Risk of Developing Subsequent Primary Lung Cancer After Receiving Radiation for Breast Cancer

Running head: Risk of Lung Cancer After Treatment of Breast Cancer

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Glossary of Abbreviations:

- National Comprehensive Cancer Network (NCCN)
- Computer tomography (CT)
- Radiotherapy (RT)
- Surveillance, Epidemiology, and End Results (SEER)
- American Joint Committee on Cancer (AJCC)
- Hazard ratio (HR)
- Confidence interval (CI)

Keywords:
lung cancer; breast cancer; radiation exposure; risk ratio

Central Picture Legend
Cumulative Incidence of Lung Cancer Stratified by receipt of Radiation Therapy

Central Message
The receipt of radiation therapy 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 Statement
Radiation therapy 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.

Ultramini-Abstract
Radiation exposure from breast cancer treatment increases the risk of developing a primary lung cancer by up to 30% after 15 years of follow-up, which is much lower than previously
published. This study can help quantify the longitudinal risk of lung cancer in patients with risk factors outside of national LCS criteria.
Abstract:

Objectives: 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 timespan of three decades to quantify this risk over time as modern oncologic treatment continues to evolve.

Methods: The SEER database was queried from 1988-2014 for patients diagnosed with non-metastatic 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 5-9, 10-15, and >15 years after breast cancer diagnosis.

Results: Of the 612,746 patients who met inclusion criteria, 319,014 (52%) patients were irradiated. 5,556 (1.74%) patients in the RT group versus 4,935 (1.68%) patients in the non-RT group subsequently developed a primary lung cancer. In a multivariable model stratified by follow up time intervals, the overall HR of developing subsequent ipsilateral lung cancer in the RT group was 1.14 (p=0.036) after 5-9 years, HR 1.28 (p=0.002) after 10-15 years, and HR 1.30 (p=0.014) 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 improvement in risk profile and this updated study is important for counseling and surveillance of breast cancer patients.

Word count: 250
Introduction

Breast and lung cancer are respectively the first and second most common cancers in the United States, with over 200,000 new cases reported for each cancer in the year 2022 alone (1,2). Although both cancers have formal screening programs supported by influential organizations such as the National Comprehensive Cancer Network (NCCN), the uptake of breast cancer screening has been much more successful than for lung cancer (3). Notably, mortality rates from breast cancer have declined over the last decade while lung cancer remains the leading cause of cancer death (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 (6). The publication of numerous landmark trials demonstrating that partial mastectomy with postoperative radiation has equivalent survival to mastectomy has changed the landscape of breast cancer management and incorporated radiation 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 radiotherapy (RT) in survivors. In prior studies, RT exposure for breast cancer has been demonstrated to be associated with the development of subsequent primary lung cancer, with risk ratios cited 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 on 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). However, most patients who are diagnosed with lung cancer fall outside of these screening guidelines, and expansion of screening criteria merits ongoing assessment, with careful weighing of risk, benefit, 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 is sourced from an area that covers approximately 35% of the country and is generalizable to the entire population. Data from 1988-2014 was included in this study. The most updated SEER data available is from 2019, so this allowed a minimum of 5 years of follow up for the most contemporary patients in our cohort. As patients are de-identified in this database, this study was exempt from review by the Stanford Institutional Review Board.

**Patient Selection**

All patients >18 years of age diagnosed with non-metastatic breast cancer were identified using American Joint Committee on Cancer (AJCC) 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 were also excluded. The cohort was then stratified into those who received radiation therapy as part of their breast cancer treatment and those who did not. Of note, details of radiation therapy such as prescribed dose and completion are not provided in the SEER database. Lastly, patients were identified 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 2-18 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 plausibly be attributable to radiation, and is consistent with study designs with similar clinical questions. Follow-up time from initial breast cancer diagnosis to subsequent primary lung cancer diagnosis was calculated by subtracting year of breast cancer diagnosis to year of lung cancer diagnosis (SEER database no longer provides the specific month of diagnosis).

**Post-operative Outcomes and Survival Analyses**

Multivariable Cox proportional hazards regression modeling was used to estimate the relative risk of developing lung cancer after radiation 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 non-random pattern against time, violating the proportional hazards assumption. We therefore stratified follow up intervals into five-year periods: 0.5-4, 5-9, 10-15, and >15 years post-breast
cancer diagnosis. Cox proportional hazards assumptions were tested using Schoenfeld test and log-minus-log plots for each 5-year interval. Cumulative incidence curves were constructed comparing cumulative incidence of ipsilateral lung cancer among irradiated and non-radiated 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) non-radiated patients who developed ipsilateral LC, and 4) non-radiated patients who developed ipsilateral LC.

**Statistical Analysis**

The data was analyzed using R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria). Baseline demographic and preoperative clinical characteristics between patients who developed a subsequent primary lung cancer and those who did not in the radiation and non-radiated groups were compared using Wilcoxon rank-sum test for continuous variables and Pearson’s Chi-squared test for discrete variables. A p-value of <0.05 was considered statistically significant.

**Results**

**Patient Cohort and Characteristics Stratified by Radiation versus No Radiation**

There were 612,746 patients who met inclusion criteria, with 319,014 (52%) patients who received radiation as part of their breast cancer treatment and 293,732 (48%) patients who did not receive radiation. 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 2000-2014 (all p<0.001) (Table 1). Irradiated patients were significantly more likely to have T1 disease, N2-3 disease, undergo chemotherapy, and undergo lumpectomy versus mastectomy (all p<0.001).

**Association of Radiation and Development of Lung Cancer Stratified by Time Since Breast Cancer Diagnosis**

Table 2 shows the hazard ratios of developing ipsilateral lung cancer after radiation exposure for breast cancer treatment, stratified by follow-up time intervals. At 5 to 9 years post-breast cancer diagnosis, radiation exposure was a significant independent risk factor for the development of lung cancer, with a HR 1.14 (95% CI 1.01, 1.29; p=0.036). Older age was also a
risk factor, along with black race (HR 1.24, [95% CI 1.06, 1.45], p=0.007). At 10 to 15 years post-breast cancer diagnosis, radiation exposure was an even stronger risk factor for the development of lung cancer with HR 1.28 (95% CI 1.09, 1.50; p=0.002), and at >15 years post-breast cancer diagnosis, the risk was the highest with HR 1.30 (95% CI 1.05, 1.60; p=0.014). Age continued to be a significant variable in the later time intervals, but all other categories, such as race, chemotherapy exposure, type of breast cancer surgery, T or N stage, did not correlate with the subsequent development of lung cancer.

In order to further delineate 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 while 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 Radiation Treatment and the Development of Subsequent Primary Lung Cancer on Overall Survival**

To assess the clinical impact of the development of lung cancer after radiation for breast cancer, supplemental figure 1 shows Kaplan Meier curves examining overall survival stratified by ipsilateral lung cancer diagnosis and receipt of radiation therapy. Patients with no radiation exposure who did not develop lung cancer comprised the reference group. As expected, patients exposed to radiation and 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 and lung cancer are the most prevalent cancers worldwide.(17–19). However, each has a starkly different average length of survivorship. While early-stage breast cancer 5-year survival rates are cited as high as 98-100%, early-stage lung cancer survival rates are significantly worse, at 60-80%(18,19). In light of this, it is important to examine the long-term effects of traditional breast cancer treatments such as radiotherapy, as previous studies have shown downstream adverse effects from radiation exposure in the development of secondary
malignancies(11,12,20,21). Contrary to older published literature, we found that the hazard of
developing lung cancer from RT for breast cancer is low. Neugut et al used SEER data from
1973 to 1986, citing relative ratios over 2.0 for the development of ipsilateral lung cancer >10
years after initial breast cancer diagnosis(10). Another study by Zablotska et al used SEER data
from 1973 to 1998 to differentiate the risk between post-mastectomy versus post-lumpectomy
patients and found that relative ratios were again over 2.0 for ipsilateral lung cancer in only the
mastectomy group(13). A more modern study conducted using Swedish national data also
found an increased incidence of both ipsilateral and contralateral lung cancer incidence 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 breast radiation, but do not reflect changing oncologic practices, as they pre-
date modern advancements in radiation oncology. Our data shows that longer follow-up time
does increase the risk of developing ipsilateral lung cancer, but even at 15 years after breast
cancer diagnosis, the overall incidence of lung cancer among breast cancer survivors is low,
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 CT scans
in general, and the availability of higher resolution scans, likely resulting in increased
detection(24,25). Although smoking is still the strongest risk factor for the development of lung
cancer, smoking rates have decreased in the second half of the 20th century, and other risk
factors need to be examined (26,27). Additionally, the interaction between radiation exposure
and smoking has also been described as possibly multiplicative for light smokers as opposed to
additive for heavy smokers, so with the decrease in overall smoking rates, more awareness of
radiation exposure as an additional potentiator of development of lung cancer becomes even
more relevant(28). We deliberately excluded patients who did not undergo surgery for treatment
of non-metastatic breast cancer as that is discordant with treatment guidelines, and likely indicates unique circumstances such as significant comorbidities that render those patients poor surgical candidates and could confound outcomes. We also controlled for other breast cancer-specific factors that likely serve as surrogates for aggressiveness of disease, such as T stage, nodal status, and receipt of chemotherapy, with the intention to minimize confounding from competing mortality from breast cancer over the follow up period.

A strength of our study is the long length of follow up in a very large patient cohort, which allowed us to measure an outcome that would otherwise be difficult to capture. However, we acknowledge the limitations in 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, lack of 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 radiation can address this potential confounder, as both groups in that comparison would inherently 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. As patients with the most follow-up data will naturally be from the earlier eras, this analysis may need to be repeated in 10 years to understand 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 radiation on breast cancer, we do see in Figure 3 that breast cancer survival
is improved in the group that received radiation, which correlates to established literature that radiation greatly improves recurrence rates. Moreover, the omission of adjuvant radiation showed higher recurrence rates and worse disease-free and overall survival, which further increased the use of radiation in breast cancer treatment (29,35). Radiation techniques have also evolved; shorter treatment courses have led to better tolerability, and current studies are now showing similar recurrence rates and cosmetic results (38). Another significant consideration is the widespread adoption of computed tomography for radiation planning after the year 2000. These practice changes in radiation oncology likely play a substantial role in our finding that the risk of developing subsequent primary lung cancer is much lower than previously documented in the 1970’s and 1980’s.

The recent focus on formalizing lung cancer screening programs is changing the landscape of lung cancer diagnosis and treatment (39,40). 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 (22,41). However, only patients with a significant smoking history are currently eligible for lung cancer screening. Our study indicates that the relative hazard of developing lung cancer secondary to radiation during breast cancer treatment is low. Thus, we do not feel that the risk ratios identified in our study would justify widespread screening of all patients with a history of breast radiation. 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 work up relevant concerning symptoms in these patients. Importantly, our results should not discourage patients from receiving radiation for breast cancer, as the evidence showing benefit from radiation treatment is conclusive. 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 radiation for breast cancer. Understanding the clinical
relationship between breast and lung cancer, the two most common cancers worldwide, will help physicians make evidence-based decisions on an individualized level.
References:


Supplemental References


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Figure 1. CONSORT diagram

Figure 2. Cumulative incidence of ipsilateral lung cancer stratified by receipt of radiation for breast cancer

Supplemental Figure 1. Survival stratified by ipsilateral lung cancer diagnosis and receipt of radiation
Table 1. Patient characteristics of study cohort, stratified by receipt of radiation treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall, n = 607,730</th>
<th>Radiation, N = 316,418</th>
<th>No radiation, N = 291,312</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at BC diagnosis</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001^2</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>59.6 (13.6)</td>
<td>58.4 (12.6)</td>
<td>60.8 (14.5)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>59.0 (49.0, 70.0)</td>
<td>58.0 (49.0, 68.0)</td>
<td>60.0 (49.0, 72.0)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001^3</td>
</tr>
<tr>
<td>Male</td>
<td>3,985 (0.7%)</td>
<td>1,046 (0.3%)</td>
<td>2,939 (1.0%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>603,745 (99.3%)</td>
<td>315,372 (99.7%)</td>
<td>288,373 (99.0%)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001^3</td>
</tr>
<tr>
<td>White</td>
<td>491,949 (80.9%)</td>
<td>257,894 (81.5%)</td>
<td>234,055 (80.3%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>57,978 (9.5%)</td>
<td>29,450 (9.3%)</td>
<td>28,528 (9.8%)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>57,803 (9.5%)</td>
<td>29,074 (9.2%)</td>
<td>28,729 (9.9%)</td>
<td></td>
</tr>
<tr>
<td>Years of diagnosis</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001^3</td>
</tr>
<tr>
<td>1988-1999</td>
<td>96,392 (15.9%)</td>
<td>41,804 (13.2%)</td>
<td>54,588 (18.7%)</td>
<td></td>
</tr>
<tr>
<td>2000-2014</td>
<td>511,338 (84.1%)</td>
<td>274,614 (86.8%)</td>
<td>236,724 (81.3%)</td>
<td></td>
</tr>
<tr>
<td>T stage for BC</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001^3</td>
</tr>
<tr>
<td>T1</td>
<td>379,772 (62.5%)</td>
<td>205,810 (65.0%)</td>
<td>173,962 (59.7%)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>184,845 (30.4%)</td>
<td>85,610 (27.1%)</td>
<td>99,235 (34.1%)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>31,481 (5.2%)</td>
<td>17,917 (5.7%)</td>
<td>13,564 (4.7%)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>11,632 (1.9%)</td>
<td>7,081 (2.2%)</td>
<td>4,551 (1.6%)</td>
<td></td>
</tr>
<tr>
<td>N stage for BC</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001^3</td>
</tr>
<tr>
<td>N0</td>
<td>408,879 (67.3%)</td>
<td>208,933 (66.0%)</td>
<td>199,946 (68.6%)</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>158,562 (26.1%)</td>
<td>81,057 (25.6%)</td>
<td>77,505 (26.6%)</td>
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</tr>
<tr>
<td>N2</td>
<td>26,397 (4.3%)</td>
<td>17,364 (5.5%)</td>
<td>9,033 (3.1%)</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>13,892 (2.3%)</td>
<td>9,064 (2.9%)</td>
<td>4,828 (1.7%)</td>
<td></td>
</tr>
<tr>
<td>Laterality for BC</td>
<td></td>
<td></td>
<td></td>
<td>0.066^4</td>
</tr>
<tr>
<td>Right</td>
<td>299,972 (49.4%)</td>
<td>156,540 (49.5%)</td>
<td>143,432 (49.2%)</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>307,758 (50.6%)</td>
<td>159,878 (50.5%)</td>
<td>147,880 (50.8%)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy for BC</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001^3</td>
</tr>
<tr>
<td>Lumpectomy</td>
<td>329,206 (54.2%)</td>
<td>252,053 (79.7%)</td>
<td>77,153 (26.5%)</td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>278,524 (45.8%)</td>
<td>64,365 (20.3%)</td>
<td>214,159 (73.5%)</td>
<td></td>
</tr>
</tbody>
</table>

1n (%)
2Wilcoxon rank sum test
3Pearson's Chi-squared test
4BC=Breast Cancer; LC=Lung Cancer
Table 2. Hazard ratio of developing ipsilateral lung cancer after radiation for BC stratified by follow-up time intervals

<table>
<thead>
<tr>
<th>5 – 9 yrs.</th>
<th>10-15 yrs.</th>
<th>&gt;15 yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RT vs no RT</strong></td>
<td><strong>RT vs no RT</strong></td>
<td><strong>RT vs no RT</strong></td>
</tr>
<tr>
<td>HR (95%CI) p-value</td>
<td>HR (95%CI) p-value</td>
<td>HR (95%CI) p-value</td>
</tr>
<tr>
<td>1.14 (1.01, 1.29) 0.036</td>
<td>1.28 (1.09, 1.50) 0.002</td>
<td>1.30 (1.05, 1.60) 0.014</td>
</tr>
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</table>

**Age at BC diagnosis (years)**

<table>
<thead>
<tr>
<th>&lt;50</th>
<th>50 – 59</th>
<th>60 – 69</th>
<th>70 – 79</th>
<th>80 +</th>
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</thead>
<tbody>
<tr>
<td>2.95 (2.40, 3.62) &lt;0.001</td>
<td>6.39 (5.26, 7.76) &lt;0.001</td>
<td>6.76 (5.51, 8.29) &lt;0.001</td>
<td>4.40 (3.35, 5.79) &lt;0.001</td>
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**Race**

<table>
<thead>
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<th>White</th>
<th>Black</th>
<th>Other/unknown</th>
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</thead>
<tbody>
<tr>
<td>1.24 (1.06, 1.45) 0.007</td>
<td>1.08 (0.88, 1.34) 0.457</td>
<td>1.18 (0.91, 1.54) 0.215</td>
</tr>
</tbody>
</table>

**Year of diagnosis**

<table>
<thead>
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<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>1.27 (1.11, 1.46) &lt;0.001</td>
<td>1.27 (1.11, 1.46) &lt;0.001</td>
</tr>
</tbody>
</table>

**Chemotherapy vs no chemotherapy**

| 0.96 (0.85, 1.08) 0.516 | 0.94 (0.81, 1.08) 0.377 | 0.97 (0.81, 1.16) 0.909 |

**Surgery for BC**

<table>
<thead>
<tr>
<th>Lumpectomy</th>
<th>Mastectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.08 (0.95, 1.22) 0.227</td>
<td>1.10 (0.93, 1.30) 0.252</td>
</tr>
</tbody>
</table>

**T stage**

<table>
<thead>
<tr>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.03 (0.92, 1.16) 0.608</td>
<td>1.07 (0.93, 1.23) 0.354</td>
<td>0.97 (0.68, 1.39) 0.872</td>
<td>0.82 (0.36, 1.88) 0.654</td>
</tr>
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</table>

**N stage**

<table>
<thead>
<tr>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.98 (0.86, 1.11) 0.728</td>
<td>1.06 (0.91, 1.23) 0.463</td>
<td>0.88 (0.66, 1.20) 0.434</td>
<td>0.95 (0.61, 1.47) 0.822</td>
</tr>
</tbody>
</table>

| No. of Ipsilateral LC cases | 1773 | 1138 | 756 |

Notes: End of follow-up on Dec 31st 2019. BC diagnosed between 2010 and 2014 developed lung cancer prior to 10+ years of survival or have no data 10+ yrs. diagnosis
**Table 3.** Hazard ratio of ipsilateral and contralateral lung cancer after radiation for BC by follow-up time from BC diagnosis

<table>
<thead>
<tr>
<th></th>
<th>5 – 9 yrs.</th>
<th>10-15 yrs.</th>
<th>&gt;15 yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adj. HR (95%CI)</td>
<td>p-value</td>
<td>Adj. HR (95%CI)</td>
</tr>
<tr>
<td>Ipsilateral LC</td>
<td>1.14 (1.01, 1.29)</td>
<td>0.036</td>
<td>1.28 (1.09, 1.50)</td>
</tr>
<tr>
<td>Contralateral LC</td>
<td>1.04 (0.91, 1.18)</td>
<td>0.563</td>
<td>1.15 (0.97, 1.37)</td>
</tr>
</tbody>
</table>

**Notes:** HR Adjusted for age, race, year of BC diagnosis, T and N stage, received chemotherapy and surgery for breast cancer. LC= Lung Cancer. BC= Breast Cancer
Patients with an initial breast cancer diagnosis
N = 871,358

Excluded cases:
- <18 years old
- Metastatic BC
- No surgery for breast cancer
- Missing data (no follow up, missing RT information, unknown laterality, survival period less than 6 months)
- Unusual radiation method (brachytherapy, radioisotopes, or not specified)
- T0, TX, NX stages

Study cohort
N = 612,746

Patients who developed lung cancer 6+ months after a primary breast cancer diagnosis
N = 10,491

Patients who did not develop lung cancer
N = 602,255

Ipsilateral lung cancer
N = 5,475

Contralateral lung cancer
N = 5,016

N = 258,612