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Research Article

Patients with Lung Cancer Followed by Breast Cancer Have a Better Prognosis than Patients with these Cancers in the Opposite Order due to Differences in Pathological Components

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Abstract

Objectives: To explore the prognostic differences between lung cancer followed by breast cancer (LFB) and breast cancer followed by lung cancer (BFL) and the reasons for the differences.

Methods: The database we chose was SEER 18 Regs, from which we retrieved data from patients diagnosed with multiple primary standardized incidence rate (MP-SIR) segments of cancer.

Results: A total of 7169 patients were included, of whom 979 were patients with LFB and 6190 were BFL patients. The proportion of small cell lung carcinoma in LFB was 4%, which was significantly lower than that in BFL (p<0.001), while the proportion of carcinoid carcinoma in LFB was significantly higher than that in BFL (p<0.001). Survival analysis of LFB and BFL showed a slightly better prognosis for the former than the latter (HR=0.871 (0.804-0.944)), and the difference was statistically significant (p<0.001). The difference was not statistically significant after adjustment for the pathological type of tumor (HR=0.911 (0.827-1.003), p=0.057).

Conclusion: LFB has a worse prognosis than BFL, and this difference is explained by the difference in the ratio of the two pathological components.

Keywords: Breast cancer, lung cancer, multiple primary cancer

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Advances in cancer screening and early detection, improvements in treatments, and better access to care all contribute to a decline in cancer mortality rates.[1] As a result, cancer survivors survive longer than ever before, which raises other questions. Longer life spans allow time for a second cancer. The term "second primary cancers" is applied to cancers that appear to be related to preexisting treated or untreated cancers but that are in fact entities that have arisen independently and not as a result of resurgence or as a result of metastasis of the original primary cancer.[2] Cancer survivors are at higher risk of developing another malignancy than the general population. Second primary cancers in cancer survivors account for 18% of all cancer diagnoses in the U.S. Surveillance, Epidemiology, and End Results (SEER) Cancer registries.[3,4] One study showed that for patients with 2 incident cancers, 13% died of their initial cancer, but greater than one-half (55%) died of their second primary malignancy.[5] Thus, for a cancer survivor, a new second primary cancer may be a serious event.

Breast cancer is the most frequently diagnosed cancer (24.2%) and the leading cause of cancer death (15%) among women.[6] Over recent decades, as a result of earlier diagnosis and more complete systematic treatment, the survival rate of breast cancer has increased considerably. Longer survival is associated with an increased probability that a new primary cancer will develop. One meta-analysis showed that women with breast cancer are at risk of second cancers within the first 10 years after the first breast cancer diagnosis (standard incidence ratio (SIR): 1.19; 95% CI: 1.06–1.33) and thereafter (SIR: 1.26; 95% CI: 1.05–1.52).[7] This finding led to the conclusion that compared to the general population, breast cancer survivors have a higher risk of experiencing multiple primary cancer (MPC). For breast cancer patients, MPC is a negative factor for overall survival compared to breast cancer alone (HR=2.192, p<0.001).[8] Most studies have focused on breast cancer followed by lung cancer (BFL). Another situation, lung cancer followed by breast cancer (LFB), is equally important and worthy of study.

MPCs are generally divided into two major groups: synchronous and metachronous. According to Moertel,[9] synchronous neoplasms are defined as those that occur within 6 months from the diagnosis of a previous malignant tumor, and metachronous neoplasms are defined as neoplasms that appear more than 6 months after the first diagnosed tumor. Some studies concluded that the prognosis for metachronous MPCs was better than that for synchronous MPCs.[10,11]

The main objective of this study was to explore the prognostic differences between LFB and BFL and the reasons for the differences.

Methods

Patients

The National Cancer Institute's SEER program collects data on all cancer patients in 18 defined geographic areas across the United States. It collects and publishes information on cancer incidence and survival for approximately 28% of the U.S. population. The database we chose was SEER 18 Regs, from which we retrieved data from patients diagnosed with multiple primary standardized incidence rate (MP-SIR) segments of cancer. The inclusion criteria for data extraction in this study were as follows:

1. {Site and Morphology. Site recode B ICD-0-3/WHO 2008} = 'Female Breast', 'Lung and Bronchus';
2. {Site and Morphology. Diagnostic Confirmation} = 'Positive histology';
3. {Cause of Death (COD) and Follow-up. Survival months}!= 'Unknown';
4. {Cause of Death (COD) and Follow-up. Survival months flag} = 'Complete dates are available and there are 0 days of survival', 'Complete dates are available and there are more than 0 days of survival';
5. {Cause of Death (COD) and Follow-up. Type of follow-up expected} = 'Active follow-up';
6. {Other. Type of Reporting Source}!= 'Autopsy only', 'Death certificate only'.

Since the data of patient included in our study were retrieved from the SEER project, ethical approval was waived. Follow-up started at the time of the first primary cancer diagnosis and ended at the earliest occurrence of the MPC diagnosis, at cause-specific death, or at the end of the study period. Demographic and clinicopathological data from all eligible cases were collected and analyzed retrospectively.

Statistical Analysis

For categorical variables, Fisher's exact test or the chi-square test was used to analyze component ratio differences. Survival curves were plotted using the Kaplan-Meier (KM) method. SEER Stat 8.3.5 software was used to extract the study cohort from the SEER dataset and to calculate the SIR. R 3.6.1 was used for other statistical analyses. For all analyses, p<0.05 was considered statistically significant.

Results

Demographic and Clinical characteristics of the Patients

A total of 7169 patients were included, of whom 979 had LFB and 6190 had BFL. Their basic clinical data are shown in Table 1. The median ages of the first primary tumor were 65

and 63 years for LFB patients and BFL patients, respectively. The median interval between the two primary tumors was 47 months for LFB patients and 86 months for BFL patients. Synchronous carcinoma accounted for 10% and 6% of LFB and BFL patients, respectively.

Pathological Differences Between LFB and BFL

The pathological differences between LFB and BFL are shown in Table 2. The proportion of infiltrating duct carcinoma was 70% and 65% for LFB and BFL, respectively, which was statistically significant (p=0.005). There was no significant difference in the proportion of lobular carcinoma or infiltrating duct and lobular carcinoma between the LFB and BFL groups. The proportion of small cell lung carcinoma in LFB was 4%, which was significantly lower than that in BFL (p<0.001), while the proportion of carcinoid carcinoma in LFB was significantly higher than that in BFL (p<0.001).

Table 1. Demographics and clinical characteristics of the study population

	LFB *	BFL +		LFB *	BFL +
Number of cases	979	6190	Right	553 (56)	3337 (54)
Age at diagnosis (First Primary Cancer), median (IQR)	65 (57-71)	63 (55-70)	Bilateral	2 (0)	73 (1)
			Unknown	12 (1)	293 (5)
Age at diagnosis (Second Primary Cancer), median (IQR)	70 (63-77)	72 (64-78)	Laterality of Breast cancer, n (%)		
			Left	465 (47)	3076 (50)
Interval between two tumors, median (IQR, month)	47 (18-99)	86 (38-154)	Right	495 (51)	3099 (50)
			Bilateral	0 (0)	2 (0)
Number of synchronous MPC #, N(%)	98 (10)	364 (6)	Unknown	19 (2)	13 (0)
Number of metachronous MPC, N(%)	881 (90)	5826 (94)	Chemotherapy of Lung cancer, n (%)		
Race, n (%)			Yes	178 (18)	2002 (32)
White	829 (85)	5204 (84)	No/Unknown	801 (82)	4118 (67)
Black	104 (11)	629 (10)	Chemotherapy of Breast cancer, n (%)		
Other	46 (5)	357 (6)	Yes	154 (16)	1383 (22)
Grade of Lung cancer, n (%)			No/Unknown	825 (84)	4803 (78)
High differentiation	135 (14)	433 (7)	Radiotherapy of Lung cancer, n (%)		
Moderate differentiation	222 (23)	1025 (17)	Yes	219 (22)	2096 (34)
Low differentiation	242 (25)	1402 (23)	No/Unknown	760 (78)	4094 (66)
Undifferentiation	62 (6)	411 (7)	Radiotherapy of Breast cancer, n (%)		
Unknown	318 (32)	2919 (47)	Yes	314 (32)	2779 (45)
Grade of Breast cancer, n (%)			No/Unknown	665 (68)	3303 (53)
High differentiation	168 (17)	983 (16)	Surgery of Lung cancer, n (%)		
Moderate differentiation	338 (35)	1800 (29)	Yes	777 (79)	1954 (32)
Low differentiation and undifferentiation	245 (25)	1428 (23)	No/Unknown	202 (21)	4236 (68)
Unknown	228 (23)	1979 (32)	Surgery of Breast cancer, n (%)		
Stage of Lung cancer, n (%)			Yes	850 (87)	6053 (98)
I	363 (37)	1415 (23)	No/Unknown	129 (13)	137 (2)
II	42 (4)	269 (4)	ER, n (%)		
III	104 (11)	1291 (21)	Positive	553 (56)	2973 (48)
IV	64 (7)	1922 (31)	Negative	147 (15)	790 (13)
Unknown	406 (41)	1293 (21)	Unknown	279 (28)	2427 (39)
Stage of Breast cancer, n (%)			PR, n (%)		
I	463 (47)	2471 (40)	Positive	477 (49)	2489 (40)
II	199 (20)	1544 (25)	Negative	213 (22)	1204 (19)
III	48 (5)	227 (4)	Unknown, N(%)	289 (30)	2497 (40)
IV	40 (4)	69 (1)	Her2, n (%)		
Unknown	229 (23)	1879 (30)	Positive	28 (3)	49 (1)
Laterality of Lung cancer, n (%)			Negative	234 (24)	432 (7)
Left	413 (42)	2551 (41)	Unknown	717 (73)	5709 (92)

* LFB: Lung cancer followed by breast cancer; + BFL: Breast cancer followed by lung cancer; # MPC: multiple primary cancer.

To explore whether the pathological type was associated with the incidence latency, further subgroup analyses were performed (Table 3). For LFB patients, carcinoid carcinoma differed between synchronous carcinoma and metachronous carcinoma (p=0.026). There was no clear evidence of a significant difference for the other pathology types in LFB. For BFL patients, the proportions of small cell lung and squamous cell carcinoma were significantly higher in synchronous carcinoma than in metachronous carcinoma (p=0.031, p=0.002), whereas the proportions of lobular and carcinoid carcinomas were significantly lower in synchronous carcinoma than in metachronous carcinoma (p=0.017, p<0.001). In addition, we explored whether lung cancer pathology types secondary to different breast cancer pathologies differed in the BFL population, but none of the results were statistically significant (Supplementary Table 1).

Table 2. Differences in constituent ratio of pathology in LFB and BFL

	LFB	BFL	p*
Pathology of Breast cancer			
Infiltrating duct carcinoma	683 (70)	4500 (65)	0.005
Lobular carcinoma	71 (7)	457 (7)	0.496
Infiltrating duct and lobular carcinoma	49 (5)	291 (4)	0.289
Other	176 (18)	1662 (24)	
Pathology of Lung cancer			
Adenocarcinoma	360 (37)	2102 (34)	0.092
Large cell carcinoma	42 (4)	169 (3)	0.010
Small cell carcinoma	35 (4)	751 (12)	<0.001
Squamous cell carcinoma	153 (16)	921 (15)	0.574
Adenosquamous carcinoma	17 (2)	64 (1)	0.077
Carcinoid tumor	88 (9)	135 (2)	<0.001
Other	284 (29)	2048 (33)	

* Chi-squire test or Fisher's exact test if appropriate.

Survival Differences Between LFB and BFL

KM plots of LFB and BFL showed a slightly better prognosis in the former than in the latter (Figure 1, HR=0.871

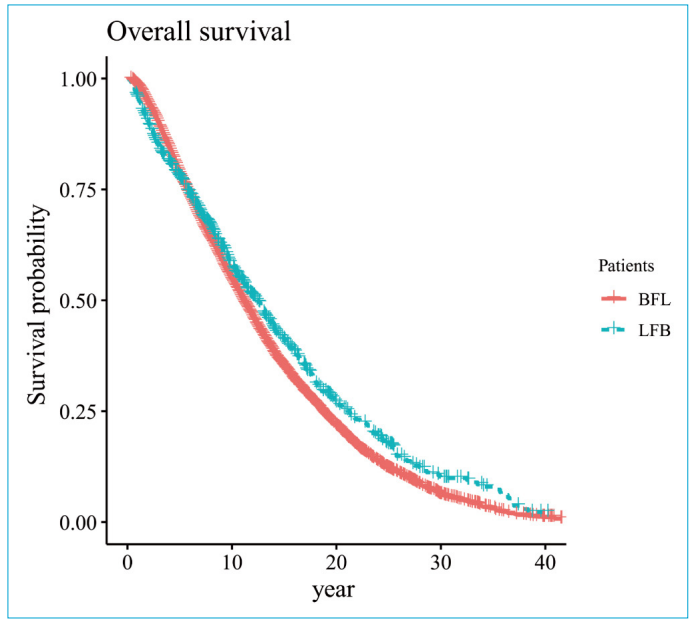

Figure 1. KM plots of lung cancer followed by breast cancer (LFB) and breast cancer followed by lung cancer (BFL).

Table 3. Differences in constituent ratio of pathology in LFB and BFL stratified by the interval between two tumors

	LFB			BFL		
	Synchronous MPC	Metachronous MPC	p*	Synchronous MPC	Metachronous MPC	p*
Pathology of Breast cancer, n (%)						
Infiltrating duct carcinoma	61 (62)	622 (71)	0.104	261 (72)	4239 (73)	0.671
Lobular carcinoma	3 (3)	68 (8)	0.102	39 (11)	418 (7)	0.017
Infiltrating duct and lobular carcinoma	4 (4)	45 (5)	0.810	19 (5)	272 (5)	0.609
Other	30 (31)	146 (17)		45 (12)	897 (15)	
Pathology of Lung cancer, n (%)						
Adenocarcinoma	43 (44)	317 (36)	0.151	135 (37)	1967 (34)	0.209
Large cell carcinoma	6 (6)	36 (4)	0.301	11 (3)	158 (3)	0.739
Small cell carcinoma	3 (3)	32 (4)	1	31 (9)	720 (12)	0.031
Squamous cell carcinoma	15 (15)	138 (16)	1	34 (9)	887 (15)	0.002
Adenosquamous carcinoma	2 (2)	15 (2)	0.684	4 (1)	60 (1)	0.789
Carcinoid tumor	3 (3)	85 (10)	0.026	21 (6)	114 (2)	<0.001
Other	26 (27)	258 (29)		128 (35)	1920 (33)	

* Chi-squire test or Fisher's exact test if appropriate.

(0.804-0.944)), and the difference was statistically significant (p<0.001). The difference was not statistically significant after adjustment for the pathological type of tumor (HR=0.911 (0.827-1.003), p=0.057). Supplementary table 2 shows the difference in prognosis of different pathology types. When infiltrating duct carcinoma was used as the reference, lobular carcinoma had a worse prognosis (HR=1.124, p=0.032). Compared to adenocarcinoma, small cell carcinoma and squamous cell carcinoma had a worse prognosis (small cell carcinoma: HR=1.675, p=0.008; squamous cell carcinoma: HR=1.354, p=0.002), and carcinoid carcinoma had a worse prognosis (HR=0.375, p<0.001).

SIR Analysis of Multiple Primary Cancer

Table 4 shows the standardized incidence rates of second primary tumors for LFB and BFL patients. Overall, the incidence of the first primary tumor, whether breast or lung, was reduced for the second primary tumor (LFB: SIR=0.9 (0.84-0.95); BFL: SIR=0.94 (0.91-0.96)). For LFB, secondary breast cancer was lower than the standardized incidence rate for either chemotherapy or radiotherapy for lung cancer (chemotherapy: SIR=0.64 (0.55-0.74); radiotherapy: SIR=0.75 (0.65-0.85)). For BFL, however, there was no such finding (chemotherapy: SIR=1.02 (0.96-1.07); radiotherapy: SIR=0.99 (0.96-1.03)). For LFB, the incidence of secondary breast cancer was lower than the standard incidence if the pathological type of lung cancer was small cell carcinoma (SIR=0.52 (0.37-0.72)).

We also incidentally investigated whether there was an association between the left and right sides of the second primary tumor and those of the first primary tumor after radiotherapy to the first primary tumor (Supplementary table 3). If the first primary tumor was left-sided breast cancer, then left-sided lung cancer was more frequent than right-sided lung cancer (RR=1.162 (1.004, 1.345)). The risk of renewed left-sided lung cancer was highest in the 2005-2014 subgroup (RR=1.340 (0.962, 1.865)).

Table 4. SIR analysis of LFB and BFL

	LFB		BFL	
	O*	SIR#	O	SIR
Overall	990	0.9 (0.84-0.95)	6494	0.94 (0.91-0.96)
Age				
<50y	30	1.13 (0.76-1.61)	195	1.87 (1.59-2.18)
≥50y	960	0.89 (0.84-0.95)	6355	0.93 (0.9-0.95)
Race				
Black	106	1.1 (0.9-1.33)	656	1.14 (1.05-1.23)
White	838	0.88 (0.82-0.94)	5,458	0.91 (0.89-0.93)
Chemotherapy of first primary cancer				
No	816	0.99 (0.92-1.06)	5502	0.92 (0.89-0.94)
Yes	287	0.64 (0.55-0.74)	1428	1.02 (0.96-1.07)
Radiotherapy of first primary cancer				
No	788	0.95 (0.88-1.02)	3889	0.89 (0.86-0.92)
Yes	296	0.75 (0.65-0.85)	2775	0.99 (0.96-1.03)
Surgery of first primary cancer				
No	194	0.62 (0.52-0.74)	56	1.18 (0.91-1.5)
Yes	787	0.99 (0.92-1.06)	6785	0.94 (0.91-0.96)
Pathology of first primary cancer				
Adenocarcinoma	363	0.89 (0.8-0.99)		
Large cell carcinoma	45	1 (0.73-1.33)		
Small cell carcinoma	37	0.52 (0.37-0.72)		
Squamous cell carcinoma	155	0.9 (0.76-1.05)		
Adenosquamous carcinoma	17	0.92 (0.54-1.48)		
Carcinoid tumor	88	1.07 (0.88-1.32)		
Infiltrating duct carcinoma			4705	0.95 (0.93-0.98)
Lobular carcinoma			484	0.85 (0.77-0.93)
Infiltrating duct and lobular carcinoma			304	0.84 (0.75-0.94)

* O, observed; # SIR, standard incidence ratio.

Conclusion

Lung cancer is still the leading cause of cancer deaths for tumor patients, and the estimated deaths are 76650 (24%) and 66020 (23%) for males and females, respectively(12). Nevertheless, with the promotion of screening programs and the development of therapeutic treatments, the number of long-term survivors, especially those with early-stage lung cancer, is gradually increasing. However, lung cancer is still more common as a second primary cancer to be studied. Breast cancer patients have a better prognosis and a long survival period. At present, there have been many studies on breast cancer patients with multiple primary tumors. In our study, we screened lung cancer survivors who developed second primary breast cancer and breast cancer patients who developed second primary lung cancer in the SEER database. We compared the prognosis and pathologic types of these two groups.

Patients with a second primary cancer usually have a poor prognosis. Female breast cancer patients showed a higher incidence of second primary malignancy, which was associated with poorer prognosis.[13] A cohort study showed that patients diagnosed with second primary lung cancer face favorable lung cancer-specific survival within the early period after diagnosis. In this study, the patients with second primary cancer were at lower risk of lung cancer-specific mortality in the first 5 years (HR, 0.77; 95% CI, 0.76-0.78 at <1 year; HR, 0.87; 95% CI, 0.86-0.89 from 1 to <5 years) but at higher risk thereafter (HR, 1.32; 95% CI, 1.27-1.37 from 5 to 10 years), independent of tumor characteristics or cancer treatment.[14] This result for carcinoid tumors was reversed. The second primary cancer had a worse HR (HR=0.375 p<0.001) than the first primary cancer. Carcinoid tumors are slow-growing malignancies that occur most frequently in the gastrointestinal tract (approximately 74%). They can also be found in the bronchus, ovary, lung, thymus, kidney or thyroid gland.[15] Due to the lower malignancy of this tumor, the first primary carcinoid tumor may survive longer than the first primary breast cancer. Additionally, we cannot neglect the difference in the sample size of the two groups. The limitations of the sample size may have contributed to this result.

In our analysis, for breast cancer, the distribution of pathological types was the same for both the first and second primary cancers. This result was consistent with the clinical observations. Adenocarcinoma was the major type of the first and second primary cancer. This may be related to the fact that all included patients were female. Additionally, there was a significant difference in the distribution of pathological characteristics in lung cancer. Small cell cancer accounted for 4% of first primary cancers and 12% of second primary lung cancers. Another different type was carcinoid tumors; this type accounted for 9% of first primary cancers and 2% of second primary cancers. The different sample sizes of the two groups and the degree of partitioning of pathological features may have contributed to this result.

Consequently, we analyzed the association between pathological type and latency. In the LFB group, carcinoid tumors showed a significant difference between synchronous (3%) and metachronous (10%) diseases. This means that lung carcinoid tumors, as the first primary cancer, may be more prone to metachronous disease with a longer latency period, which may be associated with a longer survival time for prognosis. In addition, there was no statistically significant difference in either lung or breast cancer within this group. In the BFL group, our study showed that the lobular cancer type had a favorable trend (11%) toward the synchronous situation. In other words, for this subset of patients, the latency was shorter with lobular cancer. This result is similar to that of a prior study showing that synchronous bilateral breast cancer was strongly associated with a lobular phenotype compared to metachronous bilateral breast cancer.[16] As the second primary lung cancer, small cell carcinoma tends to occur more than 6 months after the primary cancer (12% vs 9%), while carcinoid tends to occur less than 6 months after the primary cancer. The reasons for this cannot exclude the difference between the uneven size of cases and the distribution of pathological types in this study. It may also be related to the pathological characteristics of neuroendocrine tumors, which need to be further studied.

We compared the outcomes of the two groups. The BFL patients had a worse prognosis than LFB patients (HR=0.871 (0.804-0.944)). We speculate that this difference is most likely due to the difference in the proportions of the pathological components of these two populations. On the one hand, in prognostic comparisons of lung cancer pathology, small cell lung cancer had the poorest prognosis, and carcinoid tumors had the best prognosis; however, the BFL patients had a higher proportion of small cell lung cancer and a lower proportion of carcinoid tumors, and thus, this group had a worse prognosis. On the other hand, after adjustment for pathology, HR=0.911 (0.827-1.003), lost its statistical significance, indicating that the prognoses of BFL and LFB are not significantly different when the pathology types are the same. Thus, BFL has a worse prognosis than LFB, influenced by the proportion of pathology type composition. The prognostic difference between LFB and BFL patients has rarely been reported, and even lung cancer followed by other tumors has received little attention from investigators. Therefore, the molecular mechanism of the difference in prognosis is still unknown and needs to be elucidated by subsequent studies.

It is certain that radiotherapy may increase the risk of MPC in breast cancer patients.[17] Some studies have shown that breast exposure to high therapeutic doses may be associated with an excess risk for second cancer induction.[18-20] In terms of the impact of radiation treatment on breast cancer patients, studies conducted more than 20 years ago showed that RT increases the risk of lung cancer in these patients.[21] Consequently, we studied the SIRs of breast cancer patients who received radiotherapy. As shown in Supplementary table 3, patients with left-sided breast cancer had a 16.2% higher risk of developing left-sided lung cancer than right-sided lung cancer after radiotherapy. Subgroup analysis showed that patients diagnosed with breast cancer in 2005-2014 had the highest RR values. The reason for this result may be related to the introduction of IMRT. A study showed that the treatment of primary breast carcinoma with the use of IMRT results in increased probabilities for developing secondary malignancies in the healthy contralateral breast or ipsilateral lung compared to the respective risk for an unexposed population.[22] The period from 1975-1994 was the initiation period of IMRT, with low RR values; 1995-2004 was a transitional period that brought about technical developments, with the technique becoming more widespread over that decade. After 2005, the technique became very common, resulting in significantly higher RR values than in the previous period.

However, this paper has several limitations. First, the diagnoses of patients in the SEER database span nearly 40 years, leading to slight differences in anatomical staging criteria. Second, this is a retrospective study, excluding all patients with incomplete survival data, and the grouping is not randomized, resulting in selection bias. Finally, the SEER database registers information mainly on patients in the United States, so a larger study is needed to generalize the findings of this paper.

In conclusion, LFB has a worse prognosis than BFL, and this difference is explained by the difference in the ratio of the two pathological components.

Disclosures

Ethics Committee Approval: The Data Use Agreement for the SEER 1973–2016 Research Data File was completed. All procedures performed in this study involving human participants were performed in accordance with the ethical standards of the institutional research committees.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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