Risk of developing subsequent primary lung cancer after receiving radiation for breast cancer

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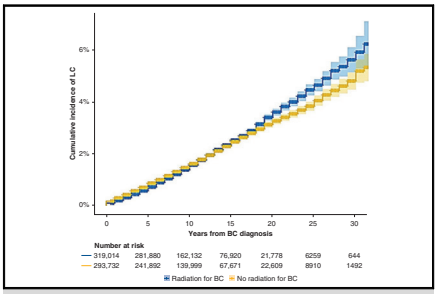
ABSTRACT

Background: Radiotherapy (RT) is integral to breast cancer treatment, especially in the current era that emphasizes breast conservation. The aim of our study was to determine the incidence of subsequent primary lung cancer after RT exposure for breast cancer over a time span of 3 decades to quantify this risk over time as modern oncologic treatment continues to evolve.

Methods: The SEER (Surveillance, Epidemiology, and End Results) database was queried from 1988 to 2014 for patients diagnosed with nonmetastatic breast cancer. Patients who subsequently developed primary lung cancer were identified. Multivariable regression modeling was performed to identify independent factors associated with the development of lung cancer stratified by follow up intervals of 5 to 9 years, 10 to 15 years, and >15 years after breast cancer diagnosis.

Results: Of the 612,746 patients who met our inclusion criteria, 319,014 (52%) were irradiated. primary lung cancer developed in 5556 patients (1.74%) in the RT group versus 4935 patients (1.68%) in the non-RT group. In a multivariable model stratified by follow-up duration, the overall HR of developing subsequent ipsilateral lung cancer in the RT group was 1.14 ($P = .036$) after 5 to 9 years of follow-up, 1.28 ($P = .002$) after 10 to 15 years of follow-up, and 1.30 ($P = .014$) after >15 years of follow-up. The HR of contralateral lung cancer was not increased at any time interval.

Conclusions: The increased risk of developing a primary lung cancer secondary to RT exposure for breast cancer is much lower than previously published. Modern RT techniques may have contributed to the improved risk profile, and this updated study is important for counseling and surveillance of breast cancer patients. (JTCVS Open 2023;16:919-28)



Cumulative incidence of lung cancer stratified by receipt of radiotherapy.

CENTRAL MESSAGE

The receipt of radiotherapy for breast cancer therapy poses a small but real increased risk of developing primary lung cancer as the years of follow-up from breast cancer diagnosis increase.

PERSPECTIVE

Radiotherapy is a risk factor that is not specified in national lung cancer screening guidelines. Although the risk ratios in our study do not merit generalized lung cancer screening for this cohort of patients, the study should provide awareness to physicians who counsel patients on the risk of developing lung cancer.

See Discussion on page 929.

Breast and lung cancer are the first and second most common cancers in the United States, respectively, with more than 200,000 new cases reported for each cancer in 2022 alone.[1,2] Although both cancers have formal screening programs supported by influential organizations, such as the National Comprehensive Cancer Network, the uptake of breast cancer screening has been much more successful than the uptake of lung cancer screening.[3] Notably, mortality rates from breast cancer have declined over the last decade, while lung cancer remains the leading cause of cancer deaths.[4,5] The higher incidence of early-stage diagnoses for breast cancer has contributed to significant practice changes over time, including the increased use of breast conservation surgery with adjuvant radiotherapy (RT).[6]

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Abbreviations and Acronyms
CI = confidence interval
HR = hazard ratio
RT = radiotherapy
SEER = Surveillance, Epidemiology, and End Results

The publication of numerous landmark trials demonstrating that partial mastectomy with postoperative RT has equivalent survival to mastectomy has changed the landscape of breast cancer management to incorporate RT as an integral aspect of multimodality treatment.[7-9]

The combination of early diagnosis, high cure rates, long patient survivorship, and changing management strategies in breast cancer highlights the importance of studying the long-term effects of RT in survivors. In prior studies, RT exposure for breast cancer has been associated with the development of subsequent primary lung cancer, with reported risk ratios of up to 2.0 for patients who live for 10 years beyond their initial breast cancer diagnosis.[10-14] However, these studies did not quantify the risk over time or evaluate the impact on patient survival and were conducted in an outdated patient cohort that does not reflect modern oncologic practices. Moreover, these increased risk ratios are not reflected in current lung cancer screening practice, as existing guidelines identify current and former smokers as the only pool of screening-eligible patients[15] but most patients who are diagnosed with lung cancer fall outside of these screening guidelines.

Expansion of screening criteria merits ongoing assessment, with careful weighing of risks, benefits, and cost-effectiveness. Our study aims to provide updated data on the incidence of subsequent primary lung cancer after RT exposure for breast cancer and to quantify this risk over time as modern oncologic treatment has continued to evolve.

METHODS

Data Source

The Surveillance, Epidemiology, and End Results (SEER) database is provided by the National Cancer Institute, which collects data from cancer diagnoses in 19 geographic areas in the United States. The data are sourced from an area that covers approximately 35% of the country and are generalizable to the entire US population. Data from 1988 to 2014 were included in this study. The most updated SEER data available are from 2019, which allowed a minimum of 5 years of follow-up for the most contemporary patients in our cohort. Because patients are deidentified in this database, this study was exempt from review by the Stanford Institutional Review Board.

Patient Selection

All patients age >18 years diagnosed with nonmetastatic breast cancer were identified using American Joint Committee on Cancer guidelines. Patients with previous malignancies prior to their breast cancer diagnosis and those with incomplete data were excluded. Patients who did not undergo surgery as part of the treatment of their breast cancer also were excluded. The cohort was then stratified into those who received RT as part of their breast cancer treatment and those who did not. Of note, details of RT, such as prescribed dose and completion, are not provided in the SEER database.

Finally, patients were classified as those who developed a subsequent primary lung cancer at least 6 months after their breast cancer diagnosis versus those who did not develop lung cancer (Figure 1).[10,13] Heterogenous studies on lead time, tumor doubling time, and prevalence/incidence ratios in lung cancer cite 2 to 18 months as the average time for development of a lung cancer.[16] This 6-month time period was chosen to exclude early lung cancers after breast cancer diagnosis that would not be plausibly attributable to radiation and is consistent with study designs with similar clinical questions. The follow-up time from initial breast cancer diagnosis to subsequent primary lung cancer diagnosis was calculated by subtracting the year of breast cancer diagnosis to year of lung cancer diagnosis (the SEER database no longer provides the specific month of diagnosis).

Postoperative Outcomes and Survival Analyses

Multivariable Cox proportional hazards regression modeling was used to estimate the relative risk of developing lung cancer after RT for breast cancer. We focused on the development of ipsilateral lung cancer but also examined overall and contralateral lung cancer rates. When the proportional hazards assumption was tested, a log-minus-log plot demonstrated a nonrandom pattern against time, violating the proportional hazards assumption. Therefore, we stratified follow-up intervals into 5-year periods: 0.5 to 4 years, 5 to 9 years, 10 to 15 years, and >15 years after breast cancer diagnosis. Cox proportional hazards assumptions were tested using the Schoenfeld test and log-minus-log plots for each 5-year interval. Cumulative incidence curves were constructed comparing the cumulative incidence of ipsilateral lung cancer among irradiated patients and nonirradiated patients. Kaplan-Meier curves were used to compare survival among (1) irradiated patients who developed ipsilateral lung cancer, (2) irradiated patients who did not develop ipsilateral lung cancer, (3) nonirradiated patients who developed ipsilateral lung cancer, and (4) nonirradiated patients who developed ipsilateral lung cancer.

Statistical Analysis

The data were analyzed using R version 4.3.0 (R Foundation for Statistical Computing). Baseline demographic and preoperative clinical characteristics between patients who developed a subsequent primary lung cancer and those who did not in the irradiated and nonirradiated groups were compared using Wilcoxon rank-sum test for continuous variables and the Pearson χ^2 test for discrete variables. A P value $< .05$ was considered statistically significant.

RESULTS

Patient Cohort and Characteristics Stratified by RT Versus no RT

A total of 612,746 patients met our inclusion criteria, including 319,014 (52%) who received RT as part of their breast cancer treatment and 293,732 (48%) who did not receive RT. Among the entire cohort, 10,491 (1.7%) later were diagnosed with lung cancer. The cumulative incidence of ipsilateral lung cancer stratified by radiation exposure for breast cancer is shown in Figure 2. Patients who were irradiated were significantly more likely to be younger, female, of white race, and diagnosed with breast cancer in the years 2000 to 2014 ($P < .001$ for all) (Table 1). Irradiated patients were significantly more likely to have T1 disease and N2-3 disease, to undergo chemotherapy, and to undergo lumpectomy versus mastectomy ($P < .001$ for all).

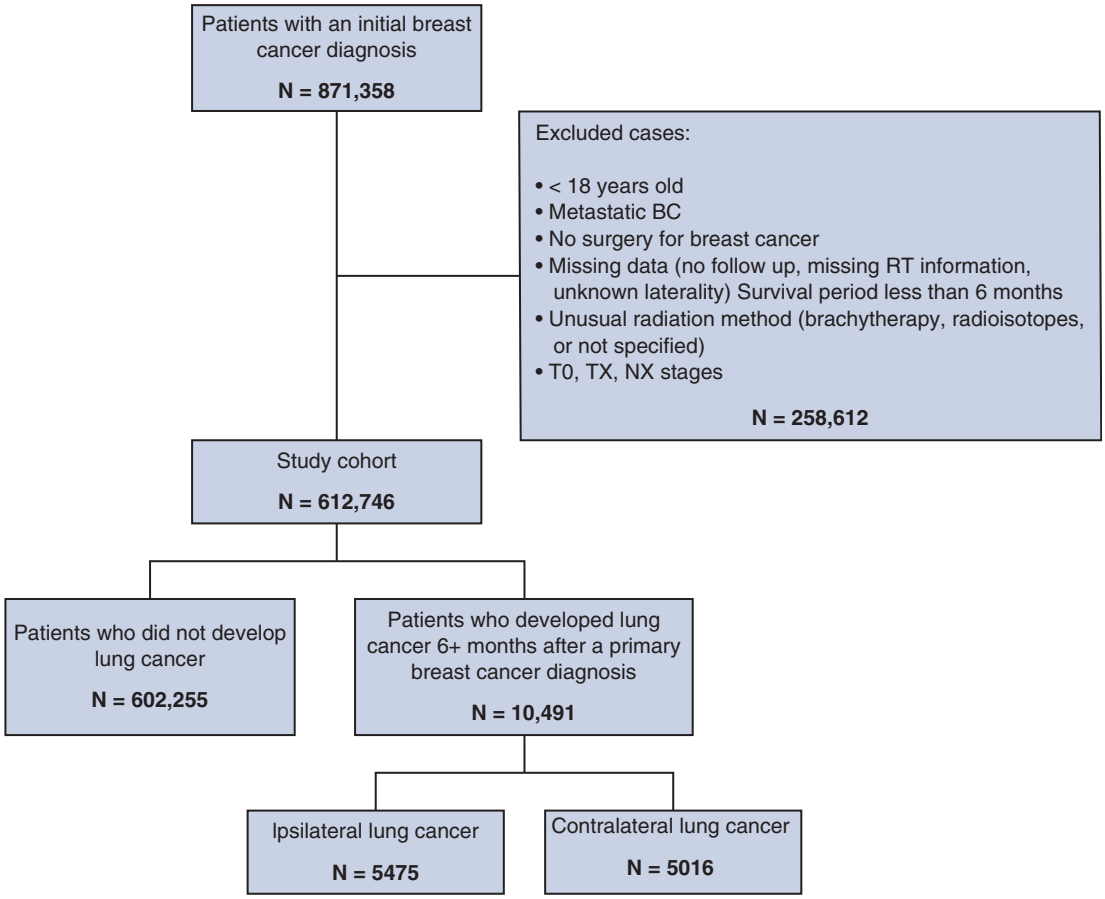

FIGURE 1. CONSORT diagram of the study. *BC*, Breast cancer.

Association of RT With the Development of Lung Cancer Stratified by Time Since Breast Cancer Diagnosis

Table 2 shows the HR of developing ipsilateral lung cancer after RT exposure for breast cancer treatment, stratified by follow-up time interval. At 5 to 9 years after breast cancer diagnosis, RT exposure was a significant independent risk factor for the development of lung cancer (hazard ratio [HR], 1.14; 95% confidence interval [CI], 1.01-1.29; $P = .036$). Older age was also a risk factor, along with black race (HR, 1.24; 95% CI, 1.06-1.45; $P = .007$). At 10 to 15 years after breast cancer diagnosis, radiation exposure was an even stronger risk factor for the development of lung cancer (HR, 1.28; 95% CI, 1.09-1.50; $P = .002$), and the risk was highest at >15 years after breast cancer diagnosis (HR, 1.30; 95% CI, 1.05-1.60; $P = .014$). Age remained a significant variable in the later time intervals, but all other categories, such as race, chemotherapy exposure, type of breast cancer surgery, and T and N stage, did not correlate with the subsequent development of lung cancer.

To further explore whether the increased risk of lung cancer was likely to be attributable to prior radiation exposure, the risk of developing contralateral lung cancer over time was also examined in an analogous multivariable model. Table 3 shows that although radiation was significantly associated with an increased risk of developing ipsilateral lung cancer, it was not associated with the development of contralateral lung cancer.

Impact of RT and the Development of Subsequent Primary Lung Cancer on Overall Survival

To assess the clinical impact of the development of lung cancer after RT for breast cancer, Kaplan-Meier curves were used to examine overall survival stratified by ipsilateral lung cancer diagnosis and receipt of RT (Figure E1). Patients without radiation exposure who did not develop lung cancer composed the reference group. As expected, irradiated patients who developed lung cancer had worse survival compared to irradiated patients who did not develop lung cancer (HR, 2.52; 95% CI, 2.42-2.63).

DISCUSSION

Breast cancer and lung cancer are the most prevalent cancers worldwide[17-19]; however, they have starkly different average lengths of survivorship. Whereas reported early-stage breast cancer 5-year survival rates are as high as

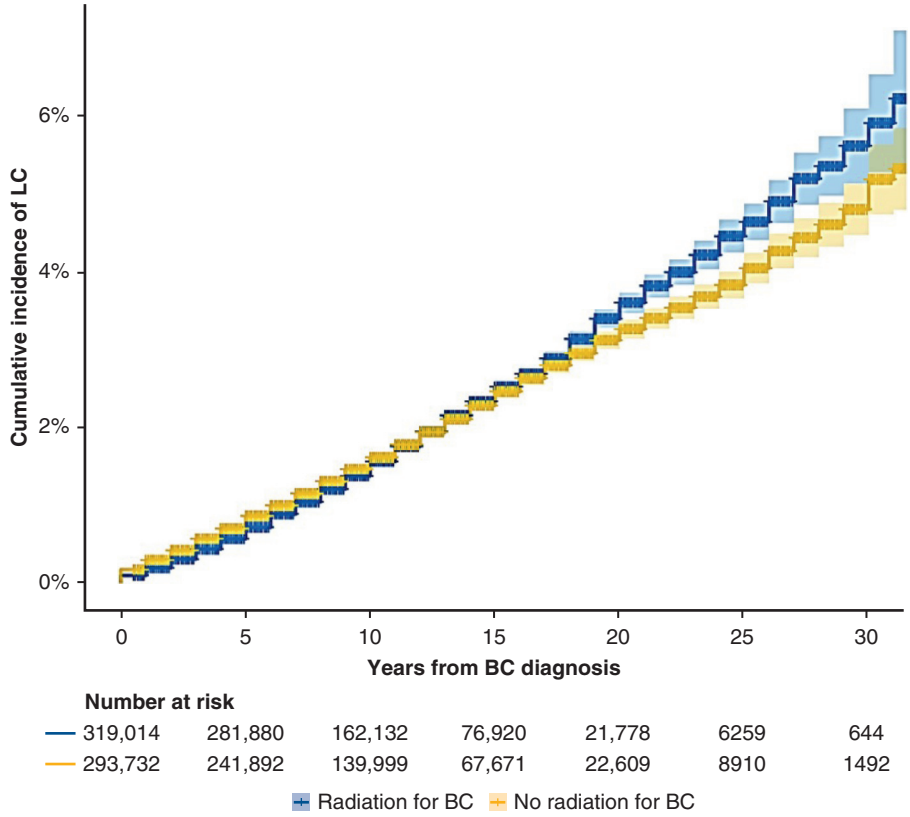

FIGURE 2. Cumulative incidence of ipsilateral lung cancer (*LC*) stratified by receipt of radiation for breast cancer (*BC*).

98% to 100%, early-stage lung cancer survival rates are significantly worse, at 60% to 80%.[18,19] In light of this, it is important to examine the long-term effects of traditional breast cancer treatments such as RT, as previous studies have shown downstream adverse effects from radiation exposure in the development of secondary malignancies.[11,12,20,21] Contrary to previous studies, we found a low risk of developing lung cancer from RT performed to treat breast cancer. Neugut and colleagues[10] used SEER data from 1973 to 1986 and reported relative ratios >2.0 for the development of ipsilateral lung cancer at >10 years after initial breast cancer diagnosis. Another study by Zablotska and Neugut used SEER data from 1973 to 1998 to differentiate the risk between postmastectomy patients and postlumpectomy patients and found relative ratios >2.0 for ipsilateral lung cancer only in the mastectomy group.[13] A more modern study conducted using Swedish national data found increased incidences of both ipsilateral and contralateral lung cancer after the 10-year mark (HR, 1.59; 95% CI, 1.37-1.84).[14] These studies provide insight into the risk of lung cancer after RT for breast cancer but do not reflect changing oncologic practices, as they predate modern advancements in radiation oncology. Our data show that longer follow-up does increase the risk of developing ipsilateral lung cancer, but even at 15 years after breast cancer diagnosis, the overall incidence of lung cancer is low in breast cancer survivors, and there is only a 30% increased risk in those with radiation exposure.

In this large series, we found higher rates of lung cancer in patients who were diagnosed with breast cancer after the year 2000. This is consistent with trends in lung cancer diagnoses in women overall.[18,22,23] This increase also coincides with more widespread use of computed tomography scans in general, as well as the availability of higher-resolution scans, likely resulting in increased detection.[24,25] Although smoking remains the strongest risk factor for the development of lung cancer, smoking rates decreased in the second half of the 20th century, and other risk factors need to be examined.[26,27] The interaction between radiation exposure and smoking also has been described as possibly multiplicative for light smokers as opposed to additive for heavy smokers; thus, with the decrease in overall smoking rates, increased awareness of radiation exposure as an additional potentiator of the development of lung cancer becomes even more relevant.[28] We deliberately excluded patients who did not undergo surgery for treatment of nonmetastatic breast cancer, because that is discordant with treatment guidelines and likely indicates unique circumstances, such as significant comorbidities that make those

TABLE 1. Patient characteristics stratified by receipt of RT

Characteristic	Overall (N = 607,730)	RT (N = 316,418)	No RT (N = 291,312)	*P* value
Age at breast cancer diagnosis, y				**<.001***
Mean (SD)	59.6 (13.6)	58.4 (12.6)	60.8 (14.5)	
Median (IQR)	59.0 (49.0-70.0)	58.0 (49.0-68.0)	60.0 (49.0-72.0)	
Sex, n (%)				**<.001†**
Male	3985 (0.7)	1046 (0.3)	2939 (1.0)	
Female	603,745 (99.3)	315,372 (99.7)	288,373 (99.0)	
Race, n (%)				**<.001†**
White	491,949 (80.9)	257,894 (81.5)	234,055 (80.3)	
Black	57,978 (9.5)	29,450 (9.3)	28,528 (9.8)	
Other/unknown	57,803 (9.5)	29,074 (9.2)	28,729 (9.9)	
Year of diagnosis, n (%)				**<.001†**
1988-1999	96,392 (15.9)	41,804 (13.2)	54,588 (18.7)	
2000-2014	511,338 (84.1)	274,614 (86.8)	236,724 (81.3)	
T stage for breast cancer, n (%)				**<.001†**
T1	379,772 (62.5)	205,810 (65.0)	173,962 (59.7)	
T2	184,845 (30.4)	85,610 (27.1)	99,235 (34.1)	
T3	31,481 (5.2)	17,917 (5.7)	13,564 (4.7)	
T4	11,632 (1.9)	7081 (2.2)	4551 (1.6)	
N stage for breast cancer, n (%)				**<.001†**
N0	408,879 (67.3)	208,933 (66.0)	199,946 (68.6)	
N1	158,562 (26.1)	81,057 (25.6)	77,505 (26.6)	
N2	26,397 (4.3)	17,364 (5.5)	9033 (3.1)	
N3	13,892 (2.3)	9064 (2.9)	4828 (1.7)	
Laterality for breast cancer, n (%)				.066†
Right	299,972 (49.4)	156,540 (49.5)	143,432 (49.2)	
Left	307,758 (50.6)	159,878 (50.5)	147,880 (50.8)	
Chemotherapy for breast cancer, n (%)	250,155 (41.2)	149,516 (47.3)	100,639 (34.5)	**<.001†**
Surgery for breast cancer, n (%)				**<.001†**
Lumpectomy	329,206 (54.2)	252,053 (79.7)	77,153 (26.5)	
Mastectomy	278,524 (45.8)	64,365 (20.3)	214,159 (73.5)	

Significant *P* values are in bold type. *RT*, Radiotherapy; *SD*, standard deviation; *IQR*, interquartile range. *Wilcoxon rank-sum test. †Pearson χ^2 test.

patients poor surgical candidates and could confound outcomes. We also controlled for other breast cancer–specific factors that likely serve as surrogates for the aggressiveness of disease, such as T stage, nodal status, and receipt of chemotherapy, with the aim of minimizing confounding from competing mortality from breast cancer over the follow-up period.

A strength of our study is the long follow-up in a very large patient cohort, which allowed us to measure an outcome that otherwise would be difficult to capture. However, we acknowledge the limitations of our study, including those inherent to any retrospective database review, as well as lack of granularity of certain data points in the SEER database, specifically the lack of smoking history, radiation field data, and radiation dosing data. For example, breast cancer patients may receive radiation to the breast, axilla, chest wall, or a combination of these fields, but these details are not specified in the database. Although smoking history is not available in the SEER database, the large sample size decreases the likelihood of a large discrepancy in smoking history among groups. Moreover, the analysis of ipsilateral versus contralateral lung cancer among patients who received RT can address this potential confounder, as both groups in that comparison inherently would have the same exposure to smoking. Despite this, there remains a risk for residual confounding between groups from unmeasured variables. Nevertheless, we believe that this study provides clinically relevant insight into the long-term consequences of radiation for breast cancer. Given that patients with the most follow-up data naturally will be from the earlier eras, this analysis may need to be repeated in 10 years to elucidate the impact of current radiation practices.

Breast cancer management has evolved over time, with increased emphasis on breast conservation approaches.[29] Although our analysis was not created to specifically evaluate the survival benefit of RT for breast cancer, we did find better breast cancer survival in the group that received radiation, which correlates with the literature showing that

TABLE 2. Hazard ratio of developing ipsilateral lung cancer after radiation for breast cancer stratified by follow-up interval

Variable	5-9 years		10-15 years		>15 years	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
RT vs no RT	1.14 (1.01-1.29)	**.036**	1.28 (1.09-1.50)	**.002**	1.30 (1.05-1.60)	**.014**
Age at breast cancer diagnosis						
<50 y						
50-59 y	2.95 (2.40-3.62)	**<.001**	2.56 (2.09-3.14)	**<.001**	1.96 (1.63-2.36)	**<.001**
60-69 y	6.39 (5.26-7.76)	**<.001**	4.39 (3.61-5.35)	**<.001**	2.06 (1.68-2.53)	**<.001**
70-79 y	6.76 (5.51-8.29)	**<.001**	3.47 (2.77-4.36)	**<.001**	–	
80+ y	4.40 (3.35-5.79)	**<.001**	1.56 (0.92-2.64)	.095	–	
Race						
White						
Black	1.24 (1.06-1.45)	**.007**	1.08 (0.88-1.34)	.457	1.18 (0.91-1.54)	.215
Other/unknown	0.65 (0.53-0.79)	**<.001**	0.58 (0.45-0.75)	**<.001**	–	
Year of diagnosis						
1988-1999						
2000-2014	1.27 (1.11-1.46)	**<.001**	1.08 (0.94-1.24)	.281	1.03 (0.86-1.24)	.718
Chemotherapy vs no chemotherapy	0.96 (0.85-1.08)	.516	0.94 (0.81-1.08)	.377	0.97 (0.81-1.16)	.909
Surgery for breast cancer						
Lumpectomy						
Mastectomy	1.08 (0.95-1.22)	.227	1.10 (0.93-1.30)	.252	1.01 (0.82-1.26)	.602
T stage						
T1						
T2	1.03 (0.92-1.16)	.608	1.07 (0.93-1.23)	.354	0.95 (0.79-1.14)	.652
T3	1.06 (0.81-1.38)	.612	0.97 (0.68-1.39)	.872	1.10 (0.71-1.70)	.982
T4	0.74 (0.42-1.29)	.295	0.82 (0.36-1.88)	.654	–	
N stage						
N0						
N1	0.98 (0.86-1.11)	.728	1.06 (0.91-1.23)	.463	0.95 (0.79-1.14)	.595
N2	0.88 (0.66-1.20)	.434	1.26 (0.87-1.85)	.217	–	
N3	0.95 (0.61-1.47)	.822	1.19 (0.63-2.25)	.595	–	
No. of ipsilateral lung cancer cases	1773		1138		756	

End of follow-up on December 31, 2019. Breast cancer diagnosed between 2010 and 2014 and developed lung cancer prior to 10+ years of survival or have an no data on 10+ years diagnoses. Significant *P* values are in bold type. *HR*, Hazard ratio; *CI*, confidence interval; *RT*, radiotherapy.

RT is associated with greatly reduced recurrence rates. Moreover, the omission of adjuvant radiation was associated with higher recurrence rates and worse disease-free and overall survival, a finding that led to further increases in the use of RT to treat breast cancer.[29-35] Radiation techniques also have evolved; shorter treatment courses have led to better tolerability, and current studies are now showing similar recurrence rates and cosmetic results.[E1-E3] Another important consideration is the widespread adoption of computed tomography scans for radiation planning after the year 2000. These practice changes in radiation oncology likely contributed significantly to the much lower risk of developing subsequent primary lung cancer today than was documented in the 1970s and 1980s.

The recent focus on formalizing lung cancer screening programs is changing the landscape of lung cancer

TABLE 3. HR of ipsilateral and contralateral lung cancer after radiation for breast cancer by follow-up time from breast cancer diagnosis

Type of lung cancer	5 to 9 years		10 to 15 years		>15 years	
	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Ipsilateral	1.14 (1.01-1.29)	**.036**	1.28 (1.09-1.50)	**.002**	1.30 (1.05-1.60)	**.014**
Contralateral	1.04 (0.91-1.18)	.563	1.15 (.97-1.37)	.103	1.12 (0.88-1.41)	.357

HR adjusted for age, race, year of breast cancer diagnosis, T and N stage, and receipt of chemotherapy and surgery for breast cancer. Signficant *P* values are in bold type. *HR*, Hazard ratio; *CI*, confidence interval.

diagnosis and treatment.[E4,E5] Increased emphasis on health maintenance and improved perceptions of cancer screening have led to the increased detection of early-stage disease and, subsequently, better survival rates.[22,E6] However, only patients with a significant smoking history are currently eligible for lung cancer screening. Our study indicates that the relative risk of developing lung cancer secondary to RT during breast cancer treatment is low, and thus we do not feel that the risk ratios identified in our study justify widespread screening of all patients with a history of breast RT. However, a broader awareness of the small but real increased risk may be informative in patients with additional risk factors, or may prompt clinicians to have a lower threshold to workup relevant concerning symptoms in these patients.

Importantly, our results should not discourage patients from receiving RT for breast cancer, given the conclusive evidence of a benefit from RT. We hope that this study can serve as a tool to help patients and providers quantify the longitudinal risk of lung cancer in patients with a history of RT for breast cancer. Understanding the clinical relationship between breast cancer and lung cancer, the 2 most common cancers worldwide, will help physicians make evidence-based decisions on an individualized level.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: lung cancer, breast cancer, radiation exposure, risk ratio

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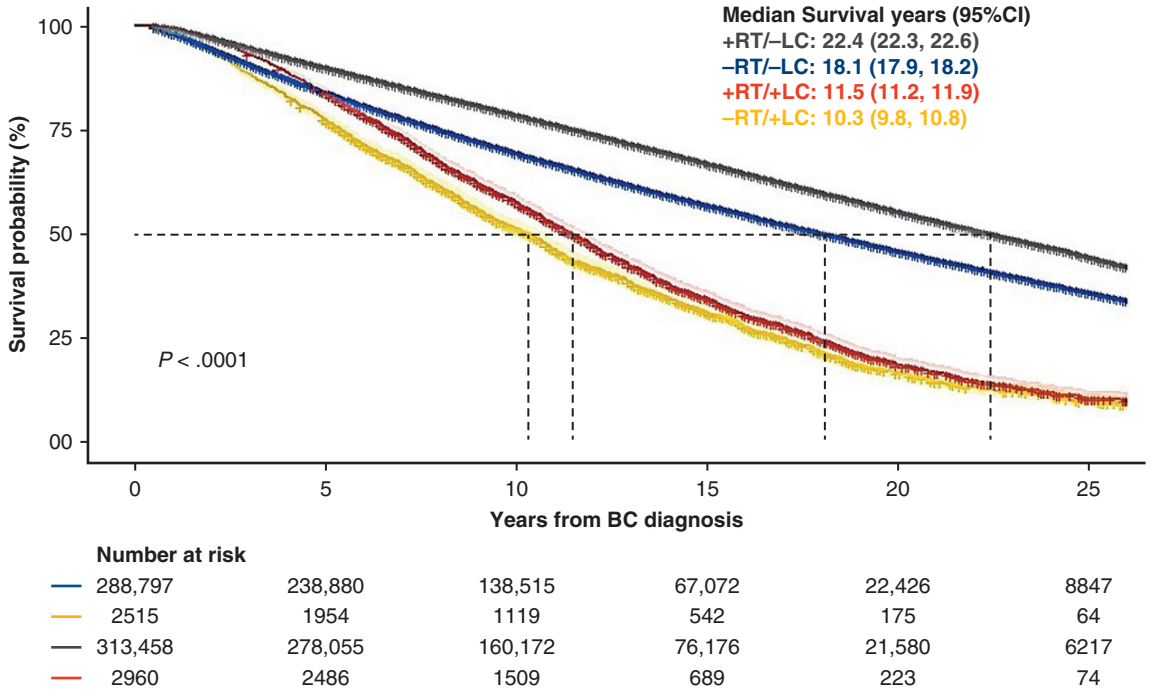

FIGURE E1. Survival stratified by ipsilateral lung cancer (*LC*) diagnosis and receipt of radiation. *CI*, Confidence interval; *RT*, radiotherapy; *BC*, breast cancer.