Epidemiology and clinicopathological features of lung cancer in patients with prior history of breast cancer

Kevin Y Wang1, James Newman2, Chung-Shien Lee3 and Nagashree Seetharamu2

Abstract
Breast cancer is the most common malignancy in women, and lung cancer, the leading cause of cancer-related mortality in the United States, is the most common subsequent primary cancer among breast cancer survivors. In this review, we examine the risk factors that cause subsequent primary lung cancer after breast cancer (referred to herein as BCLC patients) as well as the prognostic factors that may affect survival. Notable clinicopathological features include patient characteristics such as age, smoking history, and the presence of EGFR or BRCA mutations, as well as factors related to the treatment of breast cancer such as radiation, surgery, chemotherapy, stage, anti-estrogen therapy, and ER/PR/HER2 status.

Keywords
Breast cancer, lung cancer, radiation, surgery, chemotherapy, estrogen receptor (ER), progesterone receptor (PR), HER2 receptor, EGFR, BRCA, TP53

Introduction
Breast cancer (BC) is the most common noncutaneous malignancy in women. In the United States alone, it is estimated that there will be 276,480 new cases of female BC in 2020, which is 15.3% of all new cancer cases in the United States.1 In 2012, women with BC accounted for 22% of cancer survivors in the United States, representing a population of over 2.9 million, which has since increased to 22.8% of cancer survivors and over 3.8 million as of 1 January 2019.2,3 The death rate from BC has been declining since the early 1990s, which is likely related to advances in early diagnosis and treatment. However, cancer survivors are at risk for developing recurrent disease and subsequent malignancies. It has been reported that BC survivors have a 10%–60% increased risk of a subsequent primary malignancy compared to the general population.4 Lung cancer (LC), which remains the leading cause of cancer-related mortality in the United States, is one of the most common subsequent primary cancers among BC survivors.5–7 In this article, we review the literature for incidence and potential risk factors for developing a subsequent primary LC after BC as well as prognostic factors that may affect survival.

Search methodology
A thorough literature search was conducted using SCOPUS with keywords “breast cancer” and “lung cancer” in title and “link/s” or “factor/s” in title/abstract/keywords, which returned 556 document results. From here, articles published from 2014 to 2020 were examined and included if they were relevant to the topic at hand and additional articles that were published earlier were added if they were relevant to the topic and discussion.

1Department of Internal Medicine, Northshore University Hospital, Manhasset, NY, USA
2Department of Hematology Oncology, Northshore University Hospital, Manhasset, NY, USA
3St. John’s University College of Pharmacy and Health Sciences, Queens, NY, USA

Corresponding author:
Kevin Y Wang, Department of Internal Medicine, Northshore University Hospital, 300 Community Drive, Manhasset, NY 11030, USA.
Email: kevwangyu@gmail.com
Incidence

According to an analysis from the Surveillance, Epidemiology, and End Results (SEER) Program, LC was observed to be the second most common subsequent primary cancer in females with a history of BC. Patients were examined from 1973 to 2003 and only additional primary BCs were more prevalent.8 Also, in a Dutch population-based study that evaluated 58,068 patients diagnosed with invasive BC, it found that approximately one in every 20 patients will develop a subsequent non-BC within 10 years after diagnosis. In this patient cohort, there was an increase in LC incidence, notably in patients younger than 50 at BC diagnosis.9 There are also multiple recent retrospective studies, systematic reviews, and a meta-analysis of 11 older studies that demonstrate an increased risk of a subsequent primary LC 5 years or later after BC diagnosis following radiation therapy.6,10–12

Mechanisms associated with BCLC development

Two potential mechanisms that have been most studied for the development of BCLC involve radiation-induced carcinogenesis and estrogen-induced BCLC.13 Radiation therapy (RT) may be associated with the development of secondary cancers through triggering DNA double breaks, reactive oxygen species generation, genomic instability, and immunosuppression. Models for radiation-induced carcinogenesis include the linear no-threshold model where every fraction of radiation increases the risk of cancer linearly and the tolerance dose concept where a certain amount of radiation is required before carcinogenesis occurs.13 Antiestrogens and inhibitors of estrogen synthesis, such as aromatase inhibitors, have been shown to suppress the growth of LC cells in both in vivo and in vitro studies.14–16 Mechanistically, ER signaling works through activation of EGFR/HER-1 and IGF-1R pathways, and several studies have implied that LC progression may be secondary to the interaction between ER and EGFR signaling. A synergy between an EGFR inhibitor and anastrozole agents has been or is being explored in clinical trials. For example, a phase I trial of anastrozole therapy with gefitinib in postmenopausal women with advanced non-small cell lung cancer (NSCLC) demonstrated safety and potential efficacy.17 Also, a randomized phase II trial of previously treated patients with advanced NSCLC showed that the combination of fulvestrant with erlotinib had a significantly greater progression-free survival (PFS) compared to erlotinib alone in EGFR wild-type patients.17,18 Interestingly, the EGFR wild-type patients in this study were more likely to be HR+ compared to EGFR-mutated patients (50% vs 9.1%, respectively). Thus, this PFS benefit may be primarily from the antiestrogen effect of fulvestrant, highlighting the potential importance of estrogen in LC development.

Risk factors

Even though risk factors for the development of LC in BC survivors are not clearly elucidated, there are many potential contenders, which we will discuss here.

Age

According to the SEER cancer registries from 1973 to 2000, when subsequent primary BCs are excluded, the overall risk for all subsequent cancers combined is nearly equal to the general population.19 However, in a Dutch population-based study and Swedish population-based study, there was an elevation in the standardized incidence ratio (SIR) of LC for patients diagnosed with BC before the age of 50 compared to those diagnosed after which was replicated in other studies9,4,20 (Table 1). A SEER database analysis also reflects this finding with younger women aged 20–39 and 40–49 years appearing to have a greater risk for developing LC than the general population of the same age. This is illustrated with a higher SIR, even though the highest frequencies of subsequent cancers generally occur as age increases.6,21 Further subgroup analysis in one SEER study revealed that younger age was more likely to be ER+/PR+ and SIR values only decreased with age in ER+/PR− groups. This suggests that mechanistically increased estrogen levels with younger ages may increase the risk of BCLC, and lack of antiestrogen treatment may also increase the risk of subsequent LC.21

EGFR, BRCA, and P53

Recent studies have shown an association between EGFR mutational status and BC (Table 1). In a retrospective study looking at 356 LC patients with EGFR data available, 17.7% (11/62) with EGFR mutations had BC compared to 1.02% (3/294) of EGFR wild-type patients.22 Another study investigated the relationship between EGFR mutational status and hormone receptor expression in patients with simultaneous LC and BC. Unlike the phase II trial involving fulvestrant plus erlotinib, patients with EGFR-mutated LC in this study were shown to correlate with HR+ LC tissue (34.4% had HR+ compared to 0% for EGFR wild-type LC).22 Given that female LC sometimes exhibits different characteristics such as being predominantly nonsmoking with a relatively younger age of onset compared with males, this study suggests a possible link between EGFR mutation and hormone receptor-driven BCLC. In terms of genetic syndromes, preliminary data from the LIFESCREEN randomized clinical trial showed that in Li-Fraumeni syndrome, lung adenocarcinoma may also be a risk factor in addition to a core spectrum of cancers including breast and brain tumors. In the trial, out of the 23 new primary cancers diagnosed in 20 patients, 5 were lung adenocarcinomas.26 A case report also demonstrated a patient with primary breast carcinoma who later developed lung adenocarcinoma and was
found to have Li-Fraumeni syndrome after being tested for a germline TP53.²⁷

There may also be an association of BRCA mutation with LC, which has classically been associated with hereditary BC (causes around 5% of all cases) and ovarian cancer (causes 20%–30% of all cases).²⁵ This has been demonstrated in a meta-analysis of large genome studies of European ancestry which found genome-wide associations for squamous cell LC with rare variants of BRCA2 and an Asian-based study which showed patients who develop NSCLC before 50 years of age were more likely to carry germline BRCA mutations.²⁴²⁷

### Chest radiation therapy

RT plays a vital role in the treatment of early-stage BC to help reduce the risk of local recurrence. The long-term effect of this treatment and its risk on the development of LC have been frequently evaluated. According to the SEER cancer registries from 1973 to 2000, females with BC who were initially treated with RT had a significantly elevated risk for developing a new lung malignancy at least 10 years after RT with the highest risk among 20-year survivors. It also notes that the risk was greater on the lung that was ipsilateral to the BC site as it receives a higher radiation dose.¹⁹ Of note, some studies suggest that this increased risk in ipsilateral LC is primarily associated with older RT techniques. The risk with more modern practices is not as clear²⁸ (Table 2).

### Table 1. Age, EGFR, and BRCA on risk of subsequent LC in selected studies (2014–2020).

| Study                     | Study design                                      | n   | Timeline       | Results                                                                 | Comments                                                                                       |
|---------------------------|---------------------------------------------------|-----|----------------|------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Silverman²⁰              | Retrospective study of Israel National Cancer Registry | 46,090 | 1992–2006     | SIR 1.77 (1.63–1.91), age < 50 SIR 1.20 (1.15–1.24), age > 50          | Population consists of 75% Jewish women, 20% Arab women                                      |
| Wang et al.²¹            | Observational study of SEER database at the NIH, US | 6269 | 2000–2014     | SIR 2.4 (1.75–3.23), age 20–39 SIR 1.35 (1.22–1.49), age 40–49        | SIR decreased with age of BC diagnosis, however, this was only seen in ER-/PR- subgroups      |
| Hu et al.²²              | Cohort study Fudan University Shanghai Cancer center | 169 BCLC | 2000–2018 | EGFR-mutated LC - 22/64 (34.4%) were HR + compared to 0/24 (0%) for EGFR wild-type LC (p < 0.001) | Study examined LC tissue in BCLC with control of LC only, all BCLC with + HR expression also harbored EGFR mutation |
| Moran et al.²³           | Retrospective cohort of Catalan Institute of Oncology, Spain | 62 EGFR | 2008–2014     | 17.7% (11/62) of LC patients with EGFR mutations had BC, compared to 1.02% (3/294) of EGFR- WT patients (p < 0.001) | Of note, 5/6 (83.3%) BC patients treated with RT developed LC in the area of the radiation field |
| Wang et al.²⁴            | Meta-analysis of 4 genome-wide association studies of European ancestry | 10,246/11,348 | Unclear | Rare variant BRCA2 p. Lys3326X (rs11571833) has odds ratio (OR) = 2.47, p = 4.74 × 10⁻²⁰ for developing squamous cell cancer of the lung | Other findings include an association with CHEK2, and association with TP63 |
| Hu et al.²⁵              | Retrospective cohort of 10 hospitals across China | 6220 NSCLC | Unclear | Of <50 years old 16/947 (1.69%) with germline BRCA mutation versus 45/4945 (0.91%) in > 50 years old, significantly different (p = 0.036) | Positive correlation between germline BRCA mutation and early onset NSCLC with pathogenic germline BRCA mutation with BRCA 2 being the most common, 49/64 (76.5%) |

RR: relative risk; SIR: standardized incidence ratio; AR: absolute risk; HR: hazard ratio.
Confidence interval of 95% unless otherwise specified, p-value < 0.05.
Table 2. Chest RT and risk of subsequent LC in selected studies (published 2014–2020).

| Study                  | Study design                        | n              | Timeline       | Results                                      | Comments                                                                                                                                 |
|------------------------|-------------------------------------|----------------|----------------|----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Huang et al.¹⁰         | Retrospective cohort of the         | 5695 RT        | 2000–2010      | HR 10.078 (3.713–27.351),                    | For RT vs non-RT, stratified for age, stage, comorbidities (COPD, HTN, stroke), location, urbanization, and insurance premium, lacked info of radiation type/dosage and smoking history. Of note, subsequent LC was diagnosed most within first 3 years after RT (follow-up period 1 to 11 years) |
|                        | Longitudinal Health Insurance       | 1713 non-RT    |                | 128/5695 (2.25%) versus 4/1713 (0.23%)       |                                                                                                                                         |
|                        | Database of Taiwan                  |                |                | incidence                                    |                                                                                                                                         |
| Grantzau et al.¹²      | Nested case control of Danish       | 151 cases      | 1982–2007      | Excess RR/Gray 0.085 (0.031–0.233) at >5 years | Rate of LC increased linearly by 8.5% per Gray of RT when more than 5 years elapsed between BC treatment and subsequent LC diagnosis. Rate was enhanced for ever smokers with an excess rate of 17.3% per Gray |
|                        | population-based cohort             | 443 controls   |                | Excess RR/Gray 0.173 (0.045–0.540) at >5 years for ever smokers |                                                                                                                                         |
| Grantzau and Overgaard ¹ | Systemic review and meta-analysis   | 245,575 RT     | 1954–2007      | SIR 1.21 (1.05–1.4) at >5 years              | Included 11 studies looking at subsequent LC after RT vs no RT. SIR increased with increasing time from radiation therapy. Interestingly, there was no increase in LC neither overall nor over time in BC nonirradiated patients |
|                        |                                    | 277,164 non-RT |                | SIR 1.58 (1.21–2.05) at >10 years            |                                                                                                                                         |
|                        |                                    |                |                | SIR 1.91 (1.11–3.29) at >15 years            |                                                                                                                                         |
| Taylor et al.²⁹        | Systemic review and meta-analysis   | 40,781         | 2010–2015      | Excess RR/Gray 0.11 (0.05–0.2) at >10 years  | Estimated excess RR/Gray (smoking status unknown) from RT calculated from 75 RCTs was applied to modern radiation dose of 5.7 Gy for lung RT. This was applied to the smoker and nonsmoker mortality rates in LC to estimate an absolute increase in mortality of RT for smokers and nonsmokers |
|                        |                                    |                | (Radiation dosages) | 4.4% AR of mortality with RT in smokers versus 0.3% with RT in nonsmokers |                                                                                                                                         |
| Liu et al.⁶            | Observational study of SEER database | 535,941        | 1973–2014      | HR 1.65 (1.45–1.87) from 1973 to 1984        | While RT increased risk for LC from 1973 to 1984, beginning after 1995, RT became a protective factor from developing LC. However, SEER database often missing data on radiation |
|                        | at the NIH, US                      |                |                | HR 0.92 (0.87–0.99) from 1995 to 2004         |                                                                                                                                         |
|                        |                                    |                |                | HR 0.84 (0.77–0.91) from 2005 to 2014         |                                                                                                                                         |
| Lin et al.³⁰           | Retrospective cohort of the         | 32,824 w/LC    | 2000-2011      | HR 0.64 (0.33–1.25) at >3 years of BC diagnosis | While there was no increased risk in LC after RT, 3-year time frame may not be sufficient time for effects of RT to cause LC to become apparent |
|                        | Longitudinal Health Insurance       | 88,446 w/BC    |                |                                             |                                                                                                                                         |
|                        | Database of Taiwan                  |                |                |                                             |                                                                                                                                         |
| Wang et al.²¹          | Observational study of SEER database | 6269           | 2000–2014      | SIR not significant for the RT group or breast-conserving surgery group (which is a surrogate marker for radiation) | Like the study by Liu, looked through the SEER database where nearly half of BC patients are none/unknown status of RT, limiting data significance. Of note, 31% increased risk of developing subsequent LC within 1 year after BC diagnosis |
|                        | at the NIH, US                      |                |                |                                             |                                                                                                                                         |

and population data on LC rates for smokers and nonsmokers, the estimated absolute increased risk of LC mortality following RT was 4% for continued smokers and 0.3% for nonsmokers.²⁹ In addition, in a retrospective analysis of 191 Swedish patients diagnosed with breast and subsequent LC from 1958 to 2000, the relative risk for developing LC was significantly increased in patients who received RT after a latency time of at least 10 years after exposure. Subgroups analyses showed that this increased risk was present for smokers (RR = 3.17; 95% CI, 1.66–6.06), but not present for nonsmokers (RR = 0.9; 95% CI, 0.37–2.22).³⁵ The effects of RT and time elapsed can also be seen in a systematic review and meta-analysis that demonstrated increasing incidence of LC the more years that pass after RT for BC in intervals of 5, 10, and 15 years.¹¹ It is important to mention that there are other studies, including two SEER database analyses and a Taiwanese registry study, which suggested that RT may not be associated with increased risk for subsequent LC.⁶,²¹,²³ One of the SEER studies even suggested a possible protective effect of radiation on the development of LC in BC survivors leading to increased LC-specific survival.³⁶ As noted above, it is
possible that older RT techniques contributed to the higher risk of developing LC in some of the older studies. A SEER analysis breakdown showed that RT was a risk for LC in patients from 1973 to 1984, but after 1995, RT became protective. Perhaps, the newer RT techniques do not cross the tolerance threshold level to induce significant carcinogenesis and may provide beneficial effects by activating the adaptive immune response and antioxidant system. However, the newer studies, including the SEER database studies that did not demonstrate an increased risk of LC in BC survivors who received RT, lacked radiation details, and the radiation data were often incomplete or missing.

**ER/PR/HER2 receptors**

Some studies have reported an increased incidence of LC within 6 months to a year following BC and vice versa, which would not be explained by radiation-induced carcinogenesis. Perhaps, this is related to elevated hormone levels, which may drive the development of both cancers simultaneously although this may also be confounded by closer follow-up and use of radiologic imaging immediately following BC diagnosis. In two recent SEER database studies, LC incidence was numerically higher after triple-negative BC (TNBC), although for one of the studies, this difference was not statistically significant (Table 3). Compared to patients with hormone-positive (HR+) BCLC, those with HR− or TNBC also correlated with a poorer prognosis. Another SEER analysis demonstrated a higher incidence of LC with ER− BC. It is important to note that the negative HR receptors may themselves be a risk factor, and they may also act as a surrogate for antihormone treatment. HR positivity often necessitates antihormone therapy and it may be that the administration of antiestrogens in HR+ BC may have a protective effect on the development of subsequent LC. A randomized trial studying the incidence of subsequent LC with adjuvant tamoxifen showed that patients who received tamoxifen for 5 years had a significantly lower incidence of subsequent primary LC compared to patients who received tamoxifen for 2 years. This observation was also noted in a Taiwanese health insurance database where antiestrogen use was associated with reduced subsequent LC incidence in patients 50 years and older, after adjusting for age, chemotherapy, and RT. Limitations on this study include lack of smoking details and lack of LC and BC histology. Some retrospective studies have also shown that antiestrogen treatment for BC results in a lower subsequent LC mortality (Table 3).

| Study | Study design | n | Timeline | Results | Comments |
|-------|-------------|---|----------|---------|----------|
| Wang et al. | Observational study of SEER database at the NIH, US | 6269 | 2000–2014 | SIR 1.59 (1.29–1.94) TNBC SIR 1.26 (1.19–1.34) ER− SIR 1.16 (1.11–1.22) PR− SIR 1.13 (1.04–1.22) HER2− | Any negative BC receptor marker increased the risk of subsequent primary LC |
| Liu et al. | Observational study of SEER database at the NIH, US | 535,941 | 1973–2014 | HR 1.445 (0.904–2.309, p = 0.12) TNBC HR 0.905 (0.857–0.955, p = 0.0003) PR+ | TNBC was not significant for the development of LC but was significant for the development of any subsequent cancer. HER2 receptor had no apparent effect |
| Lin et al. | Retrospective cohort of the Longitudinal Health Insurance Database of Taiwan | 32,824 w/LC 88,446 w/BC | 2000–2011 | HR 3.01 (0.97–9.4, p = 0.057) HER2+ | HER2 positive causing synchronous BCLC barely not significant but was significant for the development of subsequent thyroid cancer HR = 5.29 (1.31–21.42, p = 0.02) for HER2-positive BC |
| Rosell et al. | Randomized trial of the Swedish Breast Cancer Group | 4128 | 1982–1992 | HR 0.45 (0.27–0.77) for 5-versus 2-year tamoxifen | Patients were early-stage BC and post-menopausal and were randomized to receive 2 years or 5 years of tamoxifen, 5-year period of tamoxifen also reduced risk of subsequent contralateral BC, HR 0.73 (0.56–0.96) |
| Hsu et al. | Retrospective cohort of Sun Yat-Sen Cancer center in Taipei, Taiwan | 6361 | 2000–2009 | HR 1.01 (0.45–2.2, p = 0.970) w/antiestrogen treatment HR 0.11 (0.01–0.97, p = 0.002) for mortality w/ antiestrogen treatment | Antiestrogen therapy did not reduce risk of subsequent LC however did increase cancer-specific survival. Among the 26 patients who developed BCLC, there were no smokers and all but 1 had adenocarcinoma so excluded effects of smoking and histology on confounding. No mention of length of time of antiestrogen therapy |

TNBC: triple-negative BC (ER, PR, and HER2 receptor negative).
Interestingly, an analysis of a prospective cohort of 36,588 peri and postmenopausal females aged 50–76 years showed that treatment with hormone replacement therapy (HRT) was associated with an increased incidence of LC in a duration-dependent manner. Patients who used HRT for at least 10 years had an increased risk of LC compared to those who did not use HRT (HR = 1.48; 95% CI, 1.03–2.12).43 In addition, in a post hoc analysis of a randomized, double-blind, placebo-controlled trial of 16,608 postmenopausal women who received either combined estrogen and progesterone versus placebo, the deaths from LC were higher in the HRT group, primarily from NSCLC.44 Of note, the incidence of LC was not increased in the HRT group in this study. Though this conflicts with the previous trial’s data, there was a shorter duration of treatment and follow-up (mean of 5.6 years of treatment and 2.4 years of additional follow-up), which could explain the difference in results. All of these data suggest that estrogen could be a driver of LC.

In addition, PR positivity has been found to correlate with subsequent LC development. A SEER database analysis showed an increased risk of developing LC if PR− and a reduced risk if PR+.6,21 PR receptors, if found in NSCLC, have also been associated with better clinical outcome and overall survival.45 This can possibly be related to the fact that PR+ BCs are usually better differentiated tumors, which respond to treatment with antiestrogen therapy.45 Evaluating the effect of HER2 receptor status on LC development has had more conflicting results. A SEER analysis showed an increased risk of subsequent LC when HER2 receptor was negative. Alternatively, an increased risk for synchronous LC and BC (within 6 months) was seen in patients with HER2+ cancer in a Taiwan cohort registry study.21,35

### Chemotherapy

Chemotherapy has also been associated with increased risk of subsequent LC; however, the results are controversial (Table 4). In Grantzau’s nested case–control study, use of chemotherapy was associated with an increased risk of a subsequent LC in a linear dose–response model.12 The reasoning is that the patients were treated with cyclophosphamide, which has been linked to subsequent LC in Hodgkin’s lymphoma patients.46 However, an older study found no association between cyclophosphamide, methotrexate, and fluorouracil use for BC and risk of subsequent malignancy.13

| Study | Study design | n | Timeline | Results | Comments |
|-------|--------------|---|----------|---------|----------|
| Grantzau et al.12 | Nested case control of Danish population-based cohort | 31 cases 88 controls | 1982–2007 | Excess RR 0.091 (0.007–0.316, p = 0.02) | With chemotherapy, all patients received alkylating agent cyclophosphamide in combination with other therapies |
| Chen et al.47 | Retrospective cohort of cancer registry group in Taiwan | 54 BCLC 457 LC | 2004–2014 | HR 25 (4.47–139.82, p = 0.001) of recurrence with chemotherapy HR 6.182 (1.32–28.942, p = 0.021) of prognosis with chemotherapy | Comparing LCBC with BC patients with propensity score matching for age, operation type, smoking status, and pathologic stage, but radiation not accounted for |
| Liu et al.6 | Observational study of SEER database at the NIH, US | 535,941 | 1973–2014 | HR 0.659 (0.52–0.836, p = 0.0006), from 2005 to 2014 with surgery HR 2.479 (1.301–4.721, p = 0.006) from 1995–2004 with breast implants | Years 1973–2004: surgery not significantly protective for BCLC Years 2005–2014: breast implants not significant for BCLC |
| Huang et al.10 | Retrospective cohort of the Longitudinal Health Insurance Database of Taiwan | 5695 RT 1713 non-RT | 2000–2010 | HR 19.087 (4.73–77.03) for no surgery + RT versus surgery + RT 10.63% (94/884) versus 0.56% (2/359) incidence DFS also affected, no surgery + RT associated with 0.55 DFS by year 10 compared to 0.90 DFS for no surgery and no RT | DFS affected, no surgery + RT associated with 0.55 DFS by year 10 compared to 0.90 DFS for no surgery and no RT |
| Warschkow48 | Observational study of SEER database at the NIH, US | 7955 | 1998–2002 | HR 2.51 (1.28–4.95, p = 0.005) for breast reconstruction with implants compared to autologous flaps | Analysis with both age-stratified Cox regression analysis and propensity score matching, however, cardiovascular risk factors not in SEER database and may have impacted decision for flaps versus implants |

DFS: disease-free survival.

Table 4. Selected studies (published 2014–2020) examining chemotherapy and surgery on risk of BCLC.
that patients with both BC and LC have a higher risk of recurrence of disease with chemotherapy and it is also a poor prognostic factor.\textsuperscript{47} This study had propensity score matching with control of age, operation type, smoking status, and pathologic stage, but radiation was not accounted for. However, in an older Dutch population study, chemotherapy was associated with a decreased hazard for all subsequent non-BC (SNBC) as well as decreased subsequent LC in patients younger than 50 years at BC diagnosis. This may be secondary to possible eradication of subclinical SNBC or a protective effect through premature ovarian failure. However, it is also possible that the decreased risk after chemotherapy is misinterpreted because the BC is often higher stage and any lung masses were incorrectly staged as metastatic disease.\textsuperscript{9}

\textbf{Surgery}

Some studies suggest that surgery for BC is possibly protective for the development of LC and there was a significantly decreased incidence seen with all types of surgery on a SEER database analysis\textsuperscript{6} (Table 4). This was also shown in Huang’s cohort study where patients who received RT and no surgery had an increased risk of BCLC compared to those who received both RT and surgery (incidence of 10.63\% vs 0.56\%, respectively). There was also a decrease in disease-free survival between the two groups.\textsuperscript{10} Other studies have found surgical reconstruction/implantation to be a potential risk factor for developing LC. For instance, one study examined the occurrence of subsequent malignancies among 7955 female BC patients undergoing surgical reconstruction after mastectomy by either implants or autologous flap. The incidence of subsequent cancers was similar between both groups; however, there was a significant association between LC and breast implants (HR = 2.51; 95\% CI: 1.28–4.95).\textsuperscript{48}

\textbf{Stage and grade}

SEER database and Taiwanese retrospective studies have shown that the risk for subsequent LC was only significantly increased for stage IV BC. Alternatively, stages II and III BC seemed to have a protective effect.\textsuperscript{6,47} This is seen with an HR of 0.897 (0.851–0.944) and 0.952 (0.876–1.035) for stage II and III BC compared to stage I BC respectively.\textsuperscript{6} However, the stage may also only be a surrogate for treatment exposures, as stage III BC has a higher RT rate (67\% vs 55\% in stage I and II) and use of chemotherapy (58\% vs 17\% in stage I and II), while a significant portion of stage IV BC did not undergo any RT, chemo, or treatment-directed surgery (26\% vs around 5\% for other stages).\textsuperscript{49} In terms of grade, the risk for LC development was greater in patients with grade 3 or undifferentiated BC with a SIR of 1.13 (1.04–1.22).\textsuperscript{21} Poor differentiation was also associated with an HR of 8.125 (1.575–41.926) for recurrence.\textsuperscript{47}

\textbf{Conclusion}

Some studies indicate that LC occurs more frequently in patients with prior history of BC compared to the general population. It is important to counsel patients on smoking cessation after primary BC as not only is it an independent risk factor for the development of LC but it may act synergistically with radiotherapy in increasing the risk. Treatment with antiestrogen therapy in appropriate settings may serve as primary prevention in post menopausal women with a high risk of developing LC. BC patients with high-risk characteristics, such as diagnosis at age less than 50, previous RT, triple-negative subtype, and history of breast implants, should also be more closely monitored for subsequent development of primary LC. A family history of cancer can also prompt testing for mutations such as TP53, BRCA, and EGFR.

\textbf{Limitations}

While this review attempts to capture the most relevant studies being conducted, it is not a systematic review and may not provide all the studies on the topic. Many of the studies in this review were retrospective and observation in nature with few prospective or randomized controlled trials. More studies are needed to elucidate the mechanism and shared links between BC and LC.

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\textbf{ORCID iDs}

Kevin Y Wang \(\text{https://orcid.org/0000-0002-7509-6989}\)

Chung-Shien Lee \(\text{https://orcid.org/0000-0003-3505-6402}\)

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