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Assessing the risk of second primary lung cancer in women after previous breast cancer

Yuanhui Huang[1,2]✉, Jenny J. Lin[3], Juan P. Wisnivesky[3], Chung Yin Kong[3] and Keith Sigel[3]

BACKGROUND: Breast cancer (BC) survivors may be at increased risk of developing second cancers compared to those without BC diagnosis due to shared risk factors and potential carcinogenic effects of cancer therapy. Lung cancer (LC) is the most common second primary cancer among BC survivors. This study aimed to evaluate the association between BC and the subsequent incidence of LC.

METHODS: Women aged 55–74 were identified from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. The risk of incident LC was compared by BC status using a multivariable Cox regression model with BC and smoking exposures incorporated as time-updated variables.

RESULTS: 75,951 females from the PLCO trial were identified, with 5808 diagnosed with BC after enrollment. The unadjusted incidence rate (IR) of the second LC was significantly higher among BC survivors than non-BC participants (231 vs. 172 per 100,000 person-years). The adjusted hazard ratio (HR) for the second primary LC associated with BC diagnosis was 1.24 (95% CI: 1.03–1.49).

CONCLUSIONS: BC diagnosis was an independent risk factor for the development of second primary LC. Consequently, BC survivors may derive benefits from enhanced LC screening interventions.

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INTRODUCTION

Breast cancer (BC) is the most frequently diagnosed cancer in women worldwide [1]. In the United States, it ranks as the second leading cause of cancer-related deaths among women, following lung cancer (LC). As of 2023, over 4 million women in the U.S. have been diagnosed with BC [2], with an estimated 297,790 new cases that year [3]. With improved prognosis and prolonged survival [4–6], the long-term health of the growing BC survivor population has become a major public health and clinical issue.

BC survivors are more likely to develop second non-breast cancers than the general population [7–18]. Notably, LC is the leading second malignancy in this group [8, 11, 12, 19, 20], accounting for approximately 5% of second primary cancers [19]. However, the extent to which a previous diagnosis of BC confers an increased risk for subsequent LC remains uncertain, as previous studies have reported mixed findings. For instance, based on data from 13 population-based cancer registries, Mellemkjaer et al. reported a 68% increased risk of second primary LC in BC survivors ten years after diagnosis compared to the general population [12]. However, this study did not account for smoking exposure. Conversely, a few studies have reported either minimal or no significant elevation in the risk of second LC among BC survivors [21–23]. These inconsistent findings may be attributed to factors such as a limited number of studies, small numbers of LC cases, absence of smoking information, and variation in follow-up time and radiation therapy (RT) exposure [24, 25].

As LC screening is now recommended for many older current and former smokers, and given a growing population of BC survivors, an improved understanding of second LC risk in this potentially high-risk group may help guide clinical management and inform decision-making. The risk factors for second malignancies are multifactorial, and population-based risk assessments often lack important exposure data. To overcome some of the limitations of previous studies, we used high-quality data from a large cancer screening trial, Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, to clarify LC risk among female BC survivors.

MATERIALS AND METHODS

Data source and study population

Data for this study was obtained from the PLCO Trial, and full details have been published previously [26, 27]. Briefly, PLCO was a National Cancer Institute-sponsored randomized controlled trial conducted to determine the effects of selected screening tests on cancer-related mortality and other secondary endpoints. The study enrolled a total of 154,901 men and women aged 55–74 between November 1993 and July 2001 [28]. Women were ineligible if they had a previous diagnosis of lung, colorectal, or ovarian cancer, were undergoing cancer treatment, or were participating in another screening or prevention trial. Women who had bilateral oophorectomy or were taking tamoxifen were originally ineligible but later allowed to enroll [26]. At study entry, participants completed a self-administered questionnaire providing details on demographics, personal medical records, medication use, family history of cancer, smoking status and intensity, and other detailed smoking-related exposure. In 2005, the PLCO program initiated BC-centered data collection retrospectively for all previously diagnosed BC survivors [29]. The LC screening intervention

[1]Graduate School of Biomedical Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [2]Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [3]Division of General Internal Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ✉email: yuanhui.huang@icahn.mssm.edu

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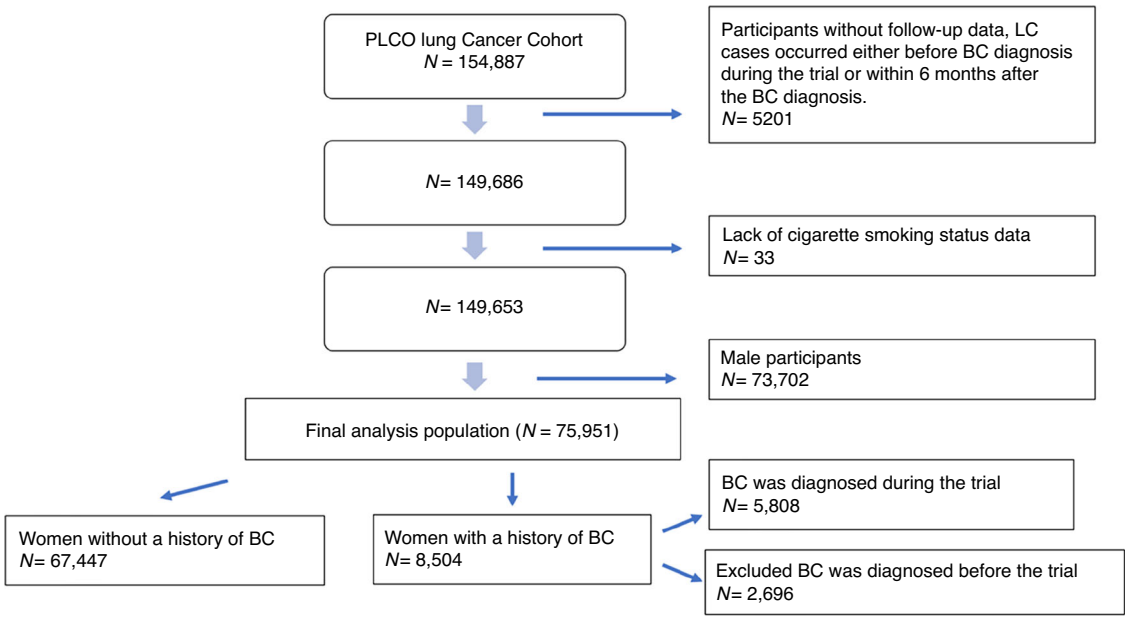

Fig. 1 Flow diagram of analysis population.

consisted of four annual chest radiographs. Control participants received regular care as recommended by their primary care providers [30, 31].

Cancer ascertainment and follow-up time

We obtained the most recent PLCO dataset with extended follow-up, including cancer registry information through 2017 and mortality data through 2020 [32]. In this retrospective cohort study, we focused on women from both LC screening intervention and control arms who had complete data. Participants without follow-up data or information about smoking status were excluded. Additionally, women with a reported history of BC prior to trial enrollment were excluded from most primary analyses. As a result, 5808 participants were identified with a BC diagnosis during the trial (hereafter referred to as BC survivors).

BC diagnosis data and its timing relative to study enrollment were extracted from study records.

Second primary LC was defined as a newly diagnosed LC occurring after a BC diagnosis. To ensure accurate classification, we included only second primary LC cases diagnosed at least six months after the initial BC diagnosis [33], leading to the exclusion of 29 LC cases that either fell within this window or occurred before the BC diagnosis date. Participants who developed second primary LC during or after the trial completion were then ascertained through 2017 or until the last documented contact if it occurred before 2017.

Follow-up time was measured from the PLCO randomization date until either LC diagnosis, death, or the last known alive date, whichever occurred first. For incidence rate calculations (but not time-to-event models), follow-up time for BC survivors began at the date of BC diagnosis.

Variables

Based on established LC risk factors, we selected covariates including age, race, education level (categorized as less than high school, high school graduate, college graduate, postgraduate), body weight index (BMI), family history of LC, chronic obstructive pulmonary disease (COPD), smoking status (categorized as never smoked cigarettes, current cigarette smoker, former cigarette smoker), and cigarette smoking intensity (calculated as pack-years) [34]. Additionally, variables from the PLCOm2012 model, a well-established LC prediction model [31], were incorporated in the time-updated Cox proportional hazards model, including the number of cigarettes smoked per day, the number of years since stopped smoking cigarettes for ever-smokers, and the duration of smoked cigarettes.

Statistical analysis

We assessed participant baseline characteristics according to BC status and cancer registry data. PLCO participants with and without a BC diagnosis during follow-up were compared using the Wilcoxon rank-sum test for continuous non-normally distributed variables, the t-test for normally distributed variables such as age at randomization, and the chi-square test for categorical variables.

We then calculated the unadjusted IR of LC among BC survivors and non-BC participants, with 95% confidence intervals (CI) derived from the Poisson distribution. Next, we evaluated the characteristics of BC survivors diagnosed during the trial, stratified by LC diagnosis, including smoking exposure, BC hormone receptors status, RT, LC stage, and other relevant clinical data.

A time-updated Cox proportional hazards model was employed to estimate the hazard ratio (HR) for LC incidence in relation to a prior BC diagnosis. This model incorporated BC diagnosis and its timing relative to study enrollment as a time-updated exposure. Notably, 2039 females changed their smoking status during the trial, and these updates were recorded in the PLCO-SQX Supplemental File, enabling smoking status to be incorporated as a time-updated exposure. Age was included as a continuous variable, along with its squared term, to capture the non-linear effects observed in previous LC incidence analyses [35]. Educational attainment was dichotomized to reflect the association identified in the PLCOm2012 model [31]. The two categories were: (1) less than 12 years or completed high school (reference group); and (2) college education and above. The model was thus adjusted for age at randomization, age squared, race/ethnicity, educational attainment, BMI, COPD, familial LC history, and smoking intensity (number of cigarettes smoked per day, number of years since stopped smoking cigarettes for ever-smokers, and total duration of smoking). To address missing data for BMI, race, educational attainment, and pack-years of smoking, multiple imputation (MI) was applied using Fully Conditional Specification (FCS).

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) with p-value < 0.05 considered statistically significant.

RESULTS

Overall, 149,686 PLCO participants completed questionnaires, with LC cases included only if diagnosed at least six months after the initial BC diagnosis. We excluded 33 participants due to ambiguous or unknown smoking status. As a result, the final analytic sample included 75,951 women (50.8%) aged 55–74 from both trial arms. The median follow-up period was approximately 16 years for non-BC participants and 17 years for BC survivors diagnosed during the trial (Fig. 1).

Baseline characteristics

Among the analytic cohort, 8504 women were identified with BC, including 5808 participants diagnosed during the trial. The 2696

Table 1. Baseline characteristics of cohort.

Characteristic	Without breast cancer $N = 67,447$	With breast cancer diagnosed during the trial $N = 5808$	p-value[a]
Age (years)	62.5	62.3	0.01
Age group, *N* [%]			0.01
≤59	23,262 (34.5)	2035 (35)	
60–64	20,345 (30.2)	1830 (31.5)	
65–69	14,728 (21.8)	1234 (21.3)	
≥70	9112 (13.5)	709 (12.2)	
Body mass index at baseline	(Missing $n = 975$)	(Missing $n = 74$)	0.6
	27.1	27.1	
Race/ethnicity, *N* [%]	(Missing $n = 25$)	(Missing $n = 2$)	<0.0001
White, Non-Hispanic	59,610 (88.4)	5241 (90.4)	
Black, Non-Hispanic	3961 (5.9)	229 (3.9)	
Hispanic	1089 (1.6)	77 (1.3)	
Asian	2265 (3.4)	211 (3.6)	
Others	497 (0.7)	48 (0.8)	
Education, *N* [%]	(Missing $n = 169$)	(Missing $n = 14$)	<0.0001
Less than high school	4535 (6.7)	291 (5)	
High school graduate	27,437 (40.8)	2185 (37.7)	
College	25,640 (38.1)	2298 (39.7)	
Postgraduate	9666 (14.4)	1020 (17.6)	
Personal history of chronic obstructive pulmonary disease, *N* [%]	4977 (7.4)	327 (5.6)	<0.0001
Lung cancer family history, *N* [%]	9031 (13.4)	742 (12.8)	0.18
Pack-years of cigarette smoking (excluded never smokers))	30.3	29.4	0.1
Smoking status, *N* [%]			<0.0001
Never smoked cigarettes	37,659 (55.8)	3165 (54.5)	
Current cigarette smoker	6638 (9.8)	480 (8.3)	
Former cigarette smoker	23,150 (34.4)	2163 (37.2)	
Follow-up time (years)	16	17	<0.0001
Lung cancer incidence, *N* [%]	1820 (2.7)	115 (2)	0.001

[a]p-value compares group without breast cancer and breast cancer survivors diagnosed during the trial.

women with a prior BC diagnosis before PLCO enrollment were excluded from the primary analyses. Within the primary analytic cohort, a total of 1935 incident LC cases were identified between 1993 and 2017.

At baseline, the average age of PLCO participants who developed BC was 62.3 years, slightly younger than the non-BC participants (62.5, $p < 0.01$). Additionally, BC survivors were predominately non-Hispanic white (90.4% vs 88.4%, $p < 0.0001$) and more likely to have graduated from college or obtained advanced degrees ($p < 0.0001$ for both comparisons). BC survivors were also more likely to be former cigarette smokers (37.2% vs 34.4%, $P < 0.01$) but were less likely to have a history of COPD (5.6% vs. 7.4%, $p < 0.01$; Table 1).

Unadjusted incidence of lung cancer

The median follow-up time was approximately 16 years for participants without BC and 17 years for BC survivors diagnosed during the trial. In the unadjusted analysis, 115 LC cases were identified among BC survivors, compared to 1820 LC cases among non-BC participants. This yielded a higher unadjusted IR of 231 per 100,000 person-years (95% CI: 189–273) for BC survivors, compared to an IR of 172 per 100,000 person-years (95% CI: 164–180) for those without BC.

Risk factors for lung cancer in breast cancer survivors

We compared the characteristics of BC survivors who developed a second LC to those who did not develop LC during the follow-up period (Table 2). BC survivors diagnosed with LC were more likely to have a personal history of COPD and cigarette smoking compared to BC survivors who did not develop subsequent LC. No significant differences were observed in terms of baseline age, race, education, BC stage, family history of LC, chemotherapy, RT, estrogen receptor (ER) status, and human epidermal growth factor receptor 2 (HER2) status in univariate comparisons. We also observed that approximately one-third of second primary LC cases were diagnosed at an early stage (stage I), regardless of BC status (Table 3).

Adjusted analyses of lung cancer incidence

In a time-updated Cox regression analysis, BC survivors had an increased hazard of developing a second LC than women without BC history (AHR 1.24; 95% CI: 1.03–1.49; Table 4) after adjusting for age, age squared, race, education level, BMI, family history of LC, personal history of COPD, and smoking patterns.

The risk of developing a second LC was more than twice as high among current cigarette smokers compared to non-smokers (AHR 2.3; 95% CI: 1.48–3.57), while no significant association was

Table 2. Baseline characteristics of BC survivors diagnosed during the trial by LC diagnosis.

Characteristic	Lung cancer ($N = 115$)		No lung cancer ($N = 5693$)		
	No.	%	No.	%	*p*-value
Age at randomization, years, median(range)	63 (55–74)		62 (54–74)		0.06
Body mass index at baseline, kg/m^2, median	26		27		0.03
Missing	7		67		
Race/Ethnicity					
White, Non-Hispanic	106	92.2	5135	90.2	0.07
Black, Non-Hispanic	5	4.3	224	3.9	
Hispanic	0	0	77	1.4	
Asian	1	0.9	210	3.7	
Other	3	2.6	45	0.7	
Missing	0	0	2	0.1	
Education					
<12 Years or completed high school	51	44.3	2425	42.5	0.72
College and above	64	55.7	3254	57.3	
Missing	0	0	14	0.2	
Breast cancer clinical stage					
Stage 0	24	20.8	1158	20.3	0.65
Stage I	59	51.3	2764	48.5	
Stage II	30	26.1	1428	25.1	
Stage III	1	0.9	220	3.9	
Stage IV	0	0	83	1.5	
Missing	1	0.9	40	0.7	
Smoking status					
Never smoked cigarettes	15	13.1	3150	55.3	<0.0001
Current cigarette smoker	45	39.1	435	7.6	
Former cigarette smoker	55	47.8	2108	37.1	
Pack-years of cigarette smoking[a]	47		29		<0.0001
Chemotherapy					
Yes	13	11.3	626	11.1	0.64
No	60	52.2	2502	43.9	
Unknown	6	5.2	166	2.9	
Missing	36	31.3	2399	42.1	
ER status					
Positive (+)	84	73	4108	72.2	0.54
Negative (−)	12	10.4	715	12.6	
Missing	0	0	78	1.4	
HER2 status					
Positive (+)	6	5.2	575	10.1	0.27
Negative (−)	49	42.6	2905	51	
Missing	1	0.9	99	1.7	
Radiation therapy					
Yes	28	24.3	1406	24.7	0.05
No	35	30.4	1064	18.7	
Unknown	7	6.1	167	2.9	
Missing	45	39.2	3056	53.7	
Personal history of COPD	14	12.2	313	5.5	0.002
Lung cancer family history	20	17.4	722	12.7	0.13

[a]Pack-years calculated among ever smokers: former smokers and current smokers.

observed for former smokers. As expected, factors such as increasing age, higher cigarette smoking intensity (measured by average cigarettes per day and smoking duration), a positive personal history of COPD, and a family history of LC were all significantly associated with an elevated risk of LC ($p < 0.0001$ for all predictors). Race was not significantly related to the hazard of developing a second LC. In contrast, higher education levels, including college and advanced degrees, were linked to a lower risk of LC (AHR 0.87; 95% CI: 0.79–0.94), and BMI was inversely related to the risk of subsequent primary LC (AHR 0.97; 95% CI: 0.96–0.98).

DISCUSSION

Using data from the PLCO trial, we evaluated the risk of LC among female participants with a BC diagnosis. Our findings suggest that BC survivorship is an independent risk factor for the incidence of subsequent primary LC, even after adjusting for established risk factors, including smoking status and intensity [31]. Women with BC diagnosis had a 24% higher risk of developing a second primary LC in comparison with women without BC. This equates to approximately 60 additional cases of LC per 100,000 women per year among BC survivors compared to non-BC participants. These findings highlight the need for LC prevention strategies in this population, such as smoking cessation and low-dose computed tomography screening.

Our findings are consistent with prior studies demonstrating that BC survivors had a modestly increased risk of developing subsequent LC [8, 12, 19, 20, 36]. For instance, a study investigating data from over half a million women across population-based cancer registries in Europe, Australia, Canada, and Singapore found that BC survivors had a 20–30% excessive risk of developing second primary non-BC cancers compared to non-BC survivors [12]. Similarly, Yi et al. examined BC survivors treated with breast-conserving surgery and RT and reported a significantly elevated risk of LC, with an 84% increase (SIR = 1.84, 95% CI: 1.25–2.42) following a first primary BC [18]. However, other studies have reported either a weak association or no elevated risk of second LC in BC survivors compared to the general population [22, 23]. These discrepancies may stem from differences in smoking data availability, variations in treatment exposures among BC survivor populations, or limitations in sample sizes.

Unsurprisingly, smoking was a strong risk factor for LC incidence in this analysis. Heterogeneity exists in smoking prevalence and cessation patterns among different BC cohorts. One study using data from the MARIE (Mammary Carcinoma Risk Factor Investigation) study found that women with BC had significantly higher odds of quitting smoking and lower odds of returning to smoking than unaffected women [37]. Similarly, a Norwegian study reported higher smoking cessation rates among female BC survivors than among cancer-free women [38]. Conversely, other studies suggested that cancer survivors

Table 3. Second primary lung cancer stage stratified by breast cancer status.

Variables	Without breast cancer $N = 67,447$	With breast cancer diagnosed during the trial $N = 5808$	p-value[a]
Lung cancer incidence, *N* [%]	1820 (2.7)	115 (1.9)	0.001
Lung cancer stage, *N* [%]	Missing ($n = 75$)	Missing ($n = 3$)	0.5
Stage I	528 (30.3)	37 (33)	
Stage II	163 (9.3)	14 (12.5)	
Stage III	404 (23.2)	27 (24.1)	
Stage IV	642 (36.8)	33 (29.5)	
Occult Carcinoma	8 (0.4)	1 (0.9)	

[a]*p*-value compares group without breast cancer and breast cancer survivors diagnosed during the trial.

Table 4. Hazard ratio for second primary lung cancer incidence for time-updated longitudinal exposure variable in adjusted Cox proportional hazards regression model.

Characteristic	Adjusted hazard ratio	95% CI
Age	1.51	1.23–1.84
Age squared	0.99	0.99–0.99
Body mass index at baseline	0.97	0.96–0.98
Race/ethnicity		
White, non-Hispanic	Reference	
Black, non-Hispanic	1.14	0.95–1.38
Hispanic	0.67	0.44–1.03
Asian	0.94	0.72–1.23
Others	1.19	0.81–1.73
Education		
<12 Years or completed high school	Reference	
College and above	0.87	0.79–0.94
Breast cancer history	1.24	1.03–1.49
Personal history of chronic obstructive pulmonary disease	1.36	1.21–1.52
Lung cancer family history	1.58	1.42–1.75
Smoking status		
Never smoked cigarettes	Reference	
Current cigarette smokers	2.30	1.48–3.57
Former cigarette smokers	1.41	0.91–2.21
Smoking intensity (average cigarettes/day)	1.31	1.26–1.37
Smoking quit time (year)	0.98	0.97–0.99
Smoking duration (per year)	1.04	1.03–1.05

generally face an increased risk of developing LC due to relatively high smoking rates, which can reach up to 50% [37, 39, 40]. Despite this, only 62% of currently smoking cancer patients have reported receiving smoking cessation counseling from their physicians [41], and fewer than half quit smoking after their cancer diagnosis [41–43]. Consequently, a substantial proportion of survivors have a history of tobacco use, with up to 35% being current or former smokers. In our study, nearly half of all female participants were ever smokers. The higher prevalence of cigarette smoking among BC survivors contributed to the increased crude incidence of LC. Notably, in our cohort, more than two-thirds of smoking measurements among BC survivors were recorded at the time of trial enrollment. Among them, 2039 females changed their smoking status during the trial, coinciding with BC status updates. To account for these changes, we obtained the PLCO-SQX Supplemental File and incorporated the corresponding smoking updates, allowing smoking status to be treated as a time-updated exposure. This approach ensured that smoking status was accurately captured even for women diagnosed with BC in the later years of the study.

Among women with early-stage (I or II) BC, approximately half undergo breast conserving surgery with adjuvant RT [44], which has been associated with a reduced risk of local recurrence and survival advantage [25, 45–48]. Previous studies have suggested that ionizing radiation may be a lung carcinogen, potentially elevating the risk of LC among BC survivors who received post-mastectomy RT [13, 15, 25, 46, 49–53]. A review of data from the Surveillance, Epidemiology and End Results (SEER) dataset found that women treated with mastectomy and RT had a 58% increased risk of developing LC within ten years compared to those treated with mastectomy alone [54]. Furthermore, the risk of second LC was greater in the ipsilateral lung among ever-smokers who received RT [55]. However, a recent systematic review and meta-analysis did not find an association between RT for BC and excess risk of LC [56]. These mixed findings might be due to the limited number of studies, the lack of smoking exposure data in most large registry-based studies, and substantial variation in the dose and volume of irradiated lung tissue as well as radiation technique [24, 25]. By design, BC was not a primary outcome of the PLCO trial. Detailed information on RT dose, irradiated lung laterality or volume, and radiation techniques were not well captured in the dataset. Albeit with a significant amount of missing data, we did not find a significant difference in the receipt of RT between BC survivors who developed LC and those who did not.

Although the factors driving the increased risk of second primary LC among BC survivors remain unclear, our findings have important implications for LC prevention efforts in this population. The independently elevated incidence of LC in BC survivors suggests that targeted interventions, such as smoking cessation and screening with low-dose computed tomography, could offer significant benefits. The benefits of these interventions will need to be evaluated in the context of the life expectancy impacts of BC survivorship, necessitating further research in this area. While we were able to adjust for many established LC risk factors, other previous studies have identified additional contributors to primary LC development following BC treatment. These include lower socioeconomic status [57], history of chemotherapy [17], frequent pulmonary infections, poorly or undifferentiated BC histological grade, and triple-negative BC subtype [36]. Furthermore, extensive preclinical data also suggest that HER2 amplification/ overexpression is present in a variable percentage of non-small cell lung cancer (NSCLC) cases and may play a role in NSCLC tumorigenesis, prognosis, and treatment response [58, 59]. Our analysis compared the available characteristics of BC survivors who developed a second primary LC to those who did not. We found no significant differences in age, race, education, BC staging, family history of LC, chemotherapy exposure, or hormone receptor

status. Although BC survivors typically have more frequent healthcare interactions and undergo cancer surveillance, raising concerns about the potential for LC overdiagnosis, we did not observe any difference in tumor stage between BC survivors and non-BC participants.

The strengths of the current study include its adjustment for established LC risk factors, such as the use of a large, well-characterized cohort with a comprehensive and standardized protocol for ascertaining BC and LC diagnosis. Furthermore, by using the Cox proportional hazards model and incorporating BC and smoking status as time-updated exposures, we enhanced the precision of hazard ratio estimates by capturing real-world exposure dynamics with the inclusion of time-updated smoking exposure information. However, our study has several limitations, and results must be interpreted within this context. First, some previous studies reported that second primary LC rates were significantly elevated among BC survivors younger than 50 [50]. Since the PLCO trial only enrolled women aged 55 and older, we could not assess LC risk in younger BC survivors. Finally, ionizing radiation has been identified as a potential lung carcinogen, and BC survivors who received RT may be at elevated risk of developing LC [13, 15, 24, 25, 49–53, 60]. However, the PLCO database lacks detailed information on BC treatment, such as chemotherapy, RT dose or volume of irradiated lung area, and radiation technique. This limitation restricted our ability to fully assess the impact of these treatment exposures on LC risk.

CONCLUSION

Our study demonstrated that previous BC diagnosis was an independent risk factor for developing LC. These findings help clarify LC risk in this large and growing population. Further research is needed to determine how these insights can inform targeted LC prevention interventions and improve the quality of life for BC survivors.

DATA AVAILABILITY

The data supporting the findings of this study are available upon request from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, sponsored by the National Cancer Institute (NCI).

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AUTHOR CONTRIBUTIONS

YH and KS designed the study, requested PLCO dataset, and analyzed the data; JJL provided funding; YH wrote the manuscript; YH, JJL, JPW, CYK and KS performed data interpretation; JJL, JPW, CYK and KS assisted with manuscript editing; and all authors made substantial contributions to acquisition of data, critically revised the manuscript, and gave final approval of the manuscript to be submitted.

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Correspondence and requests for materials should be addressed to Yuanhui Huang.

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