



Second primary malignancies among cancer patients

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Background: Rate of second primary malignancies (SPM) is steadily increasing over the last decades. New therapies, early diagnostic markers, screening tests for a larger number of individuals contribute to the increase prevalence of SPM. In the current study, we try to described the demographic composition of SPM victims, distribution of primary sites, and the impact of related factors on prognosis.

Methods: We conducted a retrospective study identifying patients over the age of 18 who were diagnosed with SPM from the 16 most common cancer sites between 2000 and 2013 from Surveillance, Epidemiology, and End Results data. Cox proportional hazards regression was used to analyze the relationship between different factors associated to the prognosis of SPM. Standard incidence rate of multiple primary (MP-SIR) was also calculated.

Results: A total of 303,753 patients were diagnosis with SPM and 76,168 of whom (25.08%) were included in our analytic cohort. Patients with prostate cancer was vulnerable to SPM, accounting for 34.59%, and SPM was prone to occur in lung and bronchus, accounting for 24.90%. The heat map shows that esophagus cancer survivors have the highest risk of developing stomachache tumors (SIR =5.08). The result of Cox regression suggests that a history of liver was associated with the shortest survival time (HR =1.64, 95% CI, 1.54–1.75, P<0.001).

Conclusions: With the advancement of medical standards, the survival time of cancer patients is prolonged, but the occurrence of SPM is also increasing, and the prognosis is not optimistic. More attention needs to be invested in the prevention and treatment of SPM.

Keywords: Second primary malignancy (SPM); SEER; epidemiological investigation; standard incidence rate (SIR); median survival time

Submitted Feb 29, 2020. Accepted for publication Apr 16, 2020.

doi: 10.21037/atm-20-2059

View this article at: <http://dx.doi.org/10.21037/atm-20-2059>

Introduction

Cancer has become the leading cause of death. In 2016, the death toll from cancer accounted for 21.8% (1). Fortunately, with the improvement of the comprehensive level of diagnosis and treatment, cancer-related mortality has declined by about 1.5% annually in both men and women, 2006–2015 (2), besides, 5-year relative survival for both sex about 67.1%, 2009–2015 (3). Cancer survivors have also increased dramatically as cancer survival rates have increased. It is reported that an estimated 13.7 million Americans with a history of cancer were alive on January 1, 2012 (4,5), However, by 2017 this figure has risen to 15.5 and that number is expected to increase to 20 million by the year 2024 (6).

Second primary malignancy (SPM) is not a phenomenon of cancer recurrence or metastasis, but it is suffering from another cancer [different from first primary malignancy (FPM)] (7,8). The prolongation of the survival time of patients and the increase in the number of survivors have led to a significant increase in the chances of SPM in this group (9), which also provides an opportunity for us to study SPM. Yang *et al.* reported that SPMs are common in cancer patients with an overall cumulative incidence of 14% at 25 years of follow-up (10). Different FPMs have different characteristics and the probability of SPM reported varies from 5.5% to 16% (9,11,12).

Most of the previous studies have observed the risk of SPM in specific cancers and each study has its own focus and there were no uniform evaluation criteria. Nicholas selected SPM cases of 10 common cancers between 1992 to 2008 and found that 1 in 12 patients were prone to SPM (13). But after ten years, the medical level and social environment have undergone tremendous changes. Updated cognition, advancing assessment, effective measures are needed. Therefore, we selected 16 common cancer cases from 2000 to 2016 from the SEER database to analyze the spectrum of SPM prevalence and studied the impact of common prognostic factors on survival time.

Methods

Study population selection

Data was acquired using the SEER database, which comprises 18 cancer registries and covers approximately 30% of U.S population. The SEER database was accessed via SEER*Stat software (Version 8.3.5; National Cancer

Institute Cancer Statistics Branch).

We identified all patients diagnosed with FPM among the 16 cancer sites with the Site Recode B ICD-O-3/WHO 2008 Definition [including prostate, female breast, lung and bronchus, brain and cranial nervous system (brain, CNS), thyroid, esophagus, stomach, liver, pancreas, colorectal, bladder, kidney, corpus uteri, cervix uteri, ovary and non-Hodgkin lymphoma (NHL)]. SPM also uses Site Recode B ICD-O-3/WHO 2008 Definition, a total of 16 sites of tumors are included in the events, including prostate, female breast, lung and bronchus, brain and cranial nervous system (brain, CNS), thyroid, esophagus, stomach, liver, pancreas, colorectal, bladder, kidney, female genital system, melanoma of skin, leukemia and non-Hodgkin lymphoma (NHL). Among them, colorectal includes ascending colon, descending colon, transverse colon, sigmoid colon, hepatic flexure, splenic flexure, rectosigmoid junction and rectum. Female genital system refers to corpus uteri, cervix uteri, ovary, uteri, not of special (NOS), vagina and vulva. Acute/chronic myeloid leukemia, monocytic leukemia and lymphocytic leukemia are outlined as leukemia. NHL includes nodal and extra-nodal NHL.

Although data were available through 2016, we limited the current study cohort to patients diagnosed between 2000 and 2013 to ensure 3 years of follow-up after a cancer diagnosis. Similar to previously published studies (13), we excluded patients with SPM diagnosed within one year or at the same site to avoid misidentifying metastatic malignancies as SPM. Cases younger than 18 years old are also excluded.

Patient demographics included age in years (18–34, 35–49, 50–64, 65–79, and 80+), race (white, black, American Indian, Alaska Native, Asian/Pacific Islander and unknown), sex (male or female) and year of diagnosis (2000–2003, 2004–2007, 2008–2010 and 2011–2013). The time interval between the time of diagnosis of SPM and FPM is defined as Month Since Index, and it was divided into 13–26, 27–44, 45–71, 72+ months by using the X-tile program (Yale University, New Haven, Connecticut, USA; *Figure S1*). Tumor characteristics included grade (Grade I, well differentiated; Grade II, moderately differentiated; Grade III, poorly differentiated; Grade IV, undifferentiated and unknown) and stage (in situ, localized, regional, distant and unstaged/unknown). SEER merged ZIP code-level data for educational level and annual household income from the 2008 US Census data. Individual-level data were imputed from the percentage of patients holding a Bachelor's degree

and the median annual household income in each patient's ZIP code, which was then stratified into quartiles (14).

Statistical analysis

We provided an overview of the spectral distribution of FPM and SPM and showed a more specific and detailed information about the site of the SPM distribution. Data on primary site of FPM, primary site of SPM, age groups, gender, race, year of diagnosis of SPM, grade, stage, Month Since Index, bachelor's degree, median household income were incorporated in the multivariate Cox proportional hazards model for overall survival. Hazard ratios (HRs) of each variable with corresponding 95% confidence intervals (CI) were calculated stratified by sex. We also calculated the distribution of causes of death (COD) in the analysis cohort and compared the proportion of COD in primary or secondary malignancies. Median survival time was estimated using Kaplan-Meier (K-M) method and the differences between the survival curves were compared using the log-rank test.

Standard incidence rate of multiple primary (MP-SIR), which is also known as the relative risk, is a relative measure of the strength of association between two cancers. It is calculated by dividing the observed number of SPM cases by the expected number [observed/expected (O/E) ratio] based on general population rates. Risks were considered significant when corresponding 95% confidence interval did not include the null value (15,16).

All statistical analyses were finished in the R software (version 3.6.0; <http://www.r-project.org/>). In all statistical analyses, a P value of <0.05 was considered significant.

Results

We identified 303,753 patients with SPM diagnosed between 2000 and 2013, among whom 76,168 patients (25.08%) meet our inclusion criteria, after excluding case of developing SPM within a year or at the same site as FPM or patients under the age of 18 (*Figure 1*). In the analytic cohort, the majority of patients (81.21%) were aged >65 years. And of those patients with SPM, 83.80% were white; 63.48% were male; and 74.67% were diagnosis after 2008. 41.32% of patients were diagnosis as Grade II, moderately differentiated or Grade III, poorly differentiated. Total of 30.22% patients are at stage of *in situ*/localized and 30.78% were distant metastasis. The specific demographic data of patients, the

characteristics of tumors and other related information were showed in *Table 1*.

The composition of the analytic cohort

The specific value of each FPM in this study and the cohort is visually shown in *Figure 2A*. Obviously, the number of patients with prostate cancer, female breast cancer, or colorectal cancer respectively ranks in the top three. Similarly, the Sector Graph in *Figure 2B* shows the proportion of FPM in the analytic cohort, and prostate cancer survivors have the largest number (34.59%) of cases of SPM. Classified according to where the events occur, *Figure 2C* shows the common location of 16 SPMs, with lung and bronchus accounting for the largest proportion (24.90%). *Figure 2D* reveal the ranking which is based on the proportion of each site of the FPM or SPM groups. The ranking shows the different performance of the same location in FPM and SPM. For example, prostate cancer ranks No.1 in FPM, but it ranks No.6 in SPM, besides, lung and bronchus are ranked No.5 in FPM, but it is the most prone to SPM (it ranks No. 1). It is worth mentioning that although there are few cases of pancreas cancer (ranked No. 15), it is the fourth site that is prone to SPM.

Table 2 shows the detail distribution information of SPM in 16 cancers. *Figure S2* shows the results in the form of Sector Graph to make the results more intuitive. As the picture shows, nearly one-fourth of the SPM of each tumor is lung and bronchus, and different tumors have different distribution preferences. Among bladder cancer survivors, lung and bronchus disease was particularly common, representing 31.82% of all SPM in this group. Breast cancer was especially common in ovary cancer, corpus uteri cancer and cervix uteri cancer survivors at 19.95%, 14.51% and 8.14%, respectively.

Follow-up characteristics of the analytic cohort

Figure 3 shows the Month Since Index (which is also recognized as month at events), the median survival time and the time of follow-up. Among them, liver cancer has the shortest time interval for developing SPM, which is usually 37.09 months. The median survival time is usually about 1 year. The prognosis of female breast cancer survivors is the worst with the median survival time is only 9 months. The mean follow-up of the entire cohort was 5.35 years (standard deviation, 0.42 years). The detailed magnitude

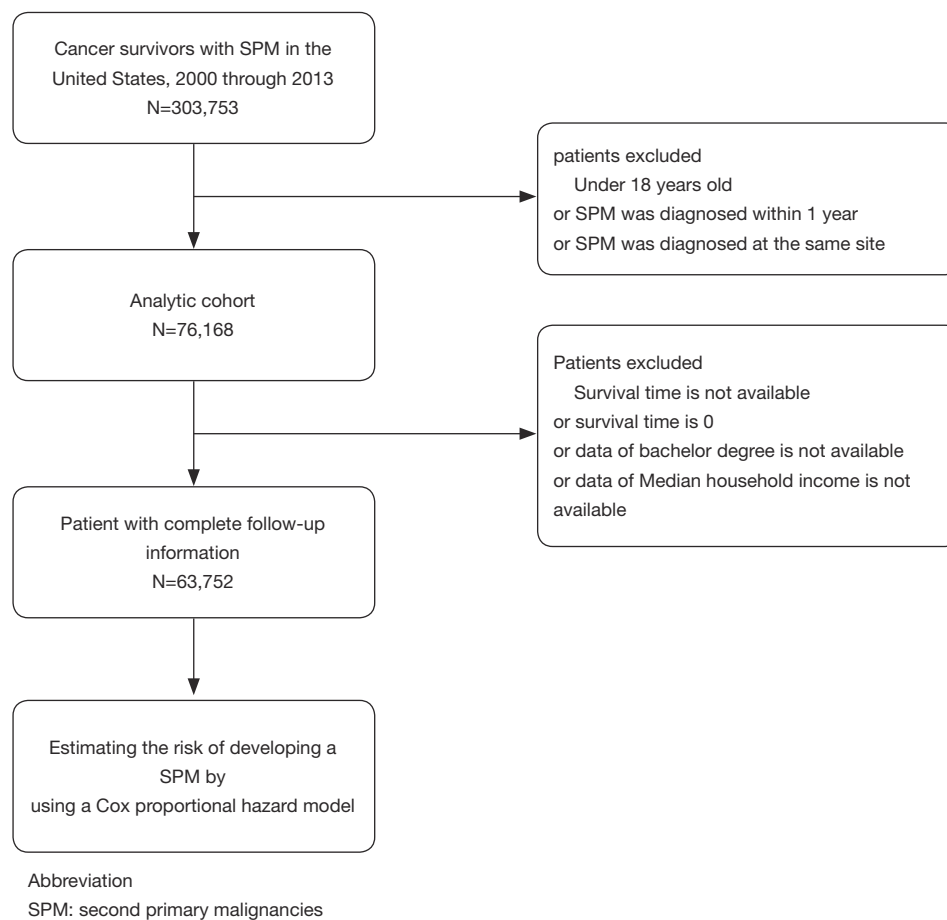


Figure 1 Flow diagram of the results of search strategy.

with standard deviation value were displayed in *Table S1*.

SPM risk assessment

Multivariate Cox proportional hazards model for overall survival was performed to estimate the impact of various factors on survival. HRs of each variable with corresponding 95% CI were displayed in the *Table 3*. The diagnosis of Liver Neoplasms is an obvious risk factor for prognosis (HR =1.64, 95% CI, 1.54–1.75, $P < 0.001$; patients with bladder neoplasms were recognized as reference), the results of both men and women also confirm this. Interestingly, with the progress of the times, the prognosis of patients with secondary cancer is improving year by year (2011–2013: HR =0.20, 95% CI, 0.15–0.25, $P < 0.001$; patients diagnosed at 2000–2003 were recognized as reference).

The heat map can simply aggregate a large amount of data, and use a progressive color band to visually show

the density or frequency of spatial data. The final result is generally better than the direct display of discrete points. In our heat map, where the data is large, the area is red and the small amount data is blue. *Figure 4A* shows the raw data of the SPM case count. The MP-SIR data obtained from the SEER database is shown in *Figure 4B*. We found that the risk of being infected with gastric cancer after esophageal cancer is highest (SIR =5.08). The normalized SIR data is shown in *Figure 4C*, which can more specifically demonstrate the risk of SPM in different parts of the same cancer, as well as highlighting the potential link between the diseases and primary site.

Survival analysis of the analysis cohort

In addition, we calculated the probability that the COD of 16 cancers is FPM or SPM (*Figure 5*), the data shows that the probability of esophageal cancer dying from FPM is

Table 1 Patient demographics of the analytic cohort

Demographics	Male, n (%)	Female, n (%)	Total, n (%)
Age group, yrs			
18–34	32 (0.05)	82 (0.13)	114 (0.18)
35–49	358 (0.56)	927 (1.45)	1,285 (2.02)
50–64	5,773 (9.06)	4,813 (7.55)	10,586 (16.60)
65–79	22,022 (34.54)	10,342 (16.22)	32,364 (50.77)
80+	12,284 (19.27)	7,119 (11.17)	19,403 (30.44)
Sex			
Female	0 (0.00)	23,283 (36.52)	23,283 (36.52)
Male	40,469 (63.48)	(0.00)	40,469 (63.48)
Race			
White	33,737 (52.92)	19,687 (30.88)	53,424 (83.80)
Black	4,787 (7.51)	2,362 (3.70)	7,149 (11.21)
American Indian/Alaska Native	119 (0.19)	79 (0.12)	198 (0.31)
Asian or Pacific Islander	1,820 (2.85)	1,152 (1.81)	2,972 (4.66)
Unknown	6 (0.01)	3 (0.00)	9 (0.01)
Year of diagnosis of events			
2000–2003	1,311 (2.06)	722 (1.13)	2,033 (3.19)
2004–2007	9,007 (14.13)	5,110 (8.02)	14,117 (22.14)
2008–2010	12,461 (19.55)	7,129 (11.18)	19,590 (30.73)
2011–2013	17,690 (27.75)	10,322 (16.19)	28,012 (43.94)
Month Since Index, months			
13–26	10,308 (16.17)	6,108 (9.58)	16,416 (25.75)
27–44	9,853 (15.46)	5,635 (8.84)	15,488 (24.29)
45–72	10,206 (16.01)	5,812 (9.12)	16,018 (25.13)
72+	10,102 (15.85)	5,728 (8.98)	15,830 (24.83)
Primary site of first cancer			
Prostate	22,163 (34.76)	0 (0.00)	22,163 (34.76)
Female breast	0 (0.00)	9,924 (15.57)	9,924 (15.57)
Colorectal	5,130 (8.05)	3,586 (5.62)	8,716 (13.67)
Bladder	5,124 (8.04)	1,142 (1.79)	6,266 (9.83)
Lung and bronchus	2,315 (3.63)	1,572 (2.47)	3,887 (6.10)
NHL	2,285 (3.58)	1,544 (2.42)	3,829 (6.01)
Kidney	1,684 (2.64)	802 (1.26)	2,486 (3.90)
Corpus uteri	0 (0.00)	2,110 (3.31)	2,110 (3.31)
Thyroid	352 (0.55)	599 (0.94)	951 (1.49)

Table 1 (continued)

Table 1 (continued)

Demographics	Male, n (%)	Female, n (%)	Total, n (%)
Stomach	479 (0.75)	263 (0.41)	742 (1.16)
Ovary	0 (0.00)	690 (1.08)	690 (1.08)
Cervix uteri	0 (0.00)	661 (1.04)	661 (1.04)
Liver	269 (0.42)	81 (0.13)	350 (0.55)
Esophagus	372 (0.58)	95 (0.15)	467 (0.73)
Pancreas	167 (0.26)	133 (0.21)	300 (0.47)
Brain, CNS	129 (0.20)	81 (0.13)	210 (0.33)
Site of events			
Lung and bronchus	10,312 (16.18)	5,680 (8.91)	15,992 (25.08)
Colorectal	3,089 (4.85)	1,760 (2.76)	4,849 (7.61)
Bladder	3,283 (5.15)	781 (1.23)	4,064 (6.37)
Pancreas	2,193 (3.44)	1,465 (2.30)	3,658 (5.74)
Prostate	3,158 (4.95)	0 (0.00)	3,158 (4.95)
Leukemia	1,627 (2.55)	1,067 (1.67)	2,694 (4.23)
NHL	1,699 (2.67)	863 (1.35)	2,562 (4.02)
Female genital system	0 (0.00)	2,458 (3.86)	2,458 (3.86)
Stomach	1,357 (2.13)	621 (0.97)	1,978 (3.10)
Female breast	0 (0.00)	1,987 (3.12)	1,987 (3.12)
Melanoma of skin	1,364 (2.14)	477 (0.75)	1,841 (2.89)
Kidney	1,187 (1.86)	491 (0.77)	1,678 (2.63)
Liver	1,011 (1.59)	292 (0.46)	1,303 (2.04)
Esophagus	1,145 (1.80)	242 (0.38)	1,387 (2.18)
Brain, CNS	771 (1.21)	393 (0.62)	1,164 (1.83)
Thyroid	182 (0.29)	281 (0.44)	463 (0.73)
Other	8,091 (12.69)	4,425 (6.94)	12,516 (19.63)
Stage			
<i>In situ</i>	1,361 (2.13)	275 (0.43)	1,636 (2.57)
Localized	11,458 (17.97)	6,168 (9.67)	17,626 (27.65)
Regional	7,578 (11.89)	4,942 (7.75)	12,520 (19.64)
Distant	12,602 (19.77)	7,022 (11.01)	19,624 (30.78)
Unknown/unstaged	7,470 (11.72)	4,876 (7.65)	12,346 (19.37)
Grade			
Grade I	1,812 (2.84)	1,424 (2.23)	3,236 (5.08)
Grade II	8,374 (13.14)	4,415 (6.93)	12,789 (20.06)
Grade III	8,577 (13.45)	4,974 (7.80)	13,551 (21.26)

Table 1 (continued)

Table 1 (continued)

Demographics	Male, n (%)	Female, n (%)	Total, n (%)
Grade IV	2,352 (3.69)	1,302 (2.04)	3,654 (5.73)
Unknown	19,354 (30.36)	11,168 (17.52)	30,522 (47.88)
% , bachelors degree, quartile			
1st	10,768 (16.89)	5,838 (9.16)	16,606 (26.05)
2nd	11,726 (18.39)	6,816 (10.69)	18,542 (29.08)
3rd	7,929 (12.44)	4,754 (7.46)	12,683 (19.89)
4th	10,046 (15.76)	5,875 (9.22)	15,921 (24.97)
Median household income, quartile			
1st	9,244 (14.50)	7,004 (10.99)	16,248 (25.49)
2nd	9,234 (14.48)	6,465 (10.14)	15,699 (24.63)
3rd	10,679 (16.75)	5,534 (8.68)	16,213 (25.43)
4th	11,312 (17.74)	4,280 (6.71)	15,592 (24.46)

5.73%, but the probability of dying from SPM is as high as 72.62%. K-M method was used to find the difference between different 16 FPMs and 16 SPMs and K-M survival curves were made separately (*Figure S3*), but due to the excessive amount of data, curves overlapped and intersected and no obvious conclusions can be drawn.

Discussion

The era of big data means that the formulation of clinical decisions and the implementation of health care policies require evidence-based medicine support, especially in the field of cancer research. We used the SPM data of the SEER database to study the following three aspects: (I) compare rate and type of SPM in 16 common FPMs. (II) Investigate the time of occurrence and median survival time of SPM. (III) Analysis of the risk of SPM in 16 common cancers and made a preliminary comparison.

Nicholas pointed out that the most common SPM is lung cancer (13), which is consistent with our findings, indicating that after ten years, lung cancer remains the difficult problem in the SPM research field. Nicholas also said that the second primary cancer caused at least 50% of all of our malignant tumor survivors (13). This conclusion is still true today. The probability of thyroid cancer dying from SPM has risen from 63% five years ago to 72.62%, and lung cancer has dropped from 36% to 26.84%. This may be related to the increased sensitivity to radiation of

cells in younger patients and the longer life-span in which an SPM may be diagnosed (7,8,12).

Lifestyle, environment, host factors and interactions and other influences are recognized as multiple primary cancers etiologic factors (9). In particular, radiation therapy is thought to play an important role in the pathogenesis of SPM and the risk of radiation-related malignancies has been investigated (17-19). Among the survivors of several primary malignancies, the most obvious are Hodgkin's lymphoma, as well as testes, breast, cervical and prostate cancers. Of course, some scholars have proposed different opinions that even if radiotherapy increases the radiation dose of adjacent organs, the second cancer risks from radiotherapy in adulthood are relatively small, especially when compared with the treatment benefits (20). Kier *et al.* draws similar conclusions in a retrospective study of 5,190 patients with germ cell cancer (21).

We found that there is a systematic connection between the recurrence position and the primary position. For example, patients with primary gynecologic tumors, SPM also prone to occur in the female genital system or female breast. Another interesting phenomenon is that gastric cancer accounts for 9.19% of patients with SPM in esophageal cancer. Similarly, esophageal cancer accounts for 5.11% of gastric cancer patients with SPM (higher than normal level), which is consistent with the result of SIR (SIR =5.08) and COX analysis (HR =1.12, 95% CI, 1.02-1.21, P=0.021). There may be some association between the

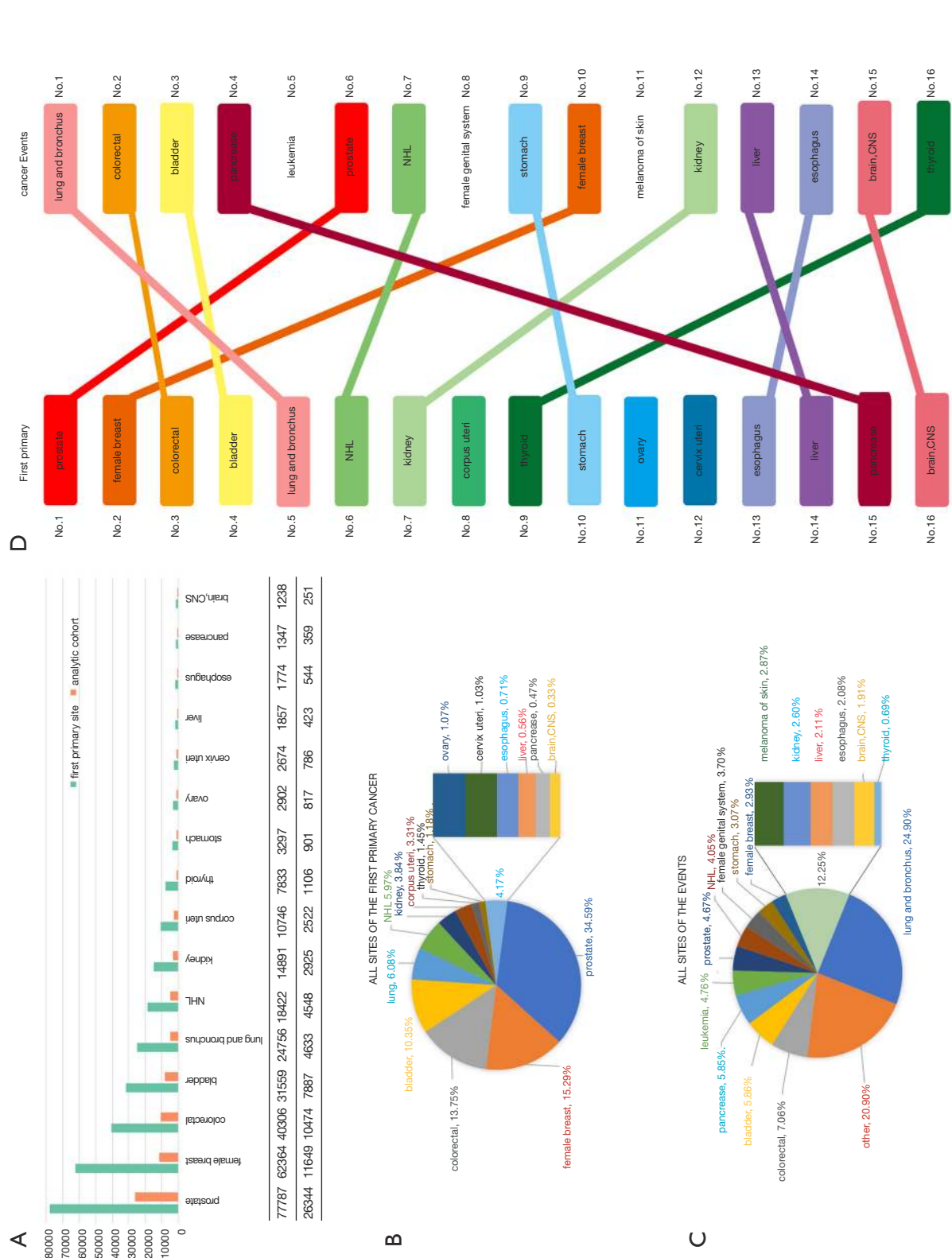


Figure 2 The specific location composition and difference of FPM and SPM. (A) Comparison of the number of all SPM patients and the number of people included stratified by the location of the FPM. (B) Distribution of patients in the analysis cohort according to the primary sites of FPM. (C) Distribution of patients in the analysis cohort according to the primary sites of SPM/events. (D) FPM and SPM/events are ranked by number of cases. FPM, first primary malignancy; SPM, second primary malignancy.

Table 2 The detail distribution information of SPM in 16 cancers

SPM	FPM, n (%)																
	Lung and bronchus	Female breast	Prostate	Colorectal	Stomach	Liver	Esophagus	Cervix uteri	Thyroid	Bladder	NHL	Pancreas	Kidney	Corpus uteri	Brain, CNS	Ovary	Total
Lung and bronchus	0 (0.00)	3,158 (27.11)	7,254 (27.54)	2,706 (25.84)	157 (17.43)	100 (23.64)	132 (24.26)	229 (29.13)	255 (23.06)	2,510 (31.82)	1,016 (22.34)	93 (25.91)	671 (22.94)	526 (20.86)	44 (17.53)	116 (14.2)	18,967 (24.9)
Female breast	418 (9.02)	0 (0.00)	0 (0.00)	591 (5.64)	44 (4.88)	13 (3.07)	13 (2.39)	64 (8.14)	101 (9.13)	125 (1.58)	183 (4.02)	21 (5.85)	111 (3.79)	366 (14.51)	16 (6.37)	163 (19.95)	2,229 (2.93)
Colorectal	431 (9.3)	967 (8.3)	2,358 (8.95)	0 (0.00)	84 (9.32)	17 (4.02)	29 (5.33)	57 (7.25)	66 (5.97)	500 (6.34)	303 (6.66)	33 (9.19)	197 (6.74)	242 (9.6)	20 (7.97)	70 (8.57)	5,374 (7.06)
Melanoma of skin	122 (2.63)	249 (2.14)	961 (3.65)	267 (2.55)	21 (2.33)	11 (2.6)	6 (1.1)	7 (0.89)	27 (2.44)	190 (2.41)	156 (3.43)	12 (3.34)	77 (2.63)	51 (2.02)	14 (5.58)	15 (1.84)	2,186 (2.87)
bladder	444 (9.58)	286 (2.46)	2,326 (8.83)	562 (5.37)	60 (6.66)	22 (5.2)	34 (6.25)	44 (5.6)	20 (1.81)	0 (0.00)	217 (4.77)	15 (4.18)	320 (10.94)	83 (3.29)	11 (4.38)	21 (2.57)	4,465 (5.86)
NHL	205 (4.42)	521 (4.47)	1,291 (4.9)	419 (4)	34 (3.77)	41 (9.69)	16 (2.94)	12 (1.53)	40 (3.62)	269 (3.41)	0 (0.00)	14 (3.9)	109 (3.73)	86 (3.41)	8 (3.19)	20 (2.45)	3,085 (4.05)
Thyroid	57 (1.23)	123 (1.06)	93 (0.35)	80 (0.76)	7 (0.78)	2 (0.47)	4 (0.74)	10 (1.27)	0 (0.00)	23 (0.29)	32 (0.7)	8 (2.23)	33 (1.13)	33 (1.31)	4 (1.59)	13 (1.59)	522 (0.69)
Kidney	165 (3.56)	228 (1.96)	858 (3.26)	259 (2.47)	33 (3.66)	9 (2.13)	12 (2.21)	13 (1.65)	45 (4.07)	178 (2.26)	94 (2.07)	10 (2.79)	0 (0.00)	54 (2.14)	7 (2.79)	17 (2.08)	1,982 (2.6)
Prostate	520 (11.22)	0 (0.00)	0 (0.00)	956 (9.13)	87 (9.66)	40 (9.46)	60 (11.03)	0 (0.00)	48 (4.34)	1,137 (14.42)	328 (7.21)	35 (9.75)	327 (11.18)	0 (0.00)	18 (7.17)	0 (0.00)	3,556 (4.67)
Leukemia	267 (5.76)	700 (6.01)	1,130 (4.29)	361 (3.45)	32 (3.55)	12 (2.84)	17 (3.13)	24 (3.05)	55 (4.97)	226 (2.87)	496 (10.91)	12 (3.34)	98 (3.35)	109 (4.32)	16 (6.37)	69 (8.45)	3,624 (4.76)
Pancreas	141 (3.04)	891 (7.65)	1,744 (6.62)	614 (5.86)	66 (7.33)	17 (4.02)	22 (4.04)	22 (2.8)	61 (5.52)	338 (4.29)	176 (3.87)	0 (0.00)	161 (5.5)	143 (5.67)	14 (5.58)	46 (5.63)	4,456 (5.85)
Liver	99 (2.14)	148 (1.27)	636 (2.41)	205 (1.96)	25 (2.77)	0 (0.00)	14 (2.57)	14 (1.78)	29 (2.62)	183 (2.32)	119 (2.62)	5 (1.39)	96 (3.28)	24 (0.95)	1 (0.4)	9 (1.1)	1,607 (2.11)
Female genital system	140 (3.02)	1446 (12.41)	0 (0.00)	432 (4.12)	36 (4.0)	9 (2.13)	7 (1.29)	116 (14.76)	68 (6.15)	101 (1.28)	153 (3.36)	13 (3.62)	62 (2.12)	156 (6.19)	10 (3.98)	69 (8.45)	2,818 (3.7)
Brain, CNS	72 (1.55)	211 (1.81)	622 (2.36)	170 (1.62)	7 (0.78)	4 (0.95)	2 (0.37)	6 (0.76)	38 (3.44)	83 (1.05)	95 (2.09)	4 (1.11)	65 (2.22)	60 (2.38)	0 (0.00)	15 (1.84)	1,454 (1.91)
Esophagus	167 (3.6)	121 (1.04)	721 (2.74)	202 (1.93)	46 (5.11)	7 (1.65)	0 (0.00)	8 (1.02)	10 (0.9)	143 (1.81)	70 (1.54)	4 (1.11)	47 (1.61)	25 (0.99)	4 (1.59)	6 (0.73)	1,581 (2.08)
Stomach	177 (3.82)	346 (2.97)	887 (3.37)	346 (3.3)	0 (0.00)	19 (4.49)	50 (9.19)	18 (2.29)	29 (2.62)	177 (2.24)	132 (2.9)	12 (3.34)	70 (2.39)	50 (1.98)	4 (1.59)	23 (2.82)	2,340 (3.07)
Other	1,208 (26.07)	2,254 (19.35)	5,463 (20.74)	2,304 (22.0)	162 (17.98)	100 (23.64)	126 (23.16)	141 (18.07)	214 (19.35)	1,704 (21.61)	978 (21.5)	68 (18.94)	481 (16.44)	514 (20.38)	60 (23.9)	145 (17.75)	15,922 (20.90)
Total	4,633 (6.08)	11,649 (15.29)	26,344 (34.59)	10,474 (13.75)	901 (1.18)	423 (0.56)	544 (0.71)	785 (1.03)	1,106 (1.45)	7,887 (10.35)	4,548 (5.97)	359 (0.47)	2,925 (3.84)	2,522 (3.31)	251 (0.33)	817 (1.07)	76,168 (100.0)

FPM, first primary malignancy; SPM, second primary malignancy.

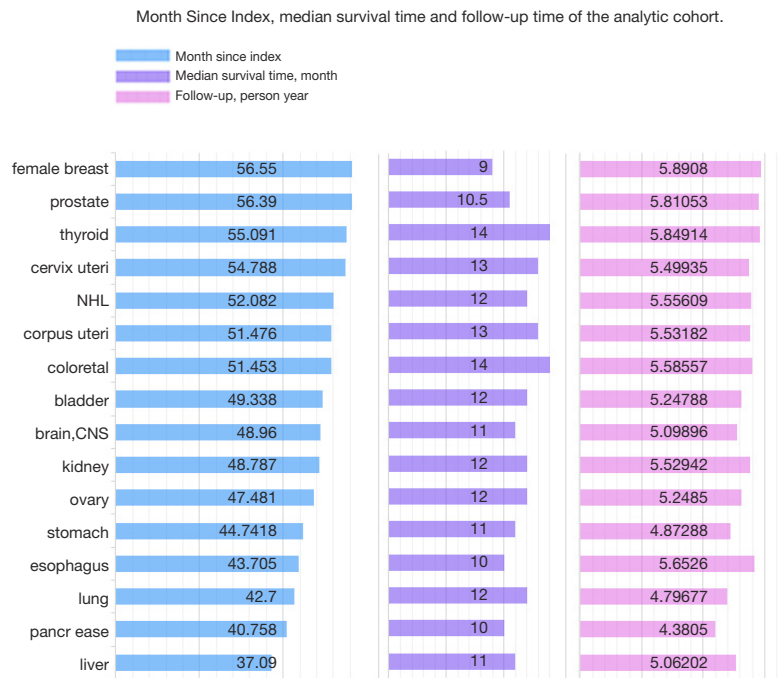


Figure 3 Month Since Index, median survival time and follow-up time of the analytic cohort.

Table 3 Multivariate Cox proportional hazards model for second primary malignancy

Variables	Subtype	All		Male		Female	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Primary site of FPM	Bladder	ref	ref	ref	ref	ref	ref
	Brain, CNS	1.17 (1.03–1.31)	0.029	1.30 (1.13–1.48)	0.003	0.97 (0.75–1.21)	0.810
	Cervix uteri	1.13 (1.04–1.21)	0.006	–	–	1.13 (1.04–1.23)	0.017
	Colorectal	0.96 (0.93–1.00)	0.029	0.97 (0.93–1.01)	0.193	0.94 (0.88–1.00)	0.070
	Corpus uteri	0.98 (0.93–1.04)	0.537	–	–	0.97 (0.90–1.05)	0.404
	Esophagus	1.12 (1.02–1.21)	0.021	1.07 (0.96–1.17)	0.238	1.38 (1.18–1.60)	0.003
	Female breast	0.92 (0.88–0.96)	<0.001	–	–	0.91 (0.85–0.97)	0.004
	Kidney	0.97 (0.93–1.02)	0.263	0.97 (0.91–1.02)	0.239	0.97 (0.88–1.07)	0.503
	Liver	1.64 (1.54–1.75)	<0.001	1.67 (1.55–1.80)	<0.001	1.58 (1.36–1.82)	<0.001
	Lung and bronchus	1.14 (1.1.0–1.18)	<0.001	1.15 (1.10–1.20)	<0.001	1.11 (1.04–1.19)	0.011
	NHL	1.04 (1.00–1.08)	0.059	1.04 (0.99–1.09)	0.172	1.04 (0.97–1.12)	0.297
	Ovary	1.09 (1.00–1.17)	0.047	–	–	1.06 (0.97–1.16)	0.204
	Pancreas	1.36 (1.24–1.48)	<0.001	1.43 (1.28–1.59)	<0.001	1.27 (1.10–1.45)	0.009
	Prostate	0.94 (0.90–0.97)	<0.001	0.94 (0.91–0.97)	<0.001	–	–
	Stomach	1.08 (1.01–1.16)	0.042	1.11 (1.02–1.21)	0.031	1.03 (0.90–1.17)	0.700
	Thyroid	1.02 (0.95–1.09)	0.574	1.05 (0.94–1.16)	0.379	0.99 (0.90–1.09)	0.918

Table 3 (continued)

Table 3 (continued)

Variables	Subtype	All		Male		Female	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Primary site of SPM	Bladder	0.45 (0.38–0.52)	<0.001	0.43 (0.34–0.51)	<0.001	0.52 (0.39–0.66)	<0.001
	Brain, CNS	ref	ref	ref	ref	ref	ref
	Colorectal	0.37 (0.30–0.44)	<0.001	0.36 (0.28–0.45)	<0.001	0.39 (0.28–0.51)	<0.001
	Esophagus	0.61 (0.53–0.69)	<0.001	0.59 (0.50–0.69)	<0.001	0.65 (0.50–0.81)	<0.001
	Female breast	0.31 (0.24–0.39)	<0.001	–	–	0.33 (0.22–0.45)	<0.001
	Female genital system	0.35 (0.28–0.42)	<0.001	–	–	0.36 (0.25–0.48)	<0.001
	Kidney	0.38 (0.30–0.45)	<0.001	0.36 (0.27–0.46)	<0.001	0.41 (0.28–0.55)	<0.001
	Leukemia	0.37 (0.30–0.45)	<0.001	0.35 (0.26–0.45)	<0.001	0.41 (0.30–0.53)	<0.001
	Liver	0.76 (0.68–0.84)	<0.001	0.77 (0.67–0.87)	<0.001	0.70 (0.55–0.86)	<0.001
	Lung and bronchus	0.53 (0.47–0.59)	<0.001	0.54 (0.46–0.61)	<0.001	0.51 (0.42–0.61)	<0.001
	Melanoma of skin	0.30 (0.23–0.38)	<0.001	0.31 (0.22–0.40)	<0.001	0.29 (0.16–0.43)	<0.001
	NHL	0.29 (0.21–0.36)	<0.001	0.27 (0.18–0.36)	<0.001	0.32 (0.21–0.44)	<0.001
	Other	0.39 (0.32–0.45)	<0.001	0.37 (0.29–0.45)	<0.001	0.42 (0.31–0.54)	<0.001
	Pancreas	0.81 (0.74–0.88)	<0.001	0.79 (0.71–0.88)	<0.001	0.84 (0.73–0.96)	0.003
	Prostate	0.28 (0.21–0.36)	<0.001	0.28 (0.19–0.36)	<0.001	–	–
	Stomach	0.57 (0.49–0.64)	<0.001	0.54 (0.45–0.63)	<0.001	0.62 (0.49–0.76)	<0.001
Thyroid	0.30 (0.19–0.41)	<0.001	0.31 (0.15–0.47)	<0.001	0.29 (0.14–0.45)	<0.001	
Age group, yrs	18–34	ref	ref	ref	ref	ref	ref
	35–49	0.89 (0.70–1.09)	0.264	0.94 (0.58–1.30)	0.739	0.88 (0.66–1.12)	0.264
	50–64	1.01 (0.82–1.20)	0.929	1.01 (0.66–1.36)	0.942	1.01 (0.79–1.25)	0.911
	65–79	1.10 (0.91–1.29)	0.304	1.11 (0.76–1.46)	0.568	1.11 (0.89–1.35)	0.376
	80+	1.37 (1.18–1.56)	0.001	1.36 (1.01–1.71)	0.083	1.38 (1.16–1.62)	0.006
Gender	Female	ref	ref	–	–	–	–
	Male	1.02 (0.99–1.05)	0.142	–	–	–	–
Race	American Indian/Alaska Native	ref	ref	ref	ref	ref	ref
	Asian or Pacific Islander	0.95 (0.81–1.10)	0.506	0.86 (0.67–1.04)	0.101	1.10 (0.88–1.34)	0.435
	Black	0.96 (0.82–1.11)	0.622	0.85 (0.67–1.04)	0.092	1.13 (0.93–1.35)	0.271
	Unknown	1.87 (0.98–2.75)	0.168	1.55 (0.41–2.70)	0.452	2.54 (1.2–3.95)	0.193
	White	0.90 (0.76–1.04)	0.140	0.80 (0.62–0.98)	0.018	1.04 (0.84–1.26)	0.701
Year of diagnosis of events	2000–2003	ref	ref	ref	ref	ref	ref
	2004–2007	0.50 (0.45–0.54)	<0.001	0.48 (0.42–0.54)	<0.001	0.53 (0.46–0.61)	<0.001
	2008–2010	0.30 (0.25–0.35)	<0.001	0.29 (0.23–0.35)	<0.001	0.32 (0.25–0.40)	<0.001

Table 3 (continued)

Table 3 (continued)

Variables	Subtype	All		Male		Female	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
	2011–2013	0.20 (0.15–0.25)	<0.001	0.19 (0.13–0.25)	<0.001	0.22 (0.15–0.30)	<0.001
Month Since Index, months	13–26	ref	ref	ref	ref	ref	ref
	27–44	1.15 (1.13–1.17)	<0.001	1.18 (1.15–1.21)	<0.001	1.11 (1.07–1.15)	<0.001
	45–71	1.45 (1.43–1.47)	<0.001	1.48 (1.45–1.51)	<0.001	1.41 (1.37–1.45)	<0.001
	72+	2.31 (2.29–2.34)	<0.001	2.39 (2.35–2.42)	<0.001	2.21 (2.17–2.25)	<0.001
	<i>In situ</i>	0.37 (0.31–0.44)	<0.001	0.37 (0.29–0.45)	<0.001	0.36 (0.21–0.52)	<0.001
Stage	Localized	0.49 (0.47–0.52)	<0.001	0.48 (0.45–0.51)	<0.001	0.52 (0.48–0.56)	<0.001
	Regional	0.61 (0.58–0.63)	<0.001	0.58 (0.55–0.61)	<0.001	0.64 (0.60–0.68)	<0.001
	Distant	ref	ref	ref	ref	ref	ref
	Unknown/unstaged	0.82 (0.79–0.84)	<0.001	0.78 (0.74–0.81)	<0.001	0.89 (0.85–0.93)	<0.001
Grade	Grade I	0.89 (0.85–0.93)	<0.001	0.88 (0.83–0.94)	<0.001	0.91 (0.85–0.97)	0.003
	Grade II	ref	ref	ref	<0.001	ref	ref
	Grade III	1.20 (1.17–1.22)	<0.001	1.18 (1.15–1.21)	<0.001	1.23 (1.19–1.27)	<0.001
	Grade IV	1.28 (1.24–1.32)	<0.001	1.30 (1.25–1.35)	<0.001	1.25 (1.19–1.31)	<0.001
	Unknown	1.25 (1.23–1.28)	<0.001	1.23 (1.20–1.26)	<0.001	1.29 (1.25–1.33)	<0.001
% , bachelors degree, 1st quartile	1st	ref	ref	ref	ref	ref	ref
	2nd	0.97 (0.95–0.99)	0.014	0.97 (0.94–1.00)	0.029	0.98 (0.94–1.02)	0.237
	3rd	0.97 (0.94–1.00)	0.026	0.97 (0.94–1.01)	0.090	0.97 (0.93–1.01)	0.167
	4th	0.97 (0.94–1.00)	0.091	0.96 (0.92–1.00)	0.048	0.99 (0.93–1.05)	0.614
	Median household income, quartile	1st	ref	ref	ref	ref	ref
	2nd	0.95 (0.93–0.98)	<0.001	0.96 (0.93–0.99)	0.013	0.95 (0.91–0.99)	0.007
	3rd	0.94 (0.92–0.97)	<0.001	0.93 (0.90–0.97)	<0.001	0.96 (0.92–1.00)	0.073
	4th	0.91 (0.88–0.94)	<0.001	0.91 (0.87–0.95)	<0.001	0.91 (0.85–0.97)	0.003

two tumors. Excessive drinking and tobacco intaking is considered a synergistic factor affecting upper digestive tract and upper respiratory tract cancer (22,23), which may explain this phenomenon.

In addition, we found that the tumors of the digestive system (except for colorectal tumors) have a lower probability of developing SPM. Possible causes include poor prognosis of digestive tract tumors and short survival time. Another possible reason is that most of these tumors are based on surgery and the intervention of radiotherapy

and chemotherapy is less than other tumors (24–26).

The advantage of our research is that we have included a large number of samples between 2000 and 2013, depicting the location of SPM and updating and enriching the relevant data. At the same time, we also conducted COX analysis on related factors and identified some risk factors. However, due to the limited permission of the SEER database and the inherent flaws in retrospective research, our data must have some limitations, although we try our best to avoid potential bias. First, we excluded the same site and cases of

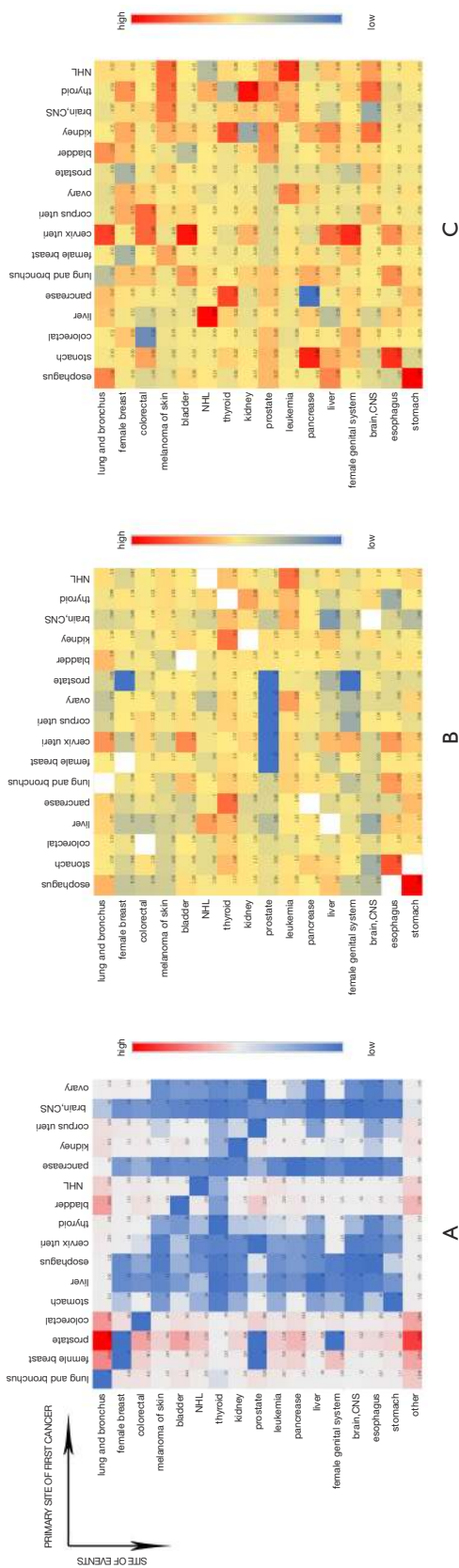


Figure 4 Number of cases and the risk of SPM in the forms of standard incidence rate of multiple primary (MP-SIR). (A). Heat map of the number of cases. (B) Heat map of the SIR of cases. (C) Heat map of the normalized SIR of cases. SIR, standardized incidence ratio

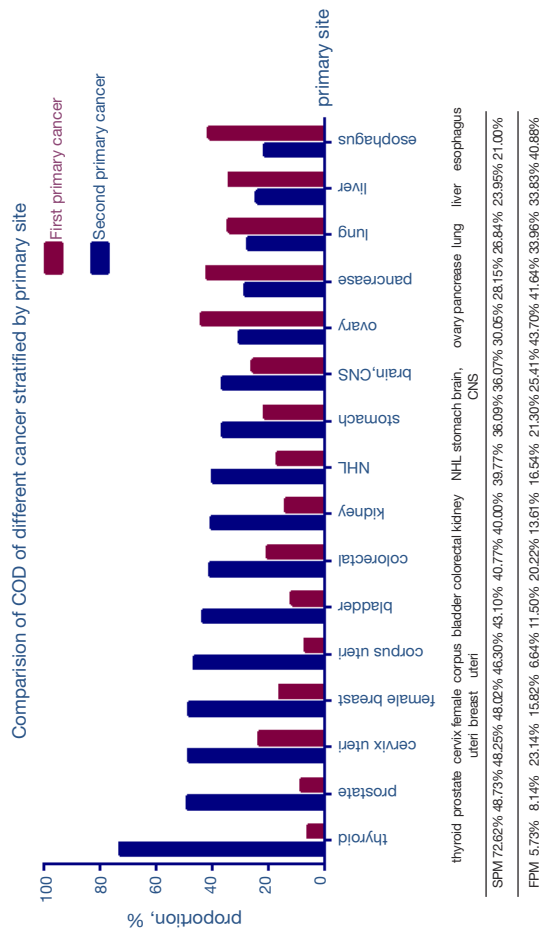


Figure 5 Comparison of COD of different cancer stratified by primary site. COD, cause of death.

SPM diagnosed within one year to avoid misclassification of metastasis and SPM, but this also directly led to the gap in the field of SPM in the primary site. To this end, we have retained the calculation of the SIR in the primary part of the SPM. The heat map can also show that this risk does exist and cannot be ignored (*Figure S4*). Second, because of the limited access to information, we have no access to patient-specific treatment information and lifestyle habits, such as tobacco and alcohol intake, radiation doses in radiation regimens, specific chemotherapy regimens and genetic mutations. These factors are considered to be closely related to the development of SPM. Third, when we chose primary site of FPM, we did not include some non-solid tumors, including Hodgkin's lymphoma, leukemia. When we chose SPM, we did not include some important parts, including the head and neck. And these are considered to be the location of SPM, and some are often fatal (27-29).

The occurrence of SPM may be the result of a combination of factors, so it is necessary to find a study of the individual factors affecting its occurrence, but more important is the grasp of the overall situation of patients and comprehensive analysis of multiple factors. It is foreseeable that with the increase in the number of cancer survivors and the longevity of cancer survivors, SPM will occur more frequently and become a medical problem and a social burden. Awareness, evaluation, counseling, and amelioration strategies are recommended (30,31). Recommendations for a research agenda, study methods, and infrastructure required to advance our understanding of SPMs and to establish the basis for evidence-based approaches to patient management and intervention strategies were derived from an NCI-sponsored workshop that included clinicians, researchers, and patient advocates (32). Therefore, more specific and long-term follow-up research is needed, and more rational clinical decisions guidelines and medical policies need to be developed and implemented.

Conclusions

The improvement of medical level has allowed the life of cancer patients to continue. At the same time, cancer survivors are also at risk of developing secondary primary malignancies. Prostate cancer patients have the highest probability of SPM and lung and bronchus are the most prone site to develop SPM. Once the SPM is diagnosed, the median survival time is usually around one year. Therefore, it is particularly important to rationally adjust the treatment plan, better define high-risk groups and strengthen targeted

interventions and clinical interventions. Our research on the population distribution of SPM and its impact on survival can provide a reference for prevention, screening, treatment and survival recommendations for specific ages.

Acknowledgments

We thank the contribution of the SEER database and the 18 registries supplying cancer research information.

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-2059>). XL serves as an unpaid section editor of *Annals of Translational Medicine* from Jan 2020 to Dec 2021. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Zheng X, Li X, Wang M, Shen J, Sisti G, He Z, Huang J, Li YM, Wu A; on behalf of Multidisciplinary Oncology Research Collaborative Group (MORCG). Second primary malignancies among cancer patients. *Ann Transl Med* 2020;8(10):638. doi: 10.21037/atm-20-2059

Supplementary

Table S1 Month at events, follow-up and median survival time for analytic cohort

Variables	Month at events		Follow-up, person year		Median survival time
	Mean	SD	Mean	SD	
Liver	37.09	26.59	5.06202	2.54	11
Pancreas	40.758	27.34	4.3805	2.66	10
Lung and bronchus	42.7	27.83	4.79677	2.82	12
Esophagus	43.705	27.94	5.6526	2.76	10
Stomach	44.7418	29.26	4.87288	2.83	11
Ovary	47.481	30.68	5.2485	2.84	12
Kidney	48.787	30.89	5.52942	2.87	12
Brain, CNS	48.96	30.28	5.09896	2.86	11
Bladder	49.338	30.18	5.24788	2.81	12
Colorectal	51.453	31.57	5.58557	2.88	14
Corpus uteri	51.476	31.14	5.53182	2.89	13
NHL	52.082	31.38	5.55609	2.88	12
Cervix uteri	54.788	34.19	5.49935	3.02	13
Thyroid	55.091	32.7	5.84914	2.89	14
Prostate	56.39	33.09	5.81053	2.97	10.5
Female breast	56.55	33.18	5.8908	2.97	9

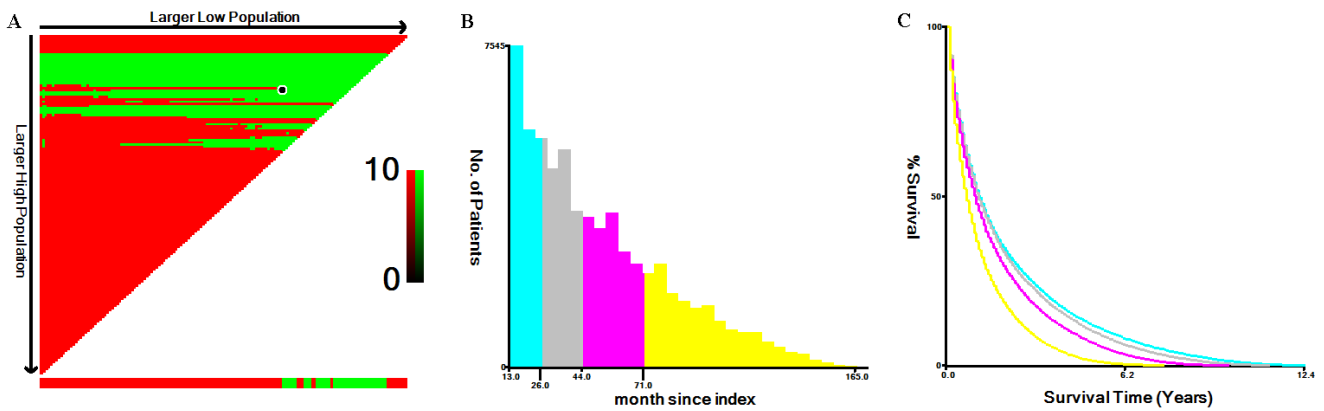


Figure S1 The results of optimal cut-off point of the Month Since Index by using the X-tile program. (A,B) The optimal cut-off value of Month Since Index was identified by X-tail. (C) The Kaplan-Meier curves for overall survival.



Figure S2 Detailed information about the distribution of SPM locations in 16 common malignancies. SPM, second primary malignancy.

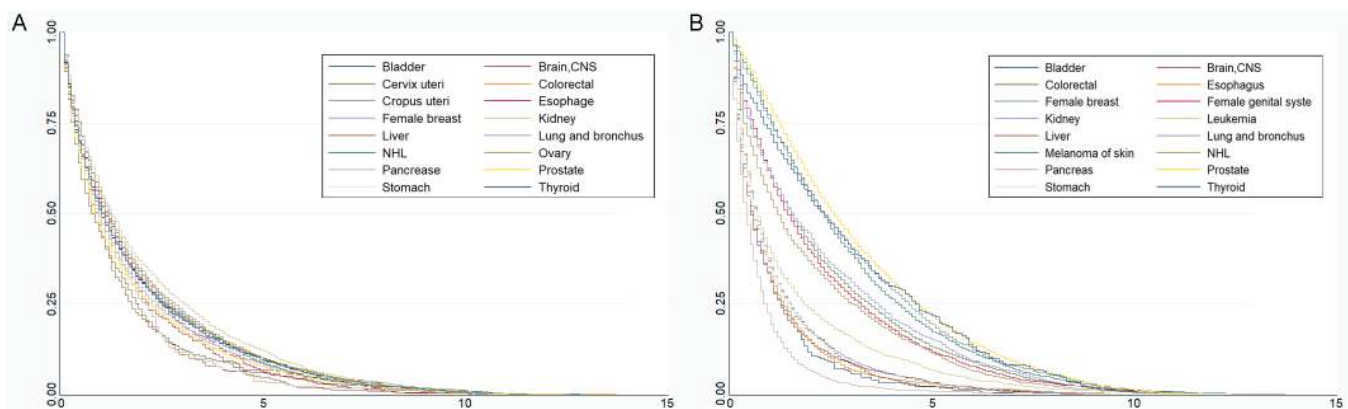


Figure S3 The survival analysis of FPM and SPM. (A) Kaplan-Meier (K-M) survival curves of FPM. (B) Kaplan-Meier (K-M) survival curves of SPM. FPM, first primary malignancy; SPM, second primary malignancy.

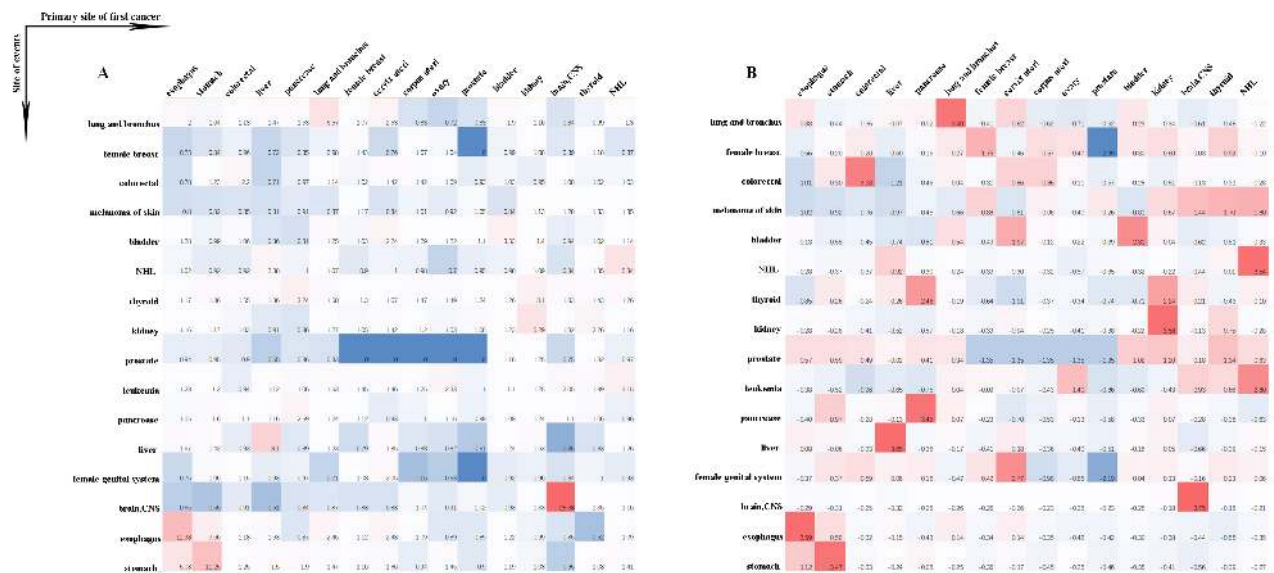


Figure S4 The risk of cases with the same site of FPM and SPM in the forms of standard incidence rate of multiple primary (MP-SIR). (A) Heat map of the SIR of cases with same site of FPM and SPM. (B) Heat map of the normalized SIR of cases with same site of FPM and SPM. FPM, first primary malignancy; SPM, second primary malignancy.