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Clinicopathological characteristics and prognosis of breast cancer patients with lung cancer: A study based on 19,807 breast cancer patients

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This study was conducted to investigate the clinicopathological characteristics and prognosis of breast cancer and lung cancer (BC-LC) and provide a theoretical basis for the diagnosis and treatment of BC-LC in clinical work. A retrospective study was conducted on breast cancer (BC) patients in our center from September 2009 to November 2020. The patients were divided into the BC-LC group and the control group. The control group was matched with both, the age at diagnosis and the time of surgery (±1 year). The clinicopathological factors, overall survival (OS), and hazard ratios (HRs) were evaluated by SPSS. A total of 19,807 BC patients were identified, among whom 124 (0.6%) had lung cancer (LC). Larger BC tumor was the only independent risk factor (OR=2.454, p<0.001) for development of LC in BC patients. We found inferior survival in patients with synchronous versus metachronous BC-LC (p=0.008). We also identified combined with hypertension (HR=3.917, p=0.003) was an independent prognostic factor for inferior OS. Therefore, BC patients with larger tumors need close follow-up. Effective prevention and active treatment of hypertension can improve the OS of BC-LC patients.

Key words: breast cancer; lung cancer; second primary malignancy; clinicopathological characteristics; prognosis

Breast cancer (BC) is the most common cancer in women and has now surpassed lung cancer (LC) to become the world's most common cancer [1]. With the continuous development and progress of BC diagnosis and treatment, the survival rate of BC patients has been significantly improved [2]. However, in view of the close follow-up and the significantly improved prognosis of BC patients, some patients have an elevated risk of developing a second primary malignancy [3]. The incidence of LC is second only to BC, but it is still the highest mortality cancer [1]. Epidemiological studies have shown that the incidence of LC in men has decreased slightly in most countries, while the incidence in women has shown an upward trend [4]. Some studies have reported that BC patients have a higher risk of primary LC than the general population, and BC accounted for the top three of LC combined with multiple primary malignancies in other organs [5, 6]. As two common cancers in women, it seems that BC and LC may have some possible associations in terms of genesis and development, such as hormonal factors, a genetic predisposition, or environmental factors.

The increased incidence of breast cancer and lung cancer (BC-LC) may be due to detection bias caused by more careful follow-up after the diagnosis of primary cancer. However, the relationship between BC and LC as well as the exact mechanism behind the relationship remains unclear. Here, we conducted a retrospective case-control study to investigate the risk factors of BC patients with LC, and to explore the prognosis of BC-LC and its influencing factors. Further understanding of the clinical correlation between BC and LC will help the treatment management of these patients.

Patients and methods

Study population. We conducted a retrospective study of 19,807 patients with BC who were diagnosed and treated from September 2009 to November 2020 at the Fourth Hospital of Hebei Medical University. The following exclusion criteria were applied: a) metastatic or recurrent BC upon first diagnosis, b) multiple primary cancers at more than two sites, c) male patients, and d) a lack of follow-up information. This study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University.

All BC and LC patients were diagnosed by pathological examination. According to the diagnostic criteria for multiple primary cancers [7], LC diagnosed within 6 months before or after BC was defined as synchronous malignancy (B=L), LC

diagnosed more than 6 months after BC was considered a metachronous second primary LC (B-L), and LC diagnosed more than 6 months before BC was categorized in the L-B group. B-L and L-B groups are collectively referred to as metachronous malignancy. The BC-LC group and the control group were matched at a ratio of 1:4. Matching was based on both the age at diagnosis and the time of surgery (±1 year). The computer randomly selected female patients with only BC in the institution as the control group, which was defined as the BC group.

Clinicopathological characteristics. We collected the clinicopathological characteristics of BC, such as date of diagnosis, age at diagnosis, menopausal status, hypertension, family history, tumor size, pathologic types, histological grading, lymph nodes metastasis, and estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki67. For ER and PR, nuclear staining in ≥1% of the tumor cells was considered positive. It was currently mainly focused on the detection of HER2 overexpressing tumors (immunohistochemistry [IHC] score 3+ or IHC2+/*in-situ* hybridization [ISH]-positive). Ki67 ≤30% was defined as low expression, and >30% was high expression. Information about LC can be obtained by reviewing the medical history in the hospital admission record or by following up the patient. The clinicopathological characteristics of LC include the date of diagnosis, pathological types, and tumor size. Pathologic assessments were performed based on the final formalin-fixed and paraffin-embedded representative sections.

Follow-up. The follow-up data for this patient cohort were acquired from the follow-up room of the Breast Center of the Fourth Hospital of Hebei Medical University. The follow-up was carried out by telephone, outpatient service, and medical record review. The last follow-up date was March 28, 2021. Overall survival (OS) is calculated from the date of diagnosis of the first cancer to the time of death or the time of the last follow-up.

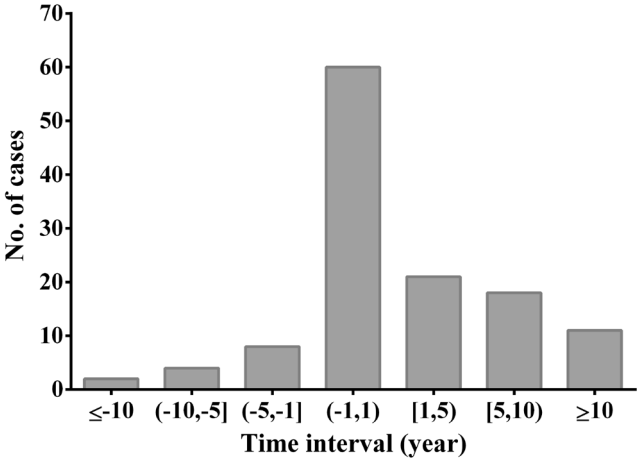

Figure 1. Time interval of LC occurrence relative to BC occurrence.

Statistical analysis. The clinicopathological characteristics of patients in the BC-LC group and BC-alone groups were compared using Pearson's χ^2 test, Fisher's exact test, or Continuity correction chi-square. A logistic regression model was used to determine the variables associated with LC in patients with BC. Survival curves of BC-LC patients were plotted using the Kaplan-Meier method, and group differences in the survival curve were investigated by the log-rank test. Univariate and multivariate analyses for OS were conducted through the Cox regression model to determine the independent risk factors. Statistical analyses were performed using SPSS version 25.0 (IBM Corp, Armonk, NY, USA). The interaction was analyzed by R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). Logistic and Cox regression models were used to evaluate the multiplicative interaction. Through the Delta method, relative excess risk ratio (RERI), attributable ratio (AP), interaction index (S), and 95% confidence interval (CI) were calculated to evaluate the additive interaction between the two variables. If there is no additive interaction between the two variables, the 95% CI of RERI and AP should contain 0, and that of S should contain 1. All analyses used two-tailed p-values, and $p<0.05$ was considered statistically significant.

Results

In this study, 19,807 BC patients were qualified for analysis, 124 (0.6%) of whom were diagnosed with LC (BC-LC). The median follow-up period was 89 months (range, 1–278 months). Specifically, 16 (13.0%) patients had LC >6 months prior to BC (L-B), 54 (43.5%) had synchronous BC and LC (B=L), and 54 (43.5%) were diagnosed with LC at least 6 months after BC (B-L). The mean time interval between BC diagnosed and LC diagnosed was 3.01±4.34 years. BC-LC mainly occurred within 1 year before and after diagnosis of BC and the first incidence rate for BC was higher than for LC (Figure 1).

Clinicopathological characteristics of patients with BC-LC. The clinicopathological characteristics of patients with BC are shown in Table 1. Patients with BC-LC were more likely to be menopausal (65.3% vs. 52.8%, p=0.012) and more likely to have hypertension (31.5% vs. 21.4%, p=0.018) than patients in the control group. Compared with patients in the BC group, patients with BC-LC had a larger invasive tumor size (56.5% vs. 36.3%, p<0.001). However, no statistical difference was detected in tumor grade, ER status, PR status, HER2 status, Ki67 expression rate, pathological type of breast cancer, or lymph node involvement.

Among 110 patients with known pathological types of lung cancer (non-small cell lung cancer vs. small cell lung cancer), the clinicopathological characteristics of patients were not significantly different between the groups, which indicates that the clinicopathological characteristics of BC do not have an impact on the pathological type of LC patients. However, the higher pathological grade (p=0.033) was associated with

Table 1. Clinical-pathological characteristics of patients with breast cancer and lung cancer versus patients with breast cancer alone.

Variables	Total (N = 620)	BC-LC (N = 124)	BC (N = 496)	p-value
Age				0.082
≤50	273 (44.0%)	46 (37.1%)	227 (45.8%)	
>50	347 (56.0%)	78 (62.9%)	269 (54.2%)	
Menopause				0.012
No	277 (44.7%)	43 (34.7%)	234 (47.2%)	
Yes	343 (55.3%)	81 (65.3%)	262 (52.8%)	
Complicated hypertension				0.018
No	475 (76.6%)	85 (68.5%)	390 (78.6%)	
Yes	145 (23.4%)	39 (31.5%)	106 (21.4%)	
Family history of malignancy				0.151
No	503 (81.1%)	95 (76.6%)	408 (82.3%)	
Yes	117 (18.9%)	29 (23.4%)	88 (17.7%)	
Tumor size [a]				0.000
≤2	301 (48.5%)	41 (33.1%)	260 (52.4%)	
>2	250 (40.3%)	70 (56.5%)	180 (36.3%)	
Unknow	69 (11.2%)	13 (10.5%)	56 (11.3%)	
ER				0.083
Positive	445 (71.8%)	77 (62.1%)	368 (74.2%)	
Negative	152 (24.5%)	36 (29.0%)	116 (23.4%)	
Unknow	23 (3.7%)	11 (8.9%)	12 (2.4%)	
PR				0.605
Positive	398 (64.2%)	73 (58.9%)	325 (65.5%)	
Negative	199 (32.1%)	40 (32.3%)	159 (32.1%)	
Unknow	23 (3.7%)	11 (8.9%)	12 (2.4%)	
HER2 [b]				0.582
Positive	142 (22.9%)	27 (21.8%)	115 (23.2%)	
Negative	382 (61.6%)	81 (65.3%)	301 (60.7%)	
Unknow	96 (15.5%)	16 (12.9%)	80 (16.1%)	
Ki67				0.956
>30%	267 (43.1%)	50 (40.3%)	217 (43.8%)	
≤30%	328 (52.9%)	62 (50.0%)	266 (53.6%)	
Unknow	25 (4.0%)	12 (9.7%)	13 (2.6%)	
Pathology				0.745[c]
In situ	22 (3.5%)	5 (4.0%)	17 (3.4%)	
Invasive	598 (96.5%)	119 (96.0%)	479 (96.6%)	
Grade				0.801
I–II	280 (45.2%)	50 (40.3%)	230 (46.4%)	
III	119 (19.2%)	20 (16.1%)	99 (20.0%)	
Unknow	221 (35.6%)	54 (43.5%)	167 (33.6%)	
pN				0.963
pN0	364 (58.7%)	74 (59.7%)	290 (58.5%)	
pN1	167 (26.9%)	33 (26.6%)	134 (27.0%)	
pN2–3	89 (14.4%)	17 (13.7%)	72 (14.5%)	

Notes: [a]size of invasive disease on final pathology; [b]only HER2 status in invasive disease was analyzed; [c]continuity correction χ^2
Abbreviations: BC-breast cancer; ER-estrogen receptor; PR-progesterone receptor; HER2-human epidermal receptor 2; pN-pathological N stage.

a LC size of >1 cm. Finally, menopause (p=0.010) is related to synchronous BC-LC. (Supplementary Tables S1–S3).

In the univariate logistic regression analysis, we explored the variables that may be related to LC in patients with BC (Supplementary Table S4). Patients with postmenopausal (odds ratio [OR] = 1.682; 95% CI: 1.117–2.534; p=0.013), combined with hypertension (OR = 1.688; 95% CI: 1.092–2.610; p=0.018) and a larger tumor size (OR = 2.466; 95% CI: 1.605–3.790; p<0.001) were more likely to have LC. Variants with p<0.10 were included in the multivariate regression model, indicating that a larger tumor size (OR = 2.454; 95% CI: 1.493–4.035; p<0.001; Figure 2) was an independent risk

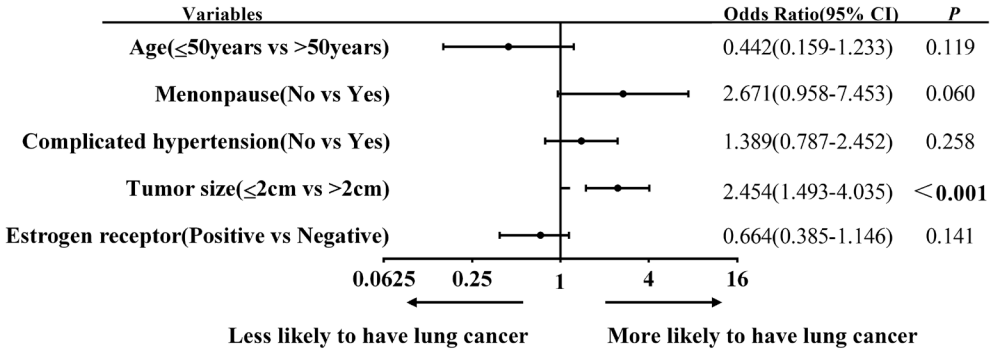

Figure 2. Multivariate logistic regression; clinicopathological characteristics of the BC-LC group.

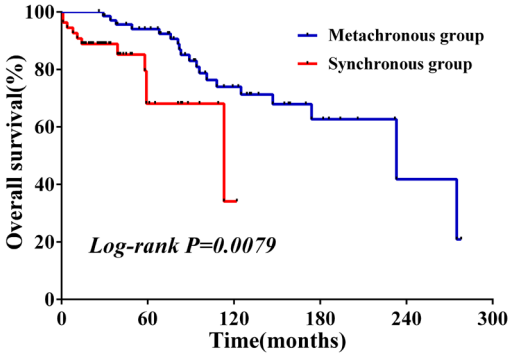

Figure 3. Comparison of OS between the synchronous group and the metachronous group.

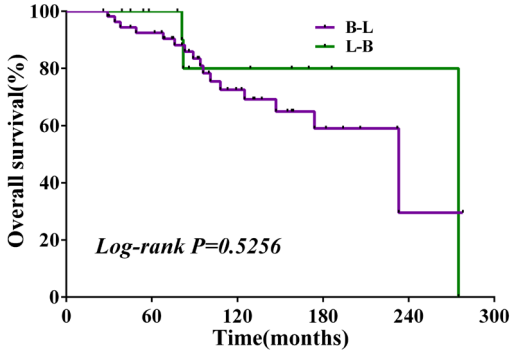

Figure 4. Comparison of OS between the B-L group and the L-B group.

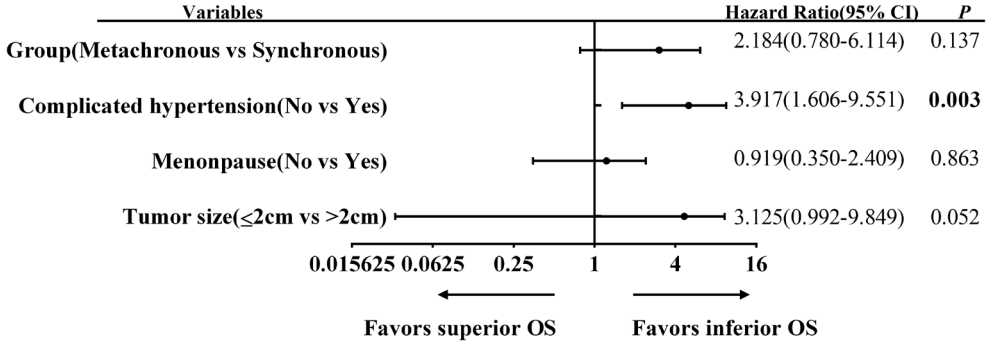

Figure 5. Multivariate Cox regression prognostic analysis of OS.

factor for BC-LC patients. There was no interaction between variables in the multivariate regression model (Supplementary Tables S5, S6).

The clinical prognosis of patients with BC-LC. We limited our cohort to patients with BC-LC. The median OS of the metachronous group and synchronous group were 233 and 113 months, respectively. In the survival analysis, the OS of patients with metachronous BC-LC was better than that of patients with synchronous cancer (5-year OS rates were 94.1% and 68.1%; whereas 10-year OS rates were 73.9% and 34.1%; p=0.0079; Figure 3). The B-L group of patients showed similar survival with the L-B group (5-year OS rates were 92.4% and 100%; whereas 10-year OS rates were 72.5% and 80.0%; p=0.5256; Figure 4). Variables with p<0.10 in the univariate Cox regression were then included in the multivariate Cox regression analysis. Complicated hypertension (hazard ratio [HR] = 3.917; 95% CI: 1.606–9.551; p=0.003; Figure 5) was the only independent prognostic factors for inferior OS, while synchronous cancer was not (HR=2.184; 95% CI: 0.780–6.114; p=0.137). And there was no interaction between variables in multivariate analysis (Supplementary Tables S7, S8).

Discussion

With the continuous advancement of cancer diagnosis and treatment technology and closer medical follow-up of cancer survivors, the incidence of multiple primary cancers is also increasing. This phenomenon seems to be attributed to the prolonged survival of cancer patients, treatment-related long-term side effects, increased diagnostic sensitivity, and the combined effects of genetic and environmental factors [8]. We retrospectively analyzed BC patients to explore the clinicopathological characteristics and prognosis of BC-LC and provide a basis for individualized management of these patients.

In the BC-LC group, the tumor size of BC was significantly larger than that of BC only group ($p<0.001$). Previous study showed BC patients with second primary cancer had larger tumor than those with BC alone [9]. Based on the analysis of 535,941 BC patients in the SEER database, Liu et al. found that the larger tumor was a risk factor for the development of the second primary cancer of BC, but the second primary LC was unrelated to the size of the BC tumor [10]. In our study, we analyzed the BC tumor size of BC-LC patients, including not only patients with secondary primary LC after BC, but also patients with synchronous cancer and secondary BC after LC. Therefore, patients with larger BC tumors should be alert to the risk of second primary cancer.

There is a strong correlation between the expression of EGFR and ER, and they play an important role in the occurrence and development of LC and BC respectively [11, 12]. A previous study showed that the EGFR mutation was significantly increased in female patients with LC, and the expression of ERβ1 was higher in these patients [13]. In a single-center retrospective study, it was found that the incidence of primary BC in patients with EGFR mutated NSCLC may be higher than patients without EGFR mutation [14]. These studies suggest that ER may represent a common factor in the occurrence and development of BC and LC, but in this study, we failed to associate BC-LC with ER status. A study on 40,900 BC patients subjected to endocrine therapy showed that the patients can reduce the risk of LC [15]. A randomized trial showed that ER-positive BC patients treated with tamoxifen for 5 years had a significantly lower incidence of secondary primary LC compared with 2 years of tamoxifen treatment [16]. Among the 597 BC patients with known ER status in our cohort, ER-positive patients accounted for the majority and all received endocrine therapy. We did not identify a connection between the ER status and LC. It may be that patients with ER-positive BC have reduced their risk of developing primary LC after standard endocrine therapy.

These observations suggest that BC radiotherapy may be a risk factor for primary LC. For BC radiotherapy, the heart and lungs will receive additional doses and will increase second primary LC and heart disease [17]. Radiotherapy may have led to an increased incidence of LC, as observed in several other studies [18, 19]. A prospective cohort study of about 300,000 women in US SEER cancer registries showed that US breast cancer radiotherapy regimens of the 1970s and early 1980s appreciably increased mortality from heart disease and LC 10–20 years afterward with, as yet, little direct evidence on the hazards after more than 20 years [20]. With the continuous advancement of BC diagnosis and treatment technology, the extensive application of radiotherapy techniques such as intensity-modulated radiotherapy, volume-arc intensity-modulated radiotherapy, and deep breathing can significantly reduce the cardiopulmonary dose of patients [21]. The above studies showed that the old radiotherapy techniques are associated with a significant increase in the risk of LC in the ipsilateral lung, but there is no clear evidence that modern radiotherapy techniques reduce the risk of LC.

There are limited data on the effect of BC-LC on the survival of patients. In our survival analysis, we reasonably considered that patients in the synchronous group had inferior OS compared with those in the metachronous group. It was believed that when developed in a short period of time, multiple primary cancers exhibit a synergistic effect similar to distant metastasis of a single primary cancer. Two previous studies have suggested that the shorter the interval between BC and multiple primary cancers, the worse the prognosis [22, 23]. A population-based cohort study showed that patients with multiple primary cancers whose BC was the second malignancy had an increased risk of BC-specific mortality compared with patients with multiple primary cancers whose first primary cancer was BC [24]. Similarly, another study reported that BC-specific survival and overall survival were significantly lower in women with BC as the second primary cancer than in women with BC as the first primary cancer [25]. However, we found that the prognosis of patients in the L-B group and the B-L group were similar, which may be due to the small number of patients or short follow-up period in our study. Interestingly, combined hypertension was an independent prognostic factor for OS in patients with BC-LC. In addition, some studies have suggested that the presence of hypertension was a higher risk factor for cancer mortality at the time of BC or LC diagnosis [26–28]. We did not report the survival data of the BC-LC group because we will obtain a worse OS compared to that of the BC group with no controversy.

There are several limitations of our study. First, the study was limited by its retrospective nature. Second, although we used large-scale data, such data were passively obtained from medical records at multiple medical institutions, leading to missing data. Finally, although worse survival was identified in patients with synchronous BC-LC, the underlying mechanism for this is unknown.

In conclusion, this study has identified that BC patients with large tumors should pay more attention to the development of LC, and the higher pathological grade was associated with a larger LC size, as well as menopause was related to synchronous BC-LC. Finally, patients with synchronous BC-

LC had poorer OS than patients with metachronous BC-LC, and hypertension was the independent prognostic risk factor for patients with BC-LC. However, the specific molecular mechanism behind these findings is still unclear. Therefore, detailed research is needed to better understand the pathogenesis of BC-LC, find it early, and effectively prevent it.

Supplementary information is available in the online version of the paper.

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Supplementary Information

Supplementary Table S1. Clinical-pathological characteristics of BC-LC patients according to pathology of lung cancer.

Variables	Total (N=110)	NSCLC (N=102)	SCLC (N=8)	p-value
Age				1.000 [c]
≤50	41 (37.3%)	38 (37.3%)	3 (37.5%)	
>50	69 (62.7%)	64 (62.7%)	5 (62.5%)	
Menopause				0.755 [c]
No	40 (36.4%)	38 (37.3%)	2 (25.0%)	
Yes	70 (63.6%)	64 (62.7%)	6 (75.0%)	
Complicated hypertension				0.414 [c]
No	76 (69.1%)	72 (70.6%)	4 (50.0%)	
Yes	34 (30.9%)	30 (29.4%)	4 (50.0%)	
Family history of malignancy				1.000 [c]
No	83 (75.5%)	77 (75.5%)	6 (75.0%)	
Yes	27 (24.5%)	25 (24.5%)	2 (25.0%)	
Tumor size [a]				0.265 [c]
≤2	41 (37.3%)	40 (39.2%)	1 (12.5%)	
>2	58 (52.7%)	52 (51.0%)	6 (75.0%)	
Unknow	11 (10.0%)	10 (9.8%)	1 (12.5%)	
ER				0.555 [c]
Positive	67 (60.9%)	66 (64.7%)	1 (12.5%)	
Negative	38 (34.6%)	32 (31.4%)	6 (75.0%)	
Unknow	5 (4.5%)	4 (3.9%)	1 (12.5%)	
PR				0.481 [c]
Positive	54 (49.1%)	49 (48.0%)	5 (62.5%)	
Negative	51 (46.4%)	49 (48.0%)	2 (25.0%)	
Unknow	5 (4.5%)	4 (4.0%)	1 (12.5%)	
HER2 [b]				0.645 [c]
Positive	27 (24.5%)	26 (25.5%)	1 (12.5%)	
Negative	66 (60.0%)	60 (58.8%)	6 (75.0%)	
Unknow	17 (15.5%)	16 (15.7%)	1 (12.5%)	
Ki67				0.361 [c]
≤30%	55 (50.0%)	53 (52.0%)	2 (25.0%)	
>30%	50 (45.5%)	45 (44.1%)	5 (62.5%%)	
Unknow	5 (4.5%)	4 (3.9%)	1 (12.5%)	
Pathology				1.000 [d]
In situ	4 (3.6%)	4 (4.0%)	0 (0.0%)	
Invasive	106 (96.4%)	98 (96.0%)	8 (100.0%)	
Grade				1.000 [c]
I–II	43 (39.1%)	40 (39.2%)	3 (37.5%)	
III	19 (17.3%)	17 (16.7%)	2 (25.0%)	
Unknow	48 (43.6%)	45 (44.1%)	3 (37.5%)	
pN				0.865 [c]
pN0	65 (59.1%)	61 (59.8%)	4 (50.0%)	
pN1–3	45 (40.9%)	41 (40.2%)	4 (50.0%)	

Notes: [a]size of invasive disease on final pathology; [b]only HER2 status in invasive disease was analyzed; [c]continuity correction chi-square; [d]Fisher's exact test. Abbreviations: NSCLC-non-small cell lung cancer; SCLC-small cell lung cancer; BC-breast cancer; ER-estrogen receptor; PR-progesterone receptor; HER2-human epidermal receptor 2; pN-pathological N stage

Supplementary Table S2. Clinical-pathological characteristics of BC-LC patients according to size of lung cancer.

Variables	Total (N=64)	≤1 cm (N=29)	>1 cm (N=35)	p-value
Age				0.533
≤50	26 (40.6%)	13 (44.8%)	13 (37.1%)	
>50	38 (59.4%)	16 (55.2%)	22 (62.9%)	
Menopause				0.169
No	25 (39.1%)	14 (48.3%)	11 (31.4%)	
Yes	39 (60.9%)	15 (51.7%)	24 (68.6%)	
Complicated hypertension				0.124
No	47 (73.4%)	24 (82.8%)	23 (65.7%)	
Yes	17 (26.6%)	5 (17.2%)	12 (34.3%)	
Family history of malignancy				0.058
No	49 (76.6%)	19 (65.5%)	30 (85.7%)	
Yes	15 (23.4%)	10 (34.5%)	5 (14.3%)	
Tumor size [a]				
≤2	27 (42.2%)	12 (41.4%)	15 (42.9%)	0.755
>2	33 (51.6%)	16 (55.2%)	17 (48.6%)	
Unknow	4 (6.2%)	1 (3.4%)	3 (8.5%)	
ER				
Positive	43 (67.2%)	23 (79.3%)	20 (57.1%)	0.060
Negative	21 (32.8%)	6 (20.7%)	15 (42.9%)	
Unknow	0 (0.0%)	0 (0.0%)	0 (0.0%)	
PR				0.136
Positive	40 (62.5%)	21 (72.4%)	19 (54.3%)	
Negative	24 (37.5%)	8 (27.6%)	16 (45.7%)	
Unknow	0 (0.0%)	0 (0.0%)	0 (0.0%)	
HER2 [b]				0.694
Positive	22 (34.4%)	11 (37.9%)	11 (31.4%)	
Negative	38 (59.4%)	17 (58.6%)	21 (60.0%)	
Unknow	4 (6.2%)	1 (3.5%)	3 (8.6%)	
Ki67				0.565
≤30%	35 (54.7%)	17 (58.6%)	18 (51.4%)	
>30%	29 (45.3%)	12 (41.4%)	17 (48.6%)	
Unknow	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Pathology				1.000 [c]
In situ	3 (4.7%)	1 (3.4%)	2 (5.7%)	
Invasive	61 (95.3%)	28 (96.6%)	33 (94.3%)	
Grade				0.033
I–II	29 (45.3%)	17 (58.6%)	12 (34.3%)	
III	13 (20.3%)	3 (10.3%)	10 (28.6%)	
Unknow	22 (34.4%)	9 (31.1%)	13 (37.1%)	
pN				0.061
pN0	41 (64.1%)	15 (51.7%)	26 (74.3%)	
pN1–3	23 (35.9%)	14 (48.3%)	9 (25.7%)	

Notes: [a]size of invasive disease on final pathology; [b]only HER2 status in invasive disease was analyzed; [c]continuity correction chi-square. Abbreviations: BC-breast cancer; ER-estrogen receptor; PR-progesterone receptor; HER2-human epidermal receptor 2; pN-pathological N stage

Supplementary Table S3. Clinical-pathological characteristics of BC-LC patients according to the time of diagnosis.

Variables	Total (N=124)	metachronous (N=70)	synchronous (N=54)	p-value
Age				0.131
≤50	46 (37.1%)	30 (42.9%)	16 (42.9%)	
>50	78 (62.9%)	40 (42.9%)	38 (42.9%)	
Menopause				0.010
No	43 (34.7%)	31 (44.3%)	12 (22.2%)	
Yes	81 (65.3%)	39 (55.7%)	42 (77.8%)	
Complicated hypertension				0.692
No	85 (68.5%)	49 (70.0%)	36 (66.7%)	
Yes	39 (31.5%)	21 (30.0%)	18 (33.3%)	
Family history of malignancy				0.486
No	95 (76.6%)	52 (74.3%)	43 (79.6%)	
Yes	29 (23.4%)	18 (25.7%)	11 (20.4%)	
Tumor size [a]				0.514
≤2	41 (33.1%)	22 (31.4%)	19 (35.2%)	
>2	70 (56.5%)	42 (60.0%)	28 (51.9%)	
Unknow	13 (10.4%)	6 (8.6%)	7 (12.9%)	
ER				0.874
Positive	77 (62.1%)	44 (62.9%)	33 (61.1%)	
Negative	36 (29.0%)	20 (28.6%)	16 (29.6%)	
Unknow	11 (8.9%)	6 (8.5%)	5 (9.3%)	
PR				0.891
Positive	73 (58.9%)	41 (58.6%)	32 (59.2%)	
Negative	40 (32.3%)	23 (32.9%)	17 (31.5%)	
Unknow	11 (8.8%)	6 (8.5%)	5 (9.3%)	
HER2 [b]				0.220
Positive	27 (21.8%)	12 (17.1%)	15 (27.8%)	
Negative	81 (65.3%)	47 (67.2%)	34 (63.0%)	
Unknow	16 (12.9%)	11 (15.7%)	5 (9.2%)	
Ki67				0.351
>30%	50 (40.3%)	31 (44.3%)	19 (35.2%)	
≤30%	62 (50.0%)	33 (47.1%)	29 (53.7%)	
Unknow	12 (9.7%)	6 (8.6%)	6 (11.1%)	
Pathology				0.223[c]
In situ	5 (4.0%)	1 (1.4%)	4 (7.4%)	
Invasive	119 (96.0%)	69 (98.6%)	50 (92.6%)	
Grade				0.877
I–II	50 (40.3%)	31 (44.3%)	19 (35.2%)	
III	20 (16.1%)	12 (17.1%)	8 (14.8%)	
Unknow	54 (43.6%)	27 (38.6%)	27 (50.0%)	
pN				0.402
pN0	74 (59.7%)	39 (55.7%)	35 (64.8%)	
pN1	33 (26.6%)	19 (27.2%)	14 (25.9%)	
pN2–3	17 (13.7%)	12 (17.1%)	5 (9.3%)	

Notes: [a]size of invasive disease on final pathology; [b]only HER2 status in invasive disease was analyzed; [c]continuity correction chi-square. Abbreviations: BC-breast cancer; ER-estrogen receptor; PR-progesterone receptor; HER2-human epidermal receptor 2; pN-pathological N stage

Supplementary Table S4. Univariate Logistic regression analysis of lung cancer in breast cancer patients.

Variants	Exposure	95% CI	p-value
Age >50 vs.≤50	1.431	0.954–2.145	0.083
Menopause Yes vs. No	1.682	1.117–2.534	0.013
Complicated hypertension Yes vs. No	1.688	1.092–2.610	0.018
Family history of malignancy Yes vs. No	1.415	0.880–2.277	0.152
Tumor size[a] >2 vs.≤2	2.466	1.605–3.790	0.000
ER negative vs. positive	1.483	0.948–2.320	0.084
PR negative vs. positive	1.120	0.729–1.721	0.605
HER2[b] negative vs. positive	1.146	0.705–1.863	0.582
Ki67>30% vs.≤30%	0.989	0.654–1.495	0.956
Pathology invasive vs. *in situ*	0.845	0.305–2.336	0.745
Grade III vs. I/II	0.929	0.526–1.643	0.801
pN pN1 vs. pN0	0.965	0.610–1.527	0.879
pN pN2-3 vs. pN0	0.925	0.514–1.664	0.795

Notes: [a]size of invasive disease on final pathology; [b]only HER2 status in invasive disease was analyzed. Abbreviations: CI-confidence interval; ER-estrogen receptor; PR-progesterone receptor; HER2-human epidermal receptor 2; pN-pathological N stage

Supplementary Table S5. The multiplicative interaction of variables in the multivariate logistic regression.

	OR (95%CI)	p-value
Age*Menopause	0.561 (0.081–3.892)	0.558
Age*Complicated hypertension	0.302 (0.089–1.020)	0.054
Age*Tumor size	0.552 (0.202–1.507)	0.246
Age*ER	1.231 (0.422–3.594)	0.704
Menopause*Complicated hypertension	0.322 (0.094–1.099)	0.070
Menopause*Tumor size	0.391 (0.137–1.113)	0.079
Menopause*ER	1.661 (0.559–4.934)	0.361
Complicated hypertension*Tumor size	0.804 (0.278–2.325)	0.687
Complicated hypertension*ER	0.901 (0.286–2.842)	0.859
Tumor size*ER	1.323 (0.445–3.928)	0.615

Abbreviations: CI-confidence interval; ER-estrogen receptor

Supplementary Table S6. The additive interaction index of variables in the multivariate logistic regression.

	RERI	AP	S
	Point estimate (95%CI)	Point estimate (95%CI)	Point estimate (95%CI)
Age*Menopause	–1.599 (–5.411–2.213)	–1.208 (–4.069–1.652)	0.168 (0.015–1.938)
Age*Complicated hypertension	–2.908 (–7.167–1.351)	–2.113 (–5.350–1.123)	0.114 (0.011–1.172)
Age*Tumor size	–1.013 (–3.655–1.628)	–0.321 (–1.175–0.533)	0.680 (0.282– 1.641)
Age*ER	0.129 (–0.757–1.014)	0.211 (–1.326–1.748)	0.752 (0.154– 3.667)
Menopause*Complicated hypertension	–2.101 (–5.535–1.332)	–1.252 (–3.400–0.896)	0.244 (0.046–1.297)
Menopause*Tumor size	–1.580 (–5.236–2.075)	–0.349 (–1.167–0.472)	0.691 (0.328–1.458)
Menopause*ER	0.290 (–0.526–1.106)	0.420 (–0.942–1.782)	0.516 (0.145–1.834)
Tumor size*Complicated hypertension	0.198 (–2.413–2.810)	0.057 (–0.665–0.778)	1.086 (0.367–3.207)
ER* Complicated hypertension	–0.132 (–1.519–1.255)	–0.154 (–1.764–1.456)	14.038 (1.7e–66–1.1e+68)
Tumor size*ER	–0.102 (–1.611–1.406)	–0.073 (–1.134–0.987)	0.797 (0.045–14.190)

Abbreviations: RERI-relative excess risk ratio; AP-attributable ratio; S-interaction index; CI-confidence interval; ER-estrogen receptor

Supplementary Table S7. The multiplicative interaction of variables in the multivariate cox regression.

	OR (95%CI)	p-value
Group*Menopause	0.773 (0.107–5.586)	0.798
Group*Complicated hypertension	0.640 (0.103–3.955)	0.631
Group*Tumor size	0.875 (0.072–10.646)	0.917
Menopause*Complicated hypertension	0.510 (0.092–2.841)	0.442
Menopause*Tumor size	0.363 (0.030–4.329)	0.423
Tumor size*Complicated hypertension	1.600 (0.204–12.533)	0.654

Abbreviations: CI-confidence interval; ER-estrogen receptor

Supplementary Table S8. The additive interaction index of variables in the multivariate cox regression.

	RERI	AP	S
	Point estimate (95%CI)	Point estimate (95%CI)	Point estimate (95%CI)
Group*Menopause	0.121 (–1.177–1.419)	0.285 (–2.846–3.415)	0.827 (0.130–5.250)
Group*Complicated hypertension	–3.746 (–10.466–2.973)	–2.228 (–7.292–2.837)	0.154 (0.005–4.845)
Group*Tumor size	0.190 (–1.727–2.108)	0.155 (–1.418–1.729)	6.169 (5.1e–28–7.4e+28)
Menopause*Complicated hypertension	–6.693 (–22.065–8.679)	–2.839 (–9.350–3.673)	0.169 (0.018–1.590)
Menopause*Tumor size	0.153 (–2.260–2.565)	0.095 (–1.453–1.643)	1.331 (0.003– 450.215)
Tumor size*Complicated hypertension	4.231 (–7.696–16.158)	0.393 (–0.401–1.187)	1.764 (0.383–8.121)

Abbreviations: RERI-relative excess risk ratio; AP-attributable ratio; S-interaction index; CI-confidence interval; ER-estrogen receptor