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Article

Racial & Ethnic Disparities in Second Primary Lung Cancer After Breast-Radiotherapy: A SEER Cohort Analysis (2000–2022)

Fares A. Qtaishat ¹, Mohammad Hamad ¹, Adham Musa ², Theeb Natsheh ³, Othman Al-Barghouthi ³, Basil A. Abusalameh ¹, Anas A. Younis ¹, Hamzeh Al-Qarallah ¹, Sara Qutaishat ⁴, Matthew P Banegas ⁵, H. Irene Su ⁶, Winta T. Mehtsun ⁷ and Tala Al-Rousan ^{8,*}

¹ School of Medicine, University of Jordan, Amman, Jordan

² College of Literature, Science, and the Arts, University of Michigan, Ann Arbor, USA

³ Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan

⁴ Department of Internal Medicine, Medstar Union Memorial Hospital, Baltimore, MD, USA

⁵ Department of Radiation Medicine and Applied Sciences, University of California San Diego School of Medicine, La Jolla, CA, USA

⁶ Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California San Diego, La Jolla, CA, USA

⁷ Division of Surgical Oncology, Department of Surgery, UC San Diego School of Medicine, La Jolla, CA, USA

⁸ Herbert Wertheim School of Public Health, University of California, San Diego, La Jolla, USA

* Correspondence: Talrousan@health.ucsd.edu

Simple Summary

Radiation therapy is an important part of breast cancer treatment and helps many patients live longer. However, it can also expose nearby organs, such as the lungs, to low levels of radiation, which may increase the chance of developing lung cancer later in life. Not all breast cancer survivors face the same level of risk, and social factors may also influence outcomes. In this study, we examined a large U.S. cancer database to understand whether the risk of developing lung cancer after breast radiation differs by race, ethnicity, and marital status, and how these factors affect survival. We found that some racial groups and unmarried patients had higher risks and worse outcomes, while others had lower risk and better survival. These findings may help researchers and clinicians improve long-term follow-up care and design more personalized lung cancer screening strategies for breast cancer survivors.

Abstract

Background: Adjuvant radiation therapy for breast cancer improves survival but may expose thoracic organs to low-dose radiation, potentially increasing the risk of second primary lung cancer (SPLC). Prior studies have not adequately examined how SPLC risk varies across racial and ethnic groups or whether social factors influence incidence and survival outcomes. **Objectives:** To quantify racial and ethnic disparities in SPLC incidence and survival among breast cancer survivors treated with radiation and assess the potential protective role of marital status. **Methods:** We used SEER-17 registry data to identify patients diagnosed with a first malignant primary breast cancer from 2000 to 2022 who received radiotherapy. Patients who died within two months of diagnosis were excluded. Standardized incidence ratios (SIRs) were calculated to compare observed to expected SPLC cases across racial and ethnic groups, stratified by latency intervals (2–11, 12–59, 60–119, and ≥120 months) and marital status. Racial categories included White, Black, Asian or Pacific Islander (API), and American Indian or Alaska Native (AI/AN); ethnicity was categorized as Hispanic or non-Hispanic. Five-year overall survival after SPLC was estimated using Kaplan–Meier analysis, and mean age at death was calculated by subgroup. **Results:** Among 558,493 radiotherapy-treated breast cancer patients, 6,674 developed SPLC (1.19%). Risk varied significantly by race ($p < 0.05$). Black survivors

had a 21% excess risk (SIR 1.21, 95% CI: [1.12–1.31]), peaking 5–10 years post-treatment (SIR 1.44, [1.26–1.63]) and remaining elevated beyond 10 years (SIR 1.24, [1.05–1.45]). API patients had a 23% overall excess risk (SIR 1.23, [1.11–1.36]), while AI/AN patients had the highest overall risk (SIR 1.82, [1.24–2.57]), particularly in the 12–59 month window (SIR 2.29, [1.25–3.84]) and ≥ 120 months (SIR 2.38, [1.19–4.26]). White survivors had no sustained increased risk (SIR 0.96, [0.93–0.98]), aside from a short-term rise in the first post-treatment year. Hispanic patients had consistently lower SPLC risk (overall SIR 0.72, [0.65–0.79]), while non-Hispanics had a transient early increase but an overall neutral risk (SIR 1.01, [0.99–1.04]). Marital status was protective: married individuals had a 12% lower SPLC incidence (SIR 0.88, 95% CI 0.85–0.91). Five-year overall survival after SPLC was 28.0%, with significant variation by race and ethnicity ($p = 0.002$). API (32.2%) and AI/AN (32.5%) patients had the highest survival, followed by White (28.0%) and Black patients (25.6%). Hispanic patients had the best outcomes, with 37.4% five-year survival and a mean age at death of 65.5 years, compared to 27.0% and 55.0 years for non-Hispanics ($p = 0.005$). Married patients had higher five-year survival (31.8%) and older mean age at death (64.3 years) compared to unmarried patients (25.0%, 48.6 years; $p < 0.001$). **Conclusion:** Radiation-associated SPLC risk and prognosis vary significantly by race, ethnicity, and marital status. Black and API survivors face sustained elevated risk; AI/AN survivors experience high early and long-term risk, while White and Hispanic survivors show no increased risk overall. Hispanic and married patients experience better survival after SPLC. These findings underscore the need for race and context aware survivorship counseling and suggest consideration of personalized lung cancer screening thresholds for breast cancer survivors receiving radiotherapy.

Keywords: breast cancer; adjuvant radiotherapy; second primary lung cancer; racial disparities; ethnic disparities; SEER database; cancer survivorship; marital status; survival outcomes; health disparities

1. Introduction

Breast cancer is the most common cancer among women in the United States and represents a significant public health burden [1]. Globally, the burden of breast cancer is expected to rise substantially, with projections estimating a 38% increase in incidence and a 68% increase in annual mortality by 2050, according to the International Agency for Research on Cancer (IARC), a specialized agency of the World Health Organization (WHO) [3]. The increased detection of early-stage breast cancer has resulted in a higher rate of breast-conserving surgeries followed by adjuvant radiotherapy (RT), now a standard component of multimodal treatment [4–7]. While advances in early detection and management have improved survival, treatment-related secondary malignancies have become increasingly recognized.

Although RT has significantly improved tumor control and survival outcomes, it also exposes adjacent thoracic structures to low dose ionizing radiation, an important and established factor in the development of second primary lung cancer (SPLC), especially among long-term survivors [8–13]. Previous studies have shown that breast cancer patients treated with RT may have up to double the risk of developing SPLC within ten years of treatment [9–14]. Additionally, recent evidence suggests that low-to-moderate radiation doses may be more carcinogenic than previously thought, and modern RT techniques have altered lung exposure patterns in clinically relevant ways. Specifically, intensity-modulated radiotherapy (IMRT) increases the volume of lung tissue exposed to low-dose radiation due to greater beam modulation, potentially elevating SPLC risk, whereas proton therapy reduces integral lung dose and may lower this risk, although long-term data remain limited [15–17]. Consequently, studies with extended follow-up beyond 10 years are needed to better define SPLC risk associated with contemporary RT techniques.

Beyond biological and treatment-related factors, social determinants of health (SDOH), including socioeconomic status, insurance coverage, race/ethnicity, education, and neighborhood environment, are key drivers of cancer outcomes [18]. Among breast cancer survivors, inequities in

access to care, health behaviors such as smoking, and continuity of follow-up contribute to disparities in both primary outcomes and long-term risks, including secondary lung cancer [19]. These factors may modify radiation-associated risk by shaping baseline susceptibility and post-treatment surveillance: in a large prospective cohort, ever-smokers had more than a threefold higher risk of second primary lung cancer than never-smokers (adjusted HR ~3.5), with risk increasing by ~24% per 10 pack-years, and nearly 80% of affected survivors did not meet current lung cancer screening criteria [20]. Understanding how SDOH intersect with cancer therapy and survivorship is essential to contextualizing observed disparities in secondary lung cancer incidence.

Research examining racial and ethnic disparities in second primary lung cancer following radiation exposure remains limited, despite consistent evidence that race and ethnicity modify cancer incidence, treatment delivery, survivorship care, and outcomes across oncology. The role of marital status in SPLC is even less well characterized; however, prior cancer research suggests that marital status may modify access to social support, adherence to post-treatment surveillance, and timeliness of medical follow-up, thereby potentially influencing SPLC detection and survival rather than risk alone. Given these gaps, a clearer understanding of how race, ethnicity, and marital status act as modifiers of SPLC risk and outcomes after radiotherapy is critically needed [21,22].

This study addresses these gaps by quantifying the incidence and survival outcomes of SPLC among breast cancer survivors treated with radiotherapy, with a specific focus on racial and ethnic disparities and the modifying effect of marital status. Using population-based data from the Surveillance, Epidemiology, and End Results (SEER) database, this analysis provides contemporary estimates of SPLC risk in the setting of modern breast cancer management and highlights the importance of incorporating demographic and social determinants into survivorship planning and lung cancer screening strategies.

2. Methods

2.1. Data Source

Patient diagnosed with a SPLC, following prior diagnosis of breast cancer treated with radiation therapy, from January 1, 2000 to December 31, 2022 were collected from the Surveillance, Epidemiology and End Results (SEER) (www.seer.cancer.gov) using SEER Stat software. We used the Incidence - SEER Research Data, 17 Registries, Nov 2023 Sub (2000-2022) - Linked to County Attributes - Time Dependent (1990-2022) Income/Rurality, 1969-2022 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2024, based on the November 2024 submission. Because SEER data are publicly available and de-identified, institutional review board (IRB) approval and informed consent were not required for this study.

2.2. Patient Selection

We included patients from the SEER database who met the following inclusion criteria: (1) diagnosed with primary breast cancer, using Site Recode ICD-O-3/WHO 2008 as "Breast" (ICD-O codes: 500-509); (2) received radiation therapy; (3) developed a SPLC (defined by SEER criteria for second primary malignancies (https://training.seer.cancer.gov/arc_neoplasms/)); (4) and had a minimum latency exclusion period of 2 months to avoid synchronous malignancies. Patients meeting the following criteria were excluded: prior cancer diagnoses, using the SEER filter for "First Primary Only" as Breast Cancer (Sequence Number = 0 or 1); incomplete follow-up or missing racial information. Race was determined based on the "Race record" variable, which included (white, black, American Indian, Asian or pacific islander). Ethnicity was determined based on "race and ethnicity" variable, which was classified into (Hispanic, Non-Hispanic).

2.3. Outcome Definition

The primary outcome was the development of secondary primary malignancies (SPMs), defined as: 1) A new malignancy diagnosed ≥ 2 months after the initial breast cancer diagnosis to exclude

synchronous cancers. 2) SPMs were identified based on SEER definitions of primary tumor sites and behavior codes, excluding recurrences and metastases. Patients were followed until death or end of follow-up period.

2.4. Covariates

We collected clinicopathological data for each patient, including the following variables: Patient ID, age, gender, race, ethnicity, marital-status, histological type, radiation therapy types, chemotherapy, and survival duration in months, tumor size, stage at diagnosis of primary tumor, metastasis at diagnosis, and laterality.

2.5. Statistical Analysis

The Multiple Primary Standardized Incidence Ratio (MP-SIR) session in SEER*Stat software version 8.4.4 and SPSS v.27 was used for all analyses. Standardized Incidence Ratios (SIRs) were calculated as the ratio of observed SPM cases in the study cohort to the expected cases in the general population. Expected cases were estimated based on age-, sex-, race-, and calendar year-adjusted incidence rates from the SEER reference population. Formula: $SIR = \text{Observed Cases} / \text{Expected Cases}$. 95% Confidence Intervals (CIs): Poisson distribution methods were used to compute confidence intervals for statistical significance. Survival analysis was performed, where OS was estimated using Kaplan-Meier survival analysis. Survival differences among patient groups were assessed using log-rank tests. To account for potential confounding factors, multivariable Cox proportional hazards regression models were used. A p-value of <0.05 was considered significant. All statistical analyses were conducted using IBM SPSS Statistics version 27.0. For subgroup analysis, SIRs were further stratified by race, ethnicity, and marital status.

3. Results

3.1. Cohort Profile

This analysis included 6,674 breast cancer survivors who received radiotherapy between 2000 and 2022 and were later diagnosed with second primary lung cancer (SPLC). On average, SPLC developed 7.01 years after the initial breast cancer diagnosis (SD 5.00), with latency ranging from 0 to 22 years. At diagnosis, the average age was 71.17 years (SD 9.90), and patients' ages ranged from 32 to 92. Most of the cohort was female (99.6%). In terms of race, 85.4% of the patients were White (n = 5,700), followed by 9.1% Black (n = 605), 5.1% Asian or Pacific Islander (n = 340), and 0.4% American Indian or Alaska Native (n = 29). Most patients (93.8%) were non-Hispanic, and 43.4% were married at the time they were first diagnosed with breast cancer. The location of the original breast tumor was almost evenly split, with 50.7% on the left side and 49.1% on the right. However, when SPLC developed, it occurred more often in the right lung (54.3%) than in the left (40.1%). The most common radiation (RA) type was beam radiation (n=6256), accounting for (94.3%) of the total sample, while radioisotopes were the least common, with only four cases in total. (Table 1).

Table 1. Baseline characteristics of 6,674 breast-cancer survivors who developed a second primary lung cancer.

Characteristics	Mean (SD)	Range(Min/Max)
Latency Period	7.01(5.003)	22(0/22)
Age	71.17(9.90)	60(32/92)
Characteristics	Frequency (N = 6674)	Percent
Race		
White	5700	85.4
Black	605	9.1
Asian	340	5.1
American/india	29	0.4
Sex		

Female	6646	99.6
Male	28	0.4
Ethnicity		
Non-Hisp	6258	93.8
Hispanic	416	6.2
Marital status		
Married (including com	2899	43.4
Widowed	1730	25.9
Divorced	876	13.1
Single (never married)	782	11.7
Unknown	326	4.9
Separated	49	0.7
Unmarried or Domestic	12	0.2
Laterality (breast)		
Left - origin of primary	3386	50.7
Right - origin of primar	3274	49.1
Paired site, but no info	12	0.2
Only one side - side uns	2	0.0
Laterality (lung)		
Right - origin of primary	3626	54.3
Left - origin of primary	2675	40.1
Paired site, but no infor	284	4.3
Bilateral, single primary	66	1.0
Only one side - side unsp	17	0.3
Not a paired site	6	0.1

3.2. Histopathology

The histopathological types of primary breast cancer in the cohort varied, with the most common being infiltrating duct carcinoma, not otherwise specified (NOS; ICD-O-3 8500/3), which accounted for 74.6% of cases (n= 4,980). Other frequently observed subtypes included mixed infiltrating duct and lobular carcinoma (8522/3) at 8.1%, and solid papillary carcinoma with intraductal features (8523/3) at 6.2%. Each of the remaining subtypes made up less than 5% of the total cases (Figure 1).

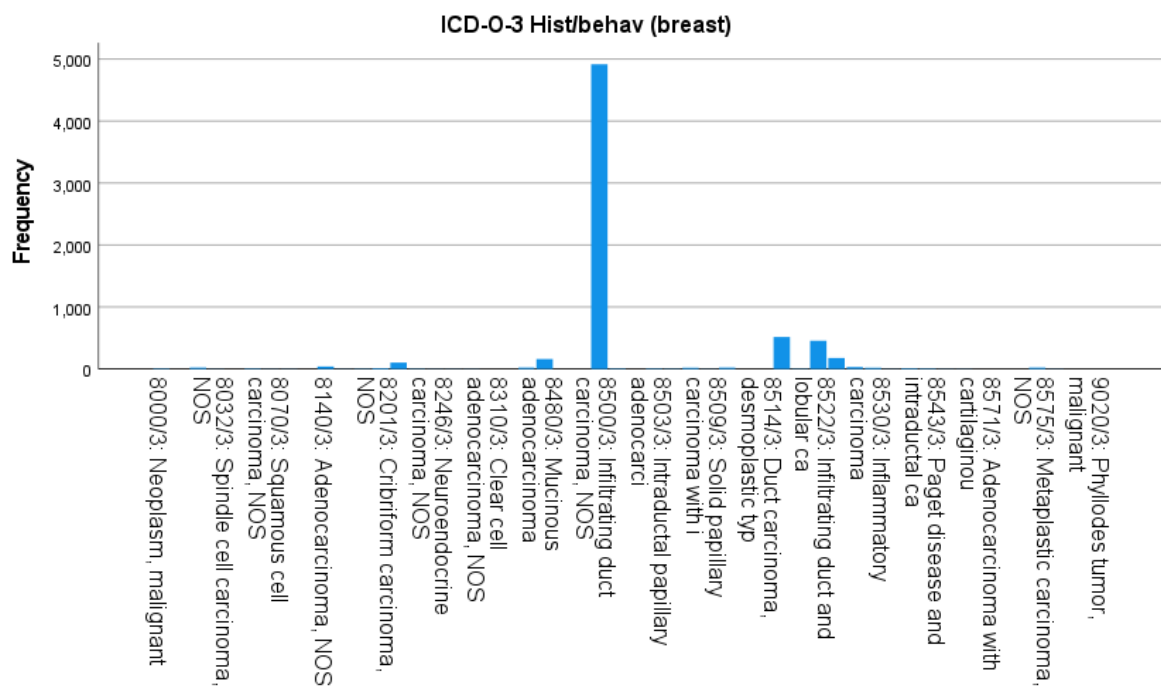


Figure 1. Histologic distribution of primary breast tumors (ICD-O-3 codes).

In terms of SPLC histology, adenocarcinoma NOS (8140/3) was the most diagnosed type, accounting for 37.5% (n = 2,500). This was followed by squamous-cell carcinoma NOS (8070/3) at 13.9% (n = 930), combined small-cell carcinoma variants (8044/3 and 8041/3) at 19.3% (n = 1,288), solid carcinoma NOS (8230/3) at 4.0% (n = 268), and atypical carcinoid tumor (8249/3) at 3.4% (n = 225). All remaining subtypes together represented 21.9% of the SPLC cases (Figure 2).

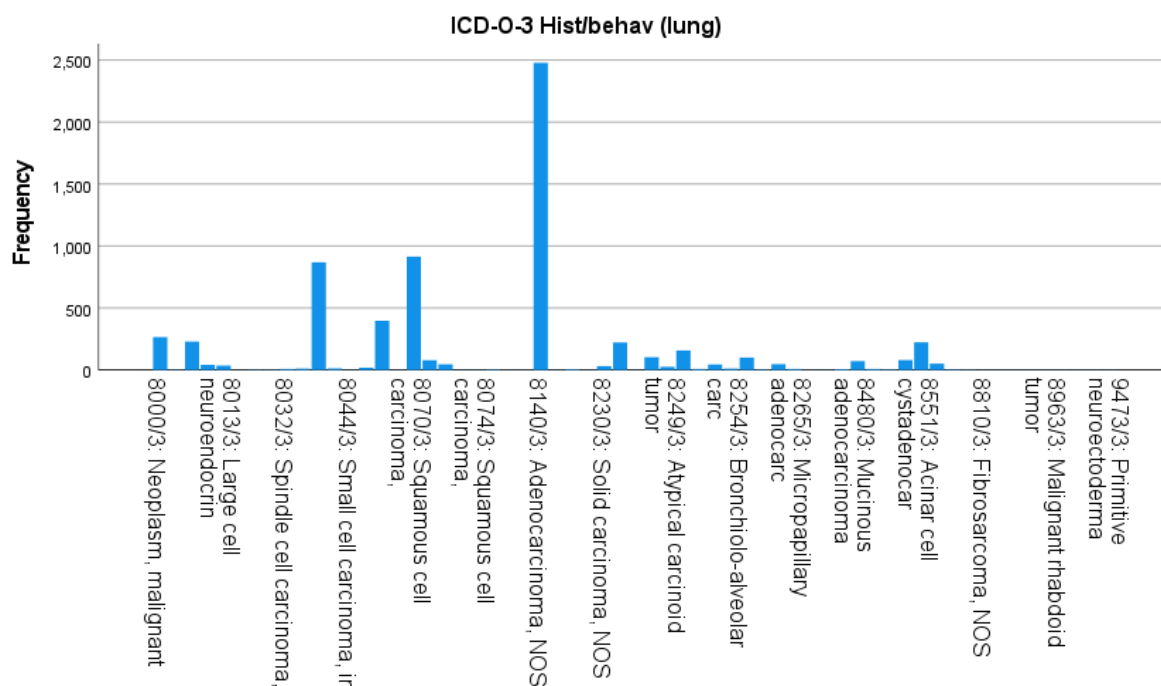


Figure 2. Histologic distribution of second primary lung cancers (ICD-O-3 codes).

3.3. Standardized Incidence Ratios (SIRs)

SIRs varied based on race and latency period. In the early phase (2–11 months), elevated SIRs were seen in Whites (1.11; 95% CI: 1.01–1.19), Blacks (1.47; 1.09–1.51), Asian/Pacific Islanders (1.61; 1.15–2.22), and American Indian/Alaska Natives (1.35; 0.16–4.87), though the latter was not statistically significant. Among White patients, risk decreased in the 12–59 month window (0.88; 0.80–0.92) and overall (0.96; 0.93–0.98). In contrast, Black patients experienced elevated risk across later periods—60–119 months (1.44; 1.26–1.63), ≥120 months (1.24; 1.05–1.45), and overall (1.21; 1.12–1.31). Asian/Pacific Islanders showed a consistently elevated overall risk (1.23; 1.11–1.36). Meanwhile, American Indian/Alaska Natives had significantly high SIRs at 12–59 months (2.29; 1.32–3.74), ≥120 months (2.38; 1.29–4.38), and overall (1.82; 1.24–2.57) (Table 3, Figure 8, Figure 9).

Table 2. Overall and subgroup survival following second primary lung cancer.

Characteristic	Mean Age of Survival	Confidence Interval (95%)	5 Year Survival	p-Value
Race				
Ameri	66.165	38.89-93.439	32.5%	0.002
Asian	68.819	56.761-80.877	32.2%	0.002
Black	54.391	45.667-63.114	25.6%	0.002
White	54.943	52.3-57.586	28%	0.002
Marital Status				
unmarried	48.638	45.702-51.575	25%	0.000
married	64.306	60.255-68.357	31.80%	0.000
Ethnicity				
Hispanic	65.480	55.085-75.876	37.40%	0.005
Non-Hisp	54.969	52.436-57.503	27%	0.005

Table 3. Standardised incidence ratios of second primary lung cancer by race and latency interval.

Among Races				
Duration	Observed	Expected	SIR	CI
White				
2-11 Months	579	527.37	1.1 #	1.01-1.19
12-59 Months	1,985	2,243.39	0.88 #	0.85-0.92
60-119 Months	1,957	2,018.48	0.97	0.93-1.01
120+ Months	1,732	1,756.82	0.99	0.94-1.03
Total	6,253	6,546	0.96 #	0.93-0.98
Black				
2-11 Months	59	50.36	1.17	0.89-1.51
12-59 Months	207	200.81	1.03	0.9-1.18
60-119 Months	235	163.44	1.44 #	1.26-1.63
120+ Months	155	125.5	1.24 #	1.05-1.45
Total	656	540.11	1.21 #	1.12-1.31
American Indian/Alaska Native				
2-11 Months	2	1.48	1.35	0.16-4.87
12-59 Months	14	6.12	2.29 #	1.25-3.84
60-119 Months	5	5.39	0.93	0.3-2.17
120+ Months	11	4.63	2.38 #	1.19-4.26
Total	32	17.61	1.82 #	1.24-2.57
Asian or Pacific Islander				
2-11 Months	39	24.21	1.61 #	1.15-2.2
12-59 Months	120	101.47	1.18	0.98-1.41

60-119 Months	119	92.03	1.29 #	1.07-1.55
120+ Months	95	85.28	1.11	0.9-1.36
Total	373	302.99	1.23 #	1.11-1.36
Unknown				
2-11 Months	1	2.02	0.5	0.01-2.76
12-59 Months	1	7.57	0.13 #	0-0.74
60-119 Months	0	5.74	0 #	0-0.64
120+ Months	0	4.4	0 #	0-0.84
Total	2	19.73	0.10 #	0.01-0.37

#: p-value less than 0.05.

Ethnic differences were also notable. Hispanic patients had consistently lower risk of developing SPLC. Their overall SIR was 0.72 (0.65–0.79), with further reductions during 12–59 months (0.56; 0.47–0.67), 60–119 months (0.75; 0.63–0.89), and ≥120 months (0.79; 0.66–0.94). By comparison, non-Hispanic patients showed a brief spike in early risk (2–11 months: 1.13; 1.05–1.23), followed by a small decrease at 12–59 months (0.94; 0.90–0.98), resulting in an overall neutral risk (1.01; 0.99–1.04) (Table 5, Figure 8).

Marital status also showed associations with SPLC risk. Married individuals had a lower overall risk (SIR 0.88; 0.85–0.91), with statistically significant reductions at 12–59 months (0.82; 0.77–0.87), 60–119 months (0.91; 0.86–0.96), and beyond 120 months (0.89; 0.84–0.94). In contrast, those who were unmarried had a higher risk during the 2–11 month interval (1.12; 1.04–1.21), a decreased risk at 12–59 months (0.91; 0.87–0.95), and a neutral overall risk (0.99; 0.96–1.01) (Table 4).

Table 4. Standardized incidence ratios by ethnicity and latency interval.

Ethnicity				
Duration	Observed	Expected	SIR	CI
Hispanic				
2-11 Months	55	53.83	1.02	0.77-1.33
12-59 Months	125	221.33	0.56 #	0.47-0.67
60-119 Months	144	191.52	0.75 #	0.63-0.89
120+ Months	127	161.58	0.79 #	0.66-0.94
Total	451	628.26	0.72 #	0.65-0.79
Non-Hispanic				
2-11 Months	624	550.24	1.13 #	1.05-1.23
12-59 Months	2,202	2,332.61	0.94 #	0.9-0.98
60-119 Months	2,172	2,088.90	1.04	1-1.08
120+ Months	1,866	1,811.24	1.03	0.98-1.08
Total	6,864	6,782.99	1.01	0.99-1.04
Unknown				
2-11 Months	1	1.37	0.73	0.02-4.06
12-59 Months	0	5.42	0.00 #	0-0.68
60-119 Months	0	4.64	0.00 #	0-0.79
120+ Months	0	3.81	0.00 #	0-0.97
Total	1	15.25	0.07 #	0-0.37

#: p-value less than 0.05.

Table 5. Standardized incidence ratios by marital status and latency interval.

Marital Status				
Duration	Observed	Expected	SIR	CI
Married				
2-11 Months	321	331.45	0.97	0.87-1.08

12-59 Months	1,180	1,443.96	0.82 #	0.77-0.87
60-119 Months	1,236	1,362.23	0.91 #	0.86-0.96
120+ Months	1,145	1,284.98	0.89 #	0.84-0.94
Total	3,882	4,422.63	0.88 #	0.85-0.91
Unmarried				
2-11 Months	680	605.44	1.12 #	1.04-1.21
12-59 Months	2,327	2,559.36	0.91 #	0.87-0.95
60-119 Months	2,316	2,285.07	1.01	0.97-1.06
120+ Months	1,993	1,976.63	1.01	0.96-1.05
Total	7,316	7,426.50	0.99	0.96-1.01

#: p-value less than 0.05.

3.4. Survival Analysis

Survival after SPLC diagnosis was generally poor, with a five-year overall survival rate of 28.0% (Figure 3). There were notable differences by race and ethnicity. Asian/Pacific Islanders had the highest five-year survival (32.2%) and the highest mean age at death (68.82 years), followed by American Indian/Alaska Natives (32.5%; 66.17 years), Whites (28.0%; 54.94 years), and Blacks (25.6%; 54.39 years), with a statistically significant difference ($p = 0.002$) (Figure 6). Marital status also played a role: married patients lived longer (mean age at death 64.31 years) and had a higher five-year survival rate (31.8%) compared to unmarried individuals (48.64 years; 25.0%, $p < 0.001$) (Figure 5). Hispanic patients also fared better than non-Hispanics, with a mean survival age of 65.48 years and a five-year survival of 37.4%, compared to 55.0 years and 27.0% in non-Hispanics ($p = 0.005$) (Table 2, Figure 4, Figure 7).

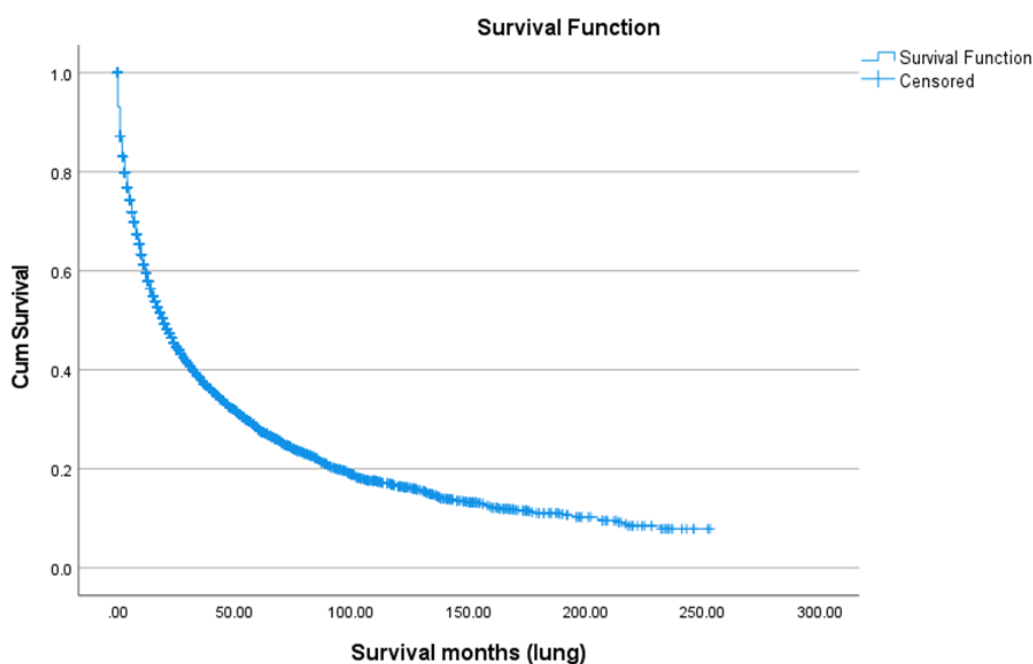


Figure 3. Overall survival among SPLC patients.

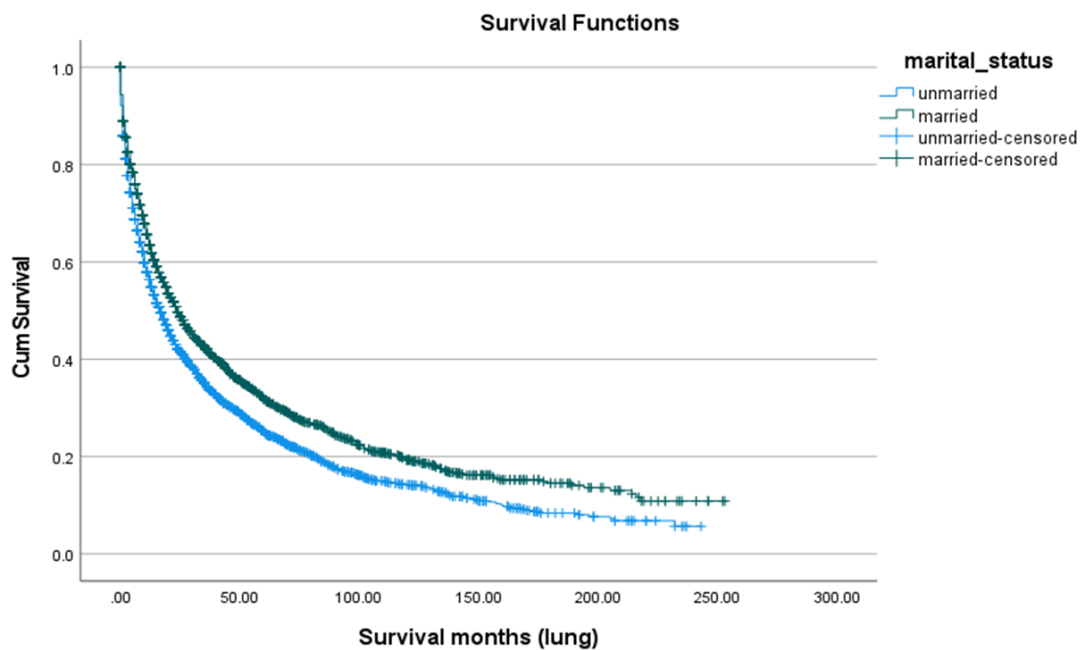


Figure 4. Survival according to marital status.

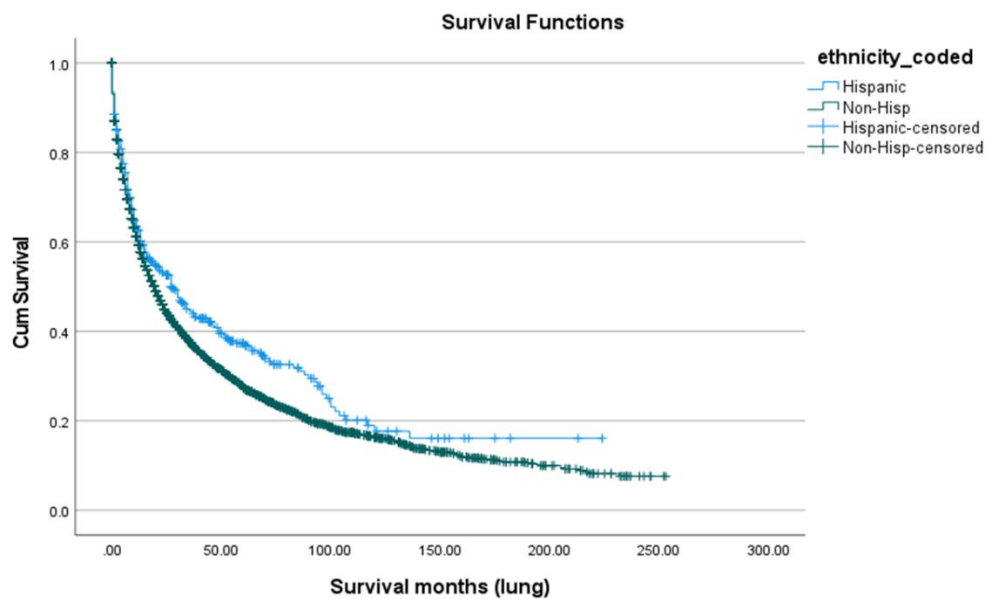


Figure 5. Survival according to ethnicity.

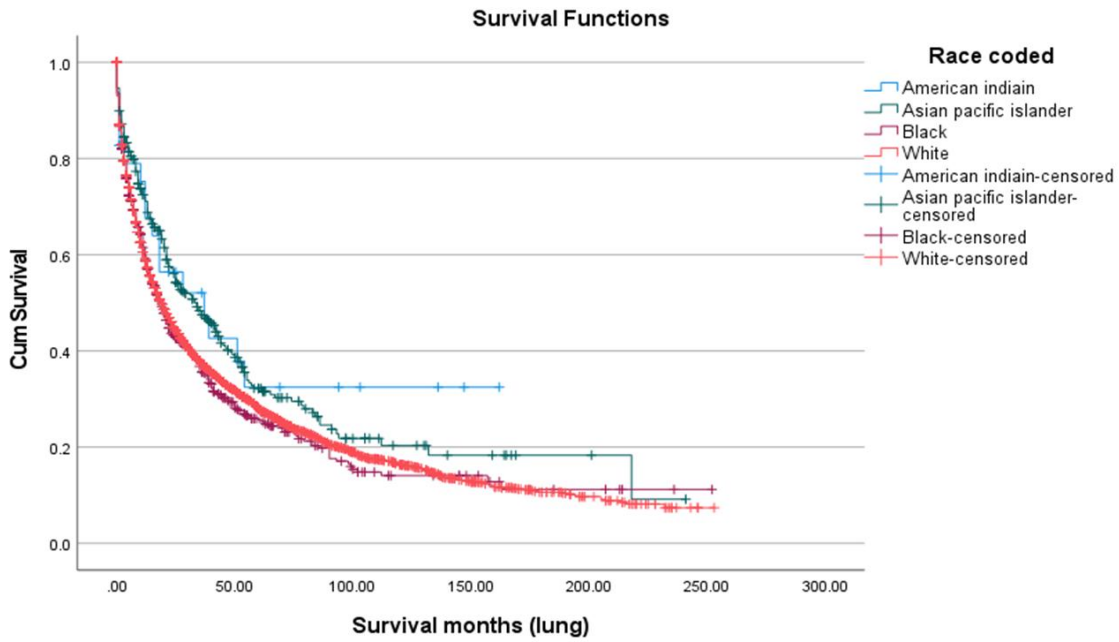


Figure 6. Survival according to race.

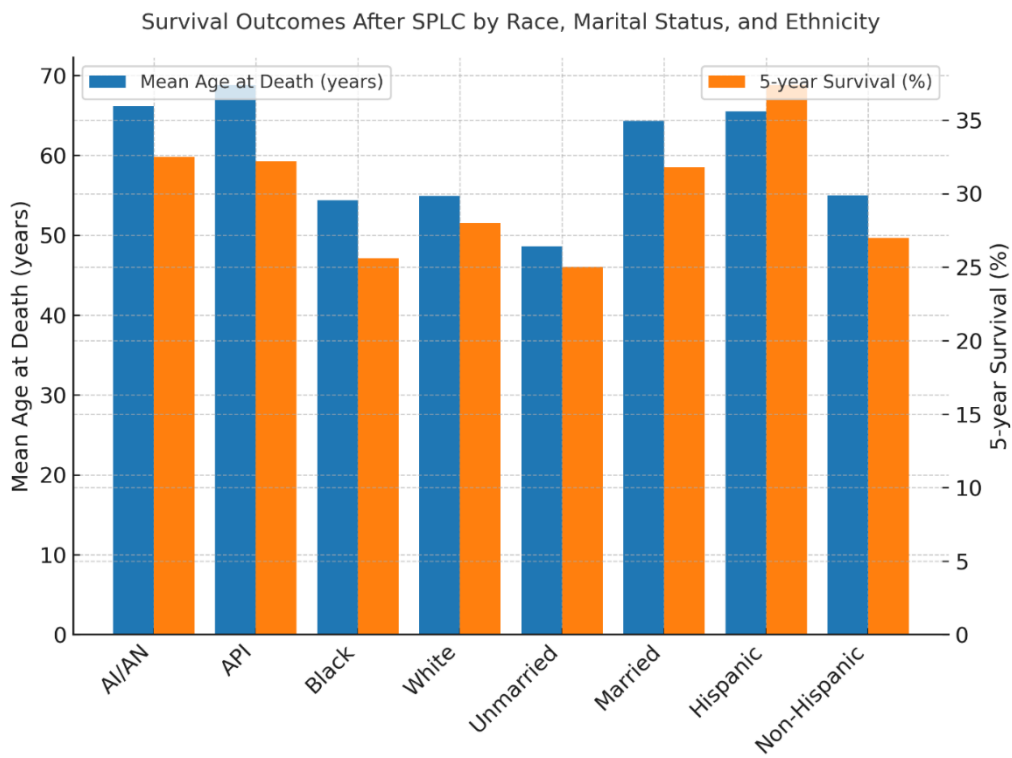


Figure 7. Combined groups' survival outcomes.

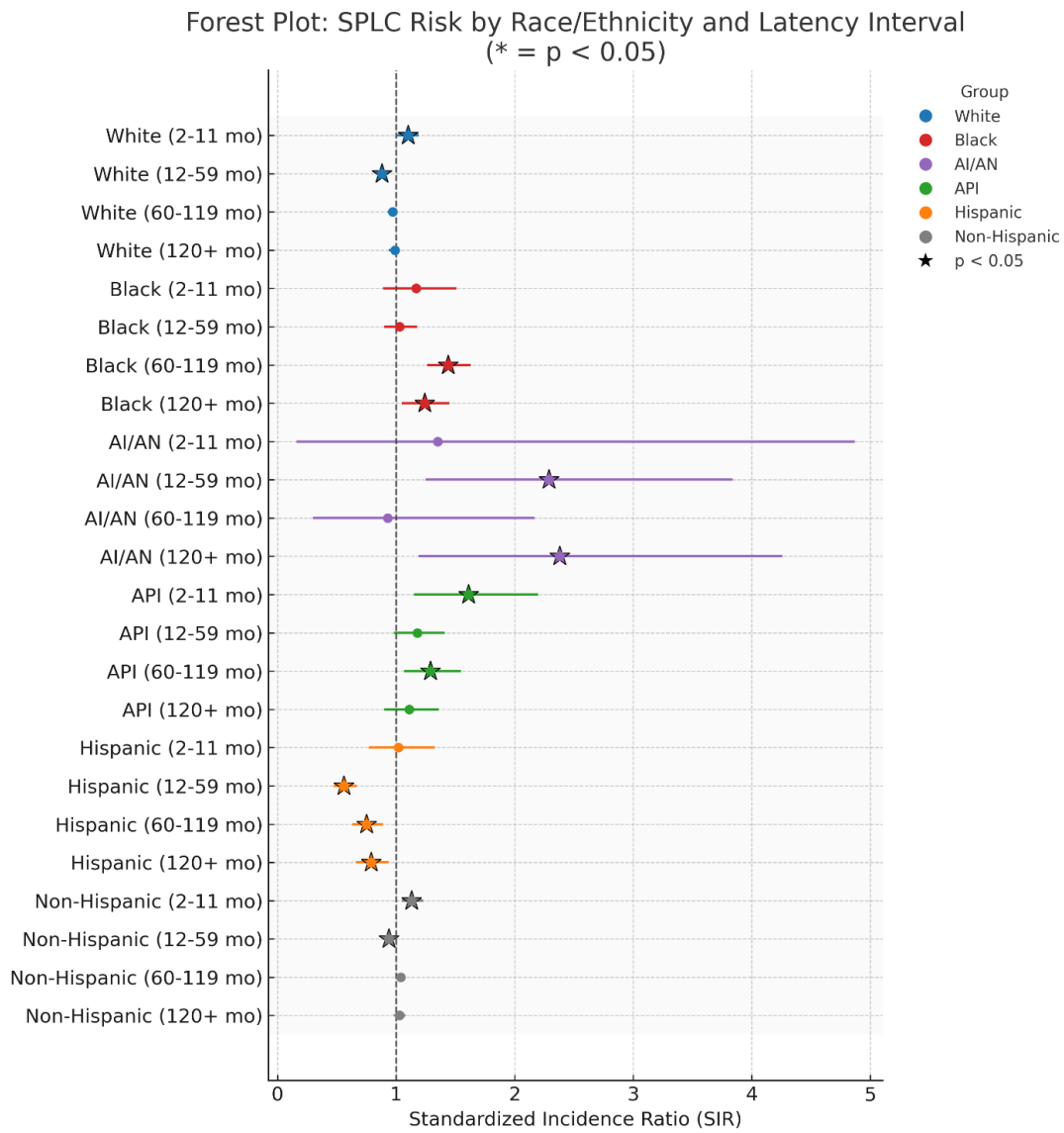
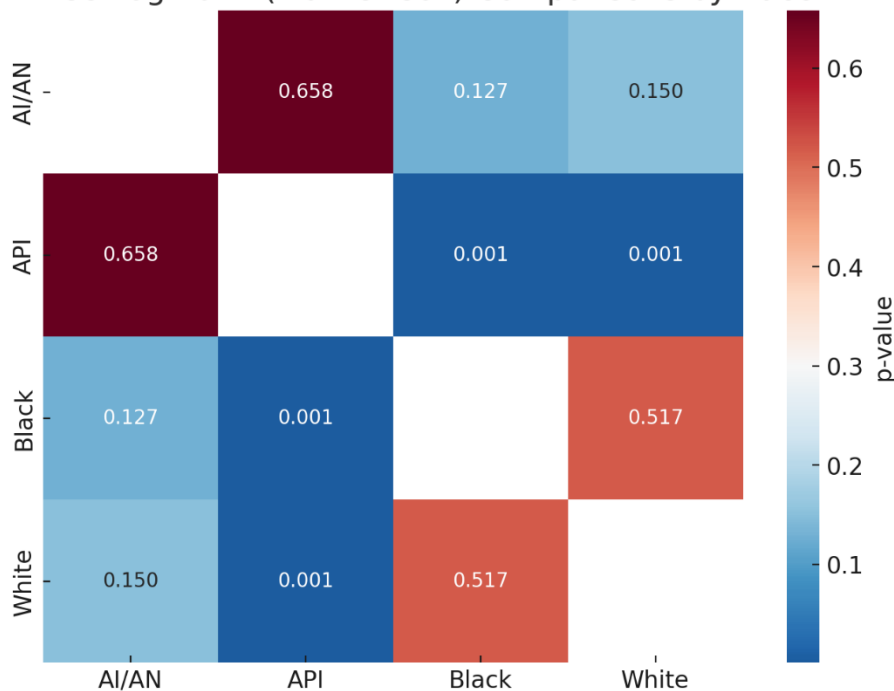


Figure 8. SPLC risk and latency interval according to race and ethnicity.

Pairwise Log Rank (Mantel-Cox) Comparisons by Race

**Figure 9.** Pairwise Log Rank (Mantel-Cox) Comparisons by Race*.

3.5. Cox Proportional Hazards Regression

The analysis identified several significant demographic and clinical predictors of mortality. Marital status was a key factor, with unmarried patients showing a higher risk of death than married patients (HR 1.139, 95% CI 1.072–1.209; $p < 0.001$). Hispanic ethnicity was associated with a lower hazard compared with non-Hispanic ethnicity (HR 0.842, 95% CI 0.741–0.957; $p = 0.009$). Overall stage was not significant ($p = 0.270$); however, Stage IV predicted increased mortality (HR 1.366, 95% CI 1.011–1.847; $p = 0.043$). Breast histology was significant in outcomes (overall $p = 0.001$), with ductal, lobular, adenocarcinoma, and mixed ductal/lobular subtypes demonstrating reduced hazards (HR range 0.680–0.772; all $p \leq 0.012$). Race was significant overall ($p = 0.049$), largely due to the lower risk among Asian/Pacific Islander patients (HR 0.857, 95% CI 0.744–0.986; $p = 0.031$). Mortality increased with age (HR 1.024 per year, 95% CI 1.020–1.027; $p < 0.001$), while tumor side ($p = 0.465$) and sex ($p = 0.869$) were not significantly associated with survival. Radiation type was not significantly associated with mortality (overall $p = 0.149$). Across radiation categories, there were no statistically significant differences in HR (beam radiation: HR 1.197, $p = 0.799$; combination: HR 1.563, $p = 0.546$; radiation NOS: HR 1.320, $p = 0.700$; radioactive implants: HR 1.017, $p = 0.982$) (Table 6)

Table 6. Cox proportional hazards regression .

		p-Value	HR	95.0% CI	
				Lower	Upper
Marital status	Unmarried vs Married*	0.000	1.139	1.072	1.209
Ethnicity	Hispanic vs Non-Hisp*	0.009	0.842	0.741	0.957
Stage	Overall	0.270			
	Stage (1)	0.716	1.032	0.870	1.224
	Stage (2)	0.545	1.055	0.886	1.257
	Stage (3)	0.598	1.052	0.871	1.272
	Stage (4)	0.043	1.366	1.011	1.847
Breast Histology	Overall	0.001			
	Ductal	0.001	0.757	0.647	0.886

	Lobular	0.001	0.723	0.600	0.870
	Adenocarcinoma	0.012	0.772	0.632	0.944
	Mixed Ductal/Lobular	0.000	0.680	0.569	0.813
Side	Overall	0.465			
	Same side	0.729	0.987	0.918	1.062
	Opposite side	0.216	0.952	0.882	1.029
Age	Mean Age	0.000	1.024	1.020	1.027
Sex	Female vs Male*	0.869	0.961	0.596	1.548
Race	Overall	0.049			
	American Indian/Alaska Native	0.185	0.724	0.449	1.167
	Asian or Pacific Islander	0.031	0.857	0.744	0.986
	Black	0.288	1.057	0.954	1.172
Radiation (RA)	Overall	0.149			
	Beam RA	0.799	1.197	0.299	4.794
	Combination of RA	0.546	1.563	0.367	6.658
	RA, (NOS)	0.700	1.320	0.322	5.405
	RA implants	0.982	1.017	0.252	4.101

#: p-value less than 0.05. *: Reference Value.

4. Discussion

In this population-based study using SEER data, we investigated the incidence and survival outcomes of SPLC following breast cancer radiotherapy, with a focus on racial/ethnic disparities and the influence of marital status. Our study demonstrated that the incidence of secondary primary lung cancer (SPLC) following breast cancer radiotherapy was elevated most significantly in American Indians and Alaska natives (AI/AN), who experienced risks more than double the expected rate. The incidence was also higher among Black individuals, as well as Asians and Pacific Islanders (API). Additionally, we observed consistently low SPLC risks among married patients, suggesting a potential protective effect.

The results on incidence of SPLC align with the findings of the current literature, which report an elevated long-term risk of SPLC after breast radiotherapy. The increased risk of SPLC following breast radiotherapy observed in Black patients, API, and AI/AN suggests a persistent biological vulnerability or environmental exposures that are not mitigated by modern radiotherapy protocols. Nevertheless, the risk is thought to be lower than previously published, with an incidence of 1.19% in our study compared to 1.74% in [23]. While the primary lung cancer incidence rate in Black individuals has been consistently higher than that in Whites [24], data showed that AI/AN had a lower incidence of primary lung cancer than Whites [25]. Our study reveals that the risk in AI/AN populations is more pronounced than previously reported. This is a significant contribution, as few studies have specifically examined this group in the context of radiation-induced cancers.

Our analysis showed that married patients have had a lower likelihood of SPLC over both 5-year and 10-year periods. While unmarried patients had a higher likelihood of SPLC during the first year, this likelihood decreased over time. This suggests that social support has a vital role to play in reducing the risk of having lung cancer, as it helps patients to recognize respiratory symptoms as they arise and may also contribute to a reduction in smoking rates [26].

The median overall survival (OS) for patients with SPLC in our study differed significantly among racial groups, with API having the longest OS at 68.8 months, followed by AI/AN and White individuals; Black patients showed the shortest OS at 54.4 months. The five-year survival also varied between racial groups, for it was highest amongst Hispanics and lowest amongst Black individuals. This is likely due to multiple variables on different levels, including patient-level factors such as socioeconomic barriers, cultural stigma, mistrust, and insurance limitations, physician-level variables such as implicit bias, stereotyping, and inconsistent treatment recommendations. Finally, system-

level factors play a crucial role and include, but are not limited to, unequal access to high-quality care, underrepresentation in trials, and delayed treatment [27].

Our study found that Hispanic breast cancer survivors had a lower risk of SPLC and better five-year survival compared with non-Hispanic patients. This pattern is consistent with the well-described lower baseline incidence of lung cancer among Hispanic populations, a trend largely attributed to lower smoking prevalence, cultural factors, and differences in environmental exposures. These established population patterns likely contribute to the reduced SPLC risk observed in our cohort. Further research is needed to clarify how these factors interact with prior radiation exposure and to ensure appropriate risk-based follow-up. [28–30].

For married individuals, survival outcomes were superior to those of unmarried patients. Likely due to psychosocial, economic, and environmental factors, having a partner or spouse is associated with a healthier lifestyle, a greater chance of detecting the disease at an earlier stage, and a higher likelihood of opting for active treatment [31].

Multiple risk factors have been described to affect the incidence of SPLC following breast radiotherapy, including smoking [32], dose [33], and type of radiation (proton vs photon therapies) [34]. Findings from our study suggest the increased risk in certain racial groups and people who are unmarried, raising the need to design a risk stratification tool to include the abovementioned risk factors and better predict the risk of SPLC associated with breast radiotherapy. Better screening and surveillance should also be implemented based on such a tool.

This study is limited by its reliance on retrospective data and the SEER database. As a registry-based dataset, SEER lacks important clinical variables such as smoking status, radiation dose, treatment details, and key comorbidities, which restricts the ability to adjust for major confounders. SEER also does not capture some essential socioeconomic indicators, limiting the robustness of statistical adjustments for social determinants of health. Additionally, SEER covers approximately half of the U.S. population, which may limit the generalizability of our findings to non-SEER regions. Follow-up and latency definitions are based on SEER multiple primary rules, which may result in shorter follow-up windows than ideal for capturing radiation-associated SPLCs. Future research using prospective cohorts with comprehensive clinical and socioeconomic information is needed to better evaluate the roles of smoking, radiation dose, comorbidities, and marital status in SPLC risk after breast radiotherapy. Moreover, further studies are needed to better characterize the biological and clinical significance of SPLCs occurring shortly after breast cancer diagnosis and radiotherapy.

5. Conclusions

This population-based cohort study demonstrates that the risk and survival outcomes of second primary lung cancer (SPLC) after breast cancer radiotherapy vary significantly by race, ethnicity, and marital status. These findings highlight the need to integrate sociodemographic factors into survivorship care and long-term surveillance strategies for breast cancer patients receiving radiotherapy. Future work should prioritize developing personalized risk-stratification models that incorporate race, social context, and treatment history to guide equitable lung cancer screening and follow-up.

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