korea, showed that men generally showed higher cancer incidence rates compared with those of women for all cancer sites combined.[17,18] In this study, older patients had more SC diagnoses, but the statistical significance was not shown with adjustment for treatment, sex, and CCI score. Cancer susceptibility might be increased in younger patients because of genetic predisposition or family history, considering their age of onset at the time of their first diagnosed cancer.[4,19–21] Therefore, further studies will be needed to investigate whether age really did not affect SPC development or if older age results in higher probability of SPCs. In addition to the risk factors analyzed in this study, familial risks could also increase the risk of SCs. Melanoma patients with parental history of melanoma showed a greatly increased risk of melanoma and SPC compared with the general population.[4,20] The HR (baseline, patients without SPC, or family history) was 1.13 for patients without SPC but with family history, 1.97 for the patients with SPC but without family history, and 2.04 for patients with SPC but with family history.[20] Also, incidence of SCs varied and was affected by different risk factors according to specific cancer site. More focused analysis by individualized specific target site should be conducted in the future.

This study confirmed that patients with SPC (SC diagnoses after 2 months from the index date in this study) showed higher mortality (HR, 1.65; 95% CI, 1.46-1.86) and medical costs (cost ratio, 1.189; 95% CI, 1.112-1.271) than patients without SCs, thus, increasing the patient's disease burden in terms of both life time and costs. As for survival in SPC, any types of SPC, with the exception of melanoma, were associated with an HR of 2.00.[22] SPC was shown as the major contributing cause of death rather than the initially diagnosed melanoma.[20,23] Data from the United States have shown that 56% of patients died of their second cancers, whereas 9% died of melanoma, which was the first cancer diagnosed, when observing the cause of death.[23] We confirmed that SPC patients in this study had increased mortality compared with patients without SCs, but we could not analyze whether the SCs were the major cause of death. The mortality of patients with SPC was affected by various factors, including characteristics of primary and second cancers (ie, stage, type, location) and the socioeconomic

environments of the patients.[24] This study focused on presenting the overall mortality rate in melanoma patients according to SC, and further studies should be conducted on individual risk factors that significantly affect the survival of SPC patients. In this study, all the patients spent approximately 60% of costs within 2 years regardless of SC development. An Australian study has reported that melanoma patients spent more in medical costs than matched controls without cancer, and that the initial phase required more resources than the continuing phase.[25] Furthermore, this study showed that patients with SPC spent $7612 (based on exchange rates in the first half of 2020) more than patients without SPC during 5 years after the first diagnosis of melanoma, suggesting that SPC management, such as early diagnosis and prevention, has economic importance as well as survival of patients. To our knowledge, the current study is the first to present excess medical costs of SPC compared with non-SPC melanoma patients. However, as a detailed cost analysis was not conducted, we cannot identify the attributable costs for the treatment of primary melanoma and SCs. Further detailed investigation on the costs according to cause would be needed.

Our study has some limitations; First, the nationwide claim database does not provide data identifying the cause of SCs after melanoma diagnosis, therefore, survival data cannot be evaluated based on the cause of SCs (SPC cancers or metastatic lesions by recurrence). Second, the SCs might be different according to histological subtype of melanoma, but we analyzed the risk for all melanoma types combined. Acral melanomas are more common among Asians including Koreans.[26,27] Therefore, the results of this study might be more attributable to acral melanomas. In addition, expenditure data does not provide breakdown of the cost and evaluate the cost for the treatment of melanoma and SCs to assess the burden of disease between primary melanoma and second cancers. Further studies should be conducted to determine the cost details for the treatment of melanoma.

In conclusion, this study quantified, based on a nationwide database, the proportion and risk of SCs among Korean patients diagnosed with melanoma. The findings demonstrate a higher risk of SCs, particularly for those patients with more comorbidities. SCs also increase medical costs and the risk of mortality, suggesting pre-emptive monitoring of the risk of SCs and preventative measures to lower this risk as much as possible.

ACKNOWLEDGMENTS

We thank the National Health Insurance Service for providing the data for this study (NHIS-2019-1-011). We also thank the Korea National Research Foundation for supporting this research (NRF-2018R1D1A3B07047356).

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the institutional review board of the Kyungpook National University (approval number: KNU-2020-0080). The database used in this study was retrospectively established in an anonymous format, and the informed consent requirement was waived.

DATA AVAILABILITY STATEMENT

Data are available from the Korean National Health Insurance Sharing Service (KNHISS). KNHISS does not allow researchers to provide data personally or share publicly and therefore, the authors cannot provide the data. However, all researchers can access the data after receiving approval from the KNHISS at the website of NHISS (https://nhiss.nhis.or.kr) in the same manner as the authors upon completing the online data request form.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Jin-Won Kwon https://orcid.org/0000-0003-3467-7805

REFERENCES

1. Lens MB, Dawes M. Global perspectives of contemporary epidemiological trends of cutaneous malignant melanoma. *Br J Dermatol*. 2004;150(2):179-185.
2. Harvey VM. Melanoma in US Hispanics: recommended strategies to reduce disparities in outcomes. *Cutis*. 2018;101(4):243-246.
3. Lyth J, Falk M, Maroti M, et al. Prognostic risk factors of first recurrence in patients with primary stages I-II cutaneous malignant melanoma—from the population-based Swedish melanoma register. *J Eur Acad Dermatol Venereol*. 2017;31(9):1468-1474.
4. Zhang H, Bermejo JL, Sundquist J, et al. Modification of second cancer risk after malignant melanoma by parental history of cancer. *Br J Cancer*. 2008;99(3):536-538.
5. Bradford PT, Freedman DM, Goldstein AM, et al. Increased risk of second primary cancers after a diagnosis of melanoma. *Arch Dermatol*. 2010;146(3):265-272.
6. Caini S, Boniol M, Botteri E, et al. The risk of developing a second primary cancer in melanoma patients: a comprehensive review of the literature and meta-analysis. *J Dermatol Sci*. 2014;75(1):3-9.
7. Spanogle JP, Clarke CA, Aroner S, et al. Risk of second primary malignancies following cutaneous melanoma diagnosis: a population-based study. *J Am Acad Dermatol*. 2010;62(5):757-767.
8. Hwang CY, Chen YJ, Lin MW, et al. Elevated risk of second primary cancer in patients with cutaneous malignant melanoma: a nationwide cohort study in Taiwan. *J Dermatol Sci*. 2010;60(3):167-172.
9. Zheng G, Chattopadhyay S, Sundquist K, et al. Second primary cancers in melanoma patients critically shorten survival. *Clin Epidemiol*. 2020;12:105-112.
10. Bae SH, Seon HJ, Choi YD, et al. Other primary systemic cancers in patients with melanoma: analysis of balanced acral and nonacral melanomas. *J Am Acad Dermatol*. 2016;74(2):333-340.
11. National Health Insurance Sharing Serivce. Customized DB. https://nhiss.nhis.or.kr/bd/ab/bdaba032eng.do. Accessed: March 1, 2020.
12. Crocetti E, Carli P. Risk of second primary cancers, other than melanoma, in an Italian population-based cohort of cutaneous malignant melanoma patients. *Eur J Cancer Prev*. 2004;13(1):33-37.
13. Lin DY, Feuer EJ, Etzioni R, et al. Estimating medical costs from incomplete follow-up data. *Biometrics*. 1997;53(2):419-434.
14. Lang K, Lines LM, Lee DW, et al. Lifetime and treatment-phase costs associated with colorectal cancer: evidence from SEER-Medicare data. *Clin Gastroenterol Hepatol*. 2009;7(2):198-204.
15. Vakharia PP, Kelm RC, Orrell KA, et al. Risks for noncutaneous second primary malignancy in cutaneous malignant melanoma survivors: an analysis of data from the Surveillance, Epidemiology, and End Results (SEER) program. *Int J Dermatol*. 2020;59(4):463-468.

16. Kim JE, Chung BY, Sim CY, et al. Clinicopathologic features and prognostic factors of primary cutaneous melanoma: a multicenter study in Korea. *J Korean Med Sci*. 2019;34(16):e126.
17. Cronin KA, Lake AJ, Scott S, et al. Annual Report to the nation on the status of cancer, part I: national cancer statistics. *Cancer*. 2018;124(13):2785-2800.
18. Jung KW, Won YJ, Kong HJ, et al. Cancer statistics in korea: incidence, mortality, survival, and prevalence in 2016. *Cancer Res Treat*. 2019;51(2):417-430.
19. Goldstein AM, Landi MT, Tsang S, et al. Association of MC1R variants and risk of melanoma in melanoma-prone families with CDKN2A mutations. *Cancer Epidemiol Biomarkers Prev*. 2005;14(9):2208-2212.
20. Chattopadhyay S, Hemminki A, Forsti A, et al. Familial risks and mortality in second primary cancers in melanoma. *JNCI Cancer Spectr*. 2018;2(4):pky068.
21. Wassberg C, Thorn M, Yuen J, et al. Second primary cancers in patients with cutaneous malignant melanoma: a population-based study in Sweden. *Br J Cancer*. 1996;73(2):255-259.
22. Zheng G, Chattopadhyay S, Sundquist K, et al. Association between tumor characteristics and second primary cancers with cutaneous melanoma survival: a nationwide cohort study. *Pigment Cell Melanoma Res*. 2020;33(4):625-632.
23. Donin N, Filson C, Drakaki A, et al. Risk of second primary malignancies among cancer survivors in the United States, 1992 through 2008. *Cancer*. 2016;122(19):3075-3086.
24. Rasmussen LA, Jensen H, Virgilsen LF, et al. Time from incident primary cancer until recurrence or second primary cancer: risk factors and impact in general practice. *Eur J Cancer Care (Engl)*. 2019;28(5):e13123.
25. Goldsbury DE, Yap S, Weber MF, et al. Health services costs for cancer care in Australia: estimates from the 45 and Up Study. *PLoS One*. 2018;13(7):e0201552.
26. Lee HY, Chay WY, Tang MB, et al. Melanoma: differences between Asian and Caucasian patients. *Ann Acad Med Singapore*. 2012;41(1):17-20.
27. Chang JW. Acral melanoma: a unique disease in Asia. *JAMA Dermatol*. 2013;149(11):1272-1273.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Park H-Y, Yang H-J, Jeon SM, Lee IH, Kwon J-W. Survival and medical costs of melanoma patients with subsequent cancer diagnoses: a South Korean population-based retrospective cohort study. *Asia-Pac J Clin Oncol*. 2022;18:e211–e219.
https://doi.org/10.1111/ajco.13582