Survival analysis of patients with primary breast duct carcinoma and lung adenocarcinoma: a population-based study from SEER

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The appeal to enroll patients with primary breast and lung cancer in clinical trials is increasing, but survival of these two primary cancers remains to be elucidated. This study analyzed the prognosis of primary breast duct carcinoma with subsequent lung adenocarcinoma (BCLA) and primary breast duct carcinoma with prior lung adenocarcinoma (LABC). Cohorts of 3,515 patients with BCLA and 654 patients with LABC were identified from the Surveillance, Epidemiology, and End Results database. Patients were classified into simultaneous two primary cancer (sTPC), metachronous two primary cancer (mTPC1), or mTPC2 groups when the interval times between breast and lung cancer were within 6 months, between 7 and 60 months, or over 60 months, respectively. The propensity score matching program (PSM) was applied to determine the survival of BCLA/LABC relative to single breast/lung cancer. Cox proportional hazard regression model and competing risk modes were performed to identify confounders associated with all-cause and cancer-specific death, respectively. Survival of patients with LABC/BCLA relative to single breast/lung cancer was accessed via median survival time. The survival of patients with BCLA/LABC was generally poor compared with the survival of those with single breast cancer. The PSM-estimated HR in the sTPC group with BCLA and in the mTPC1 and mTPC2 groups with LABC were 0.75 (95% CI 0.62–0.90), 0.52 (95% CI 0.27–0.98), and 0.36 (95% CI 0.20–0.65), respectively, whereas the SHR in the sTPC group with BCLA and in the mTPC1 and mTPC2 groups with LABC were 0.80 (95% CI 0.66–0.97), 0.68 (95% CI 0.34–1.34), and 0.46 (95% CI 0.27–0.80), respectively, compared with those in the single lung cancer group. By contrast, the survival rates of the remaining patients did not differ. The median survival times since secondary malignancy were 42, 23, and 20 months in the sTPC, mTPC1, and mTPC2 groups with BCLA, respectively, and 18, 60, and 180 months in those with LABC, respectively. For patients with BCLA, the adjusted Cox regression suggested incidences of all-cause deaths in mTPC1 group were statically higher than those in sTPC group, whereas the incidences of all-cause and cancer-specific death in the mTPC1 and mTPC2 groups were statistically lower than those in the sTPC group. The prognosis of patients with breast cancer and subsequent lung cancer of over 18 months was not significantly different than that of single lung cancer, which supported the profound appeal to increase the involvement of these two primary cancers in potential beneficial clinical trials. For patients with lung cancer and prior breast cancer of within 6 months and subsequent breast cancer of over 18 months, prognosis was improved relative to single lung cancer. Therefore, additional attention is needed to eliminate the potential bias may when these patients are recruited in the clinical trials.

Adenocarcinoma and duct carcinoma are the main histologies of lung and breast malignancies in the United States, respectively1,2. Breast cancer prognosis has been considerably improved, with an approximately 90% 5-year (2011–2017) rate of relative survival. In lung cancer, the prognosis is discouraging because the 5-year (2011–2017) rate of relative survival is less than 20%3,4. With advanced diagnosis and increased life span, the
number of patients diagnosed with primary lung adenocarcinoma after/before primary breast duct carcinoma has increased. The two primary cancers are considered simultaneous if the interval between them is within 6 months, whereas others are considered metachronous. Enrolling these patients in clinical trials that may benefit survival has increased appeal, but the uncertainty of the prior cancer history's effect on the prognosis causes hesitation in the decision. Indeed, accumulating evidences suggest that a cancer may enhance the ability of invasion through fusion and transfer of exosomes between two cancer types. Therefore, the prognosis of patients with simultaneous two primary cancers (sTPCs), metachronous two primary cancers (mTPCs), and single cancer of the same histological type at the same anatomic site may vary. In contrast to most population-based research focusing on the incidence and site of secondary primary cancer (SPC) after breast/lung cancer, the estimates of indicated histology of breast and lung cancers are lacking. Although several clinical observations showed the prognosis of these patients, the conclusions are contradictory [11-14]. Understanding these results is difficult, partly due to the limited scale of patients involved and the different histological types of malignancies in these reports. Another challenge is evaluating the first and secondary primary malignant stages with various criteria.

The prognosis of breast cancer and prior lung cancer may differ from that of breast cancer and subsequent lung cancer. Radiotherapy plays an important role in breast and lung cancer management. However, the risks of side effects, such as radiation pneumonitis and heart disease, from current regular radiation in breast cancer after lung cancer radiation therapy, particularly at the same side, are higher than those in lung cancer management after breast cancer radiotherapy. Moreover, malignancies may share the same characteristics despite having different histological origins. Therefore, targeting drugs for breast malignancy may target lung malignancy, and vice versa.

With data from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute, this study was designed to depict the prognosis of two simultaneous and metachronous primary cancers, namely, first primary breast duct carcinoma–secondary primary breast duct carcinoma (BCLA) and first primary lung adenocarcinoma–secondary primary breast duct carcinoma (LABC), relative to that of single breast/lung cancer. This study also aimed to characterize other clinical and sociodemographic factors associated with survival in patients with primary breast and lung cancers.

Methods
In accordance with the rule of international multiple primary cancers, records of primary breast duct carcinoma and primary lung and bronchus (lung) adenocarcinoma diagnosed from January 1975 to December 2018 were collected from the SEER database via SEER*Stat software version 8.3.5 (accession number: 12223-Nov2018). Information such as race, sex, insurance and marital status, age at diagnosis, malignant site, malignant histology, surgical status, and radiation were collected. Chemo-treatment was not included because related information was missing in most patients. The International Classification of Diseases for Oncology Site Recode (third edition, ICD-O-3) was applied to identify the anatomical site of malignancy, and SEER historic Stage A was used in classifying the patients’ clinical stages (localize, regional, distant, and unknown). After incomplete medical records and records of only autopsy or death certificate were excluded, 3,515 patients with BCLA and 654 patients with LABC were included. In addition, 705,725 patients with single breast duct carcinoma and 282,486 patients with lung adenocarcinoma diagnosed from January 1975 to December 2018 were selected (Table S7). The sequence of breast and lung cancers was determined using SEER sequence number as reported [14]. In brief, “00” was assigned to patients with single cancer. For those with two primary cancers, the first and second diagnosed cancers were indicated as “01” and “02,” respectively. The interval time between the diagnosis of first primary cancer (FPC) and SPC was subsequently calculated. FPC and SPC were considered sTPCs and mTPCs if the interval was within 6 months and over 6 months, respectively [17]. To be noted, FPC and SPC were considered mTPC1 if the interval was within indicated as “01” and “02,” respectively. The interval time between the diagnosis of first primary cancer (FPC) in patients with primary breast and lung cancers.

The year of secondary malignancy diagnosis was classified into three groups to reduce the confounding variables, such as survival time prolonged by medical progression: before 1995, between 1995 and 2005, and after 2005. Overall survival was accessed using median survival time, which was obtained via Kaplan–Meier method. Variables such as race, sex, first and secondary marital status, and first and secondary insurance status were included in Cox proportional hazard regression model if the p value of the indicated variable regression was not more than 0.1. Cause of death was defined based on the International Statistical Classification of Diseases and Related Health Problems (10th Revision) [18]. In brief, events such as breast-, lung-, and liver-related deaths were considered primary malignant stages with various criteria.

Subsequently, the selected linear or quadratic function of covariates was plugged into the program. For the mTPC1 group with first primary breast/lung cancer, the matched patients with single cancer were required to have a survival time of at least 18 months. For the mTPC2 group, the patients with single cancer were required to have a survival time of at least 60 months.

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the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. Because of the retrospective nature of this study, patients’ informed consent was also exempted by the institute.

Results

Basic characteristics. A total of 3515 patients with BCLA, 654 patients with LABC, 705,725 patients with single breast duct carcinoma, and 282,486 patients with lung adenocarcinoma were identified. The median ages at secondary diagnosis in the sTPC, mTPC1, and mTPC2 groups with BCLA were 67, 70, and 73 years, respectively, whereas the median ages at secondary diagnosis in the sTPC, mTPC1, and mTPC2 groups with LABC were 69, 67, and 64 years, respectively. In patients with BCLA or LABC, the highest and lowest ratios of breast surgery performed were found in the mTPC2 and sTPC groups, respectively. In patients with BCLA, the highest and lowest ratios of lung surgery performed were found in the sTPC and mTPC2 groups, respectively, whereas the highest and lowest ratios in those with LABC were found in the mTPC2 and sTPC groups, respectively. Other baseline characteristics of the selected patients are shown in Table 1 and Tables S1,S2.

Survival relative to single cancer. After the PSM program was conducted, 688 patients with single breast cancer and BCLA were included in the matched cohort. Survival estimates suggested that the median overall survival times since the secondary malignancy of BCLA and single breast cancer were 115 and 184 months, respectively. Based on interval time, patients with BCLA were categorized into groups (sTPC, mTPC1, and mTPC2), and each categorized group was subsequently matched with single breast cancer. The median overall survival times of the sTPC, mTPC1, and mTPC2 groups were general shorter than those of the matched patients with single breast cancer. When divided by year of diagnosis, the median survival time of categorized sTPC, mTPC1, and mTPC2 groups were general shorter than that of corresponding single breast cancer (Table 2). Cox analysis suggested that the incidences of all-cause and cancer-specific death in the sTPC, mTPC1, and mTPC2 groups were general lower than in the corresponding patients (Table S3).

A total of 1,306 patients with single lung adenocarcinoma and BCLA were selected using another PSM program. The median overall survival times of single lung adenocarcinoma and BCLA were 24 and 29 months, respectively. When stratified by interval time, the median overall survival times in the sTPC, mTPC1, and mTPC2 groups with BCLA were 42, 25, and 29 months, respectively. In the matched patients with single lung cancer, the median overall survival times were 27, 24, and 26 months, respectively. When classified by year of diagnosis, median survival times of both sTPC and mTPC2 groups diagnosed after 2005 was statically longer than that of matched single lung cancer (Table 2). The incidences of all-cause and cancer-specific deaths in the sTPC group were statistically lower (sTPC group: all-cause death rate, 0.75; 95% CI 0.62–0.90; cancer-specific death rate, 0.80; 95% CI 0.66–0.97) than those in patients with single lung cancer. In the mTPC1 and mTPC2 groups, the incidences of all-cause and cancer-specific death did not statistically differ (Table S4).

The prognosis of breast cancer and prior lung cancer may differ from that of breast cancer and subsequent lung cancer. A total of 274 patients with single lung adenocarcinoma and LABC were included in the matched cohort. The median overall survival times of patients with secondary cancer and single lung cancer with LABC were 34 and 99 months, respectively. In the sTPC, mTPC1, and mTPC2 groups with LABC, the median overall survival times were 20, 151, and 335 months, respectively; in the corresponding patients, the median overall survival times were 27, 40, and 257 months, respectively. When stratified by year of diagnosis, median survival time of both mTPC1 and mTPC2 groups diagnosis between 1995 and 2005 were longer than that of matched single lung cancer (Table 3). The incidences of all-cause deaths in the mTPC1 and mTPC2 groups were statistically lower than those in the corresponding patients (mTPC1: 0.52; 95% CI 0.27–0.98; mTPC2: 0.36; 95% CI 0.20–0.65), and cancer-specific deaths in mTPC2 groups was lower than matched group. In the sTPC group, the incidences of all-cause and cancer-specific deaths did not statistically differ (Table S5).

For patients with single breast cancer and LABC in the matched cohort, the median overall survival times in the sTPC, mTPC1, and mTPC2 groups were 17, 47, and 180 months, respectively, whereas the median overall survival times of the corresponding breast cancer patients were -, -, and – months, respectively. When stratified by year of diagnosis, median survival time of classified sTPC, mTPC1, and mTPC2 groups were shorter than that of matched single breast cancer (Table 4). The incidence of all-cause and cancer-specific deaths in the sTPC and mTPC1 groups increased compared with that in single breast cancer. In the mTPC2 group, the difference between the incidence of all-cause death and that of cancer-specific death was not significant (Table S6).

Survival between synchronous and metachronous two primary cancers. Among the primary causes of death in patients with primary breast and lung cancer, lung cancer was the leading cause of cancer-related death in patients with BCLA or LABC, whereas heart disease and chronic obstructive pulmonary disease accounted for most noncancerous deaths (Table 1). In patients with BCLA, the median overall survival since secondary diagnosis in the sTPC, mTPC1, and mTPC2 groups were 42, 23, and 20 months, respectively and estimated survival was displayed in Fig. 1. When divided by first cancer stage, median survival time of 'regional stage' was statically longer than that of 'localized stage,' and 'distant stage' was statically shorter than 'localized stage' in sTPC group. For mTPC1 and mTPC2 groups, there was no statical difference between 'regional stage' and 'localized stage,' as well as 'distant stage' and 'localized stage.' (Table 4). Adjusted for the first malignant stage, age at secondary diagnosis, and secondary surgery status, the incidences of all-cause deaths in the mTPC1 group was statically higher than sTPC group, whereas incidences of all-cause deaths in the mTPC2 group was not statically different from those in the sTPC groups (Figs. 2 and 3). In particular, secondary diagnosis age over 75 (versus secondary diagnosis age less than 55), breast malignancy at the distant stage (versus localized), year of secondary diagnosis between 1955 and 2005 and before 1995 (versus over 2005), lung malignancy at the regional
|               | BCLA (All) | sTPC | mTPC1 | mTPC2 | LABC (All) | sTPC | mTPC1 | mTPC2 |
|---------------|------------|------|-------|-------|------------|------|-------|-------|
| No            | 3515       | 530  | 1056  | 1929  | 654        | 212  | 277   | 165   |
| Race          |            |      |       |       |            |      |       |       |
| NHW           | 2813       | 418  | 845   | 1550  | 520        | 167  | 219   | 134   |
| NHB           | 300        | 48   | 85    | 167   | 77         | 23   | 37    | 17    |
| NHA           | 219        | 37   | 68    | 114   | 29         | 12   | 11    | 6     |
| Hispanic      | 166        | 26   | 53    | 87    | 24         | 9    | 8     | 7     |
| Others        | 17         | 1    | 5     | 11    | 4          | 1    | 2     | 1     |
| Sex           |            |      |       |       |            |      |       |       |
| Men           | 28         | 5    | 14    | 9     | 8          | 1    | 5     | 2     |
| Women         | 3487       | 525  | 1042  | 1920  | 646        | 211  | 272   | 163   |
| First diagnosis of year |            |      |       |       |            |      |       |       |
| > 2005        | 1102       | 340  | 504   | 258   | 296        | 131  | 137   | 28    |
| 1995–2005     | 1436       | 134  | 379   | 923   | 215        | 52   | 90    | 73    |
| < 1995        | 977        | 56   | 173   | 748   | 143        | 29   | 50    | 64    |
| Age of first diagnosis |        |      |       |       |            |      |       |       |
| Median        | 64         | 67   | 61    | 67    | 69         | 67   | 66    | 66    |
| IQR           | 55–71      | 60–75| 59–73 | 53–68 | 60–74      | 63–75.5| 61–74| 57–70 |
| First marital status |        |      |       |       |            |      |       |       |
| Single        | 1516       | 275  | 482   | 759   | 322        | 118  | 133   | 71    |
| Married       | 1884       | 233  | 533   | 1118  | 303        | 83   | 131   | 89    |
| Unknown       | 115        | 22   | 41    | 52    | 29         | 11   | 13    | 5     |
| First insurance |        |      |       |       |            |      |       |       |
| Uninsured     | 12         | 5    | 6     | 1     | 5          | 2    | 3     | 0     |
| Insured       | 952        | 311  | 448   | 193   | 257        | 117  | 117   | 23    |
| Unknown       | 2351       | 214  | 602   | 1735  | 392        | 93   | 157   | 142   |
| First cancer stage |        |      |       |       |            |      |       |       |
| Localized     | 2408       | 298  | 765   | 1345  | 258        | 47   | 128   | 83    |
| Regional      | 951        | 144  | 256   | 551   | 161        | 39   | 79    | 43    |
| Distant       | 81         | 36   | 28    | 17    | 144        | 96   | 41    | 7     |
| Unknown       | 75         | 52   | 7     | 16    | 91         | 30   | 29    | 32    |
| First site    |            |      |       |       |            |      |       |       |
| Breast        | 8500       | 8500 | 8500  | 8500  | 8140       | 8140 | 8140  | 8140  |
| First histology |        |      |       |       |            |      |       |       |
| First surgery |            |      |       |       |            |      |       |       |
| Yes           | 131        | 101  | 19    | 11    | 201        | 129  | 60    | 12    |
| No            | 3371       | 421  | 1034  | 1916  | 450        | 83   | 214   | 153   |
| Unknown       | 13         | 8    | 3     | 2     | 3          | 0    | 3     | 0     |
| First radiotherapy |      |      |       |       |            |      |       |       |
| Yes           | 11         | 7    | 4     | 0     | 9          | 3    | 6     | 0     |
| No            | 2351       | 353  | 746   | 1252  | 323        | 109  | 151   | 63    |
| Unknown       | 1153       | 170  | 306   | 677   | 322        | 100  | 120   | 102   |
| Interval time |            |      |       |       |            |      |       |       |
| Mean          | 70         | 2    | 33    | 125   | 23         | 1    | 28    | 100   |
| IQR           | 25–132     | 1–3  | 21–45 | 90–177 | 2–62       | 0–2  | 16–39 | 77–140 |
| Secondary diagnosis of year |      |      |       |       |            |      |       |       |
| > 2005        | 2361       | 344  | 624   | 1393  | 397        | 132  | 164   | 101   |
| 1995–2005     | 827        | 131  | 310   | 386   | 169        | 51   | 76    | 42    |
| < 1995        | 327        | 55   | 122   | 150   | 88         | 29   | 37    | 22    |
| Secondary marital status |      |      |       |       |            |      |       |       |
| Single        | 1808       | 279  | 506   | 1023  | 333        | 113  | 138   | 82    |
| Married       | 1542       | 230  | 496   | 816   | 279        | 85   | 122   | 72    |
| Unknown       | 165        | 21   | 54    | 90    | 42         | 14   | 17    | 11    |
| Secondary insurance |      |      |       |       |            |      |       |       |
| Uninsured     | 22         | 5    | 4     | 13    | 4          | 2    | 1     | 1     |
| Continued     |            |      |       |       |            |      |       |       |
stage (versus localized), and lung malignancy at the distant stage (versus localized) were remarkably associated with increased all-cause and cancer-specific deaths. Insured at first diagnosis (versus uninsured) and lung surgery performed (versus not performed) were remarkably associated with decreased all-cause and cancer-specific deaths (Table 5).

In patients with LABC, the median overall survival since secondary diagnosis in the sTPC, mTPC1, and mTPC2 groups were 18, 60, and 180 months, respectively and displayed in Fig. 1. When divided by first cancer stage, median survival time of ‘regional and distant’ stage were statically shorter than that of ‘localized stage’ in the sTPC, mTPC1, and mTPC2 groups (Table 4). Adjusted for the first malignant stage, first surgery status, and secondary surgery status, the incidence of all-cause death since secondary diagnosis in the mTPC2 group was remarkably lower than that in the sTPC group, and the incidence of cancer-specific death in the mTPC1 and mTPC2 groups was lower than that in the sTPC group (Figs. 4 and 5). In detail, lung adenocarcinoma at the distant stage (versus localized) and year of secondary diagnosis before 1995 (versus over 2005) were remarkably associated with increased all-cause and cancer-specific deaths, whereas breast and lung surgery performed (versus not performed) was remarkably associated with decreased all-cause and cancer-specific deaths (Table 6).

**Discussion**

In this study, the survival of patients with primary breast and lung cancers was analyzed. The results suggested that the survival rate of patients with BCLA was generally poorer than that of patients with matched single breast cancer but not inferior to that of patients with single lung cancer. In addition, the primary causes of cancer- and noncancer-related deaths in patients with BCLA were identical to those in patients with single lung cancer. For patients with LABC, the survival since lung cancer was poorer than that in corresponding single breast cancer. The survival of patients with simultaneous LABC was similar to that of patients with single lung cancer, whereas the survival of patients with metachronous LABC was generally improved. To the knowledge of the authors, this study was the largest population-based study of survival in primary breast duct carcinoma and lung adenocarcinoma.

| BCLA | LABC |
|------|------|
|      |      |
| **All** | sTPC | mTPC1 | mTPC2 | All | sTPC | mTPC1 | mTPC2 |
| Insured | 2160 | 318 | 568 | 1274 | 351 | 116 | 145 | 90 |
| Unknown | 1333 | 207 | 484 | 642 | 299 | 94 | 131 | 74 |

**Table 1.** Summary of identified two primary cancer patients. NHW Non-Hispanic White, NHB Non-Hispanic Black, NHA Non-Hispanic Asian or Pacific Islander, 8500: duct carcinoma, 8140: Adenocarcinoma. Major cancer-related death1: percent of cancer-related death in total death; Major noncancer-related death1: percent of noncancer-related death in total death. COPD chronic obstructive pulmonary disease.
|       | All          | sTPC         | mTPC1        | mTPC2        |
|-------|--------------|--------------|--------------|--------------|
|       | NO | 50% | 95% CI | NO | 50% | 95% CI | NO | 50% | 95% CI | NO | 50% | 95% CI |
| **SBC** |       |       |       |       |       |       |       |       |       |       |       |       |
| > 2005 | 335 | -   | 83    | -   | 219 | -   | 66   | -   | 157 | -   | -   | 150 | -   | -   |
| 1995–2005 | 192 | -   | -    | -   | 96  | 178 | 152  | -   | 114 | 148 | 92 | 254 | -   | -   |
| < 1995 | 145 | 110 | 60   | 251 | 41  | 205 | 106  | -   | 61  | 102 | 61 | 165 | 224 | -   | -   |
| Overall | 672 | 184 | 138  | -   | 356 | 187 | 152  | -   | 332 | 167 | 114 | 241 | 628 | -   | -   |
| **BCLA** |       |       |       |       |       |       |       |       |       |       |       |       |       |
| > 2005 | 348 | 72  | 62   | 92   | 229 | 40  | 27   | 87   | 158 | 57  | 50  | 87  | 158 | 121 | 108  |
| 1995–2005 | 194 | 120 | 98   | 135  | 97  | 38  | 25   | 47   | 115 | 55  | 49  | 63  | 251 | 158 | 145  | 173 |
| < 1995 | 145 | 215 | 182  | 251  | 39  | 41  | 15   | 75   | 59  | 67  | 56  | 79  | 219 | 222 | 198  | 244 |
| Overall | 687 | 115 | 103  | 127  | 365 | 40  | 29   | 52   | 332 | 167 | 114 | 241 | 628 | 175 | 161  | 184 |
| **SLA** |       |       |       |       |       |       |       |       |       |       |       |       |       |
| > 2005 | 664 | 33  | 27   | 37   | 234 | 24  | 20   | 34   | 394 | 28  | 23  | 36  | 380 | 29  | 25  | 36  |
| 1995–2005 | 337 | 17  | 14   | 23   | 101 | 31  | 19   | 41   | 171 | 18  | 15  | 24  | 166 | 22  | 13  | 33  |
| < 1995 | 191 | 21  | 14   | 28   | 91  | 30  | 14   | 89   | 91  | 26  | 18  | 44  | 89  | 15  | 10  | 19  |
| Overall | 1192 | 24  | 21   | 30   | 386 | 27  | 22   | 34   | 656 | 24  | 20  | 29  | 635 | 26  | 21  | 30  |

Table 2. Overall-survival analysis between patients with BCLA and matched single breast/lung cancer. BCLA breast cancer with subsequent primary lung cancer; SBC Single breast cancer; SLA Single lung cancer, – not reached; Overall survival was determined by median survival time (month).

|       | All          | sTPC         | mTPC1        | mTPC2        |
|-------|--------------|--------------|--------------|--------------|
|       | NO | 50% | 95% CI | NO | 50% | 95% CI | NO | 50% | 95% CI | NO | 50% | 95% CI |
| **SLA** |       |       |       |       |       |       |       |       |       |       |       |       |
| > 2005 | 184 | 75  | 31   | -   | 86  | 29  | 18   | 34   | 84  | 40  | 34  | 116 | 20  | -   | -   |
| 1995–2005 | 52  | 18  | 11   | 39   | 43  | 18  | 9    | 47   | 18  | 34  | 25  | 83  | 46  | -   | -   |
| < 1995 | 11  | 26  | 4    | -   | 20  | 17  | 8    | 102  | -   | -   | -   | -   | 36  | 216 | 114  | 320 |
| Overall | 247 | 34  | 25   | 33   | 411 | 42  | 34   | 54   | 674 | 25  | 22  | 30  | 660 | 29  | 24  | 34  |
| **LABC** |       |       |       |       |       |       |       |       |       |       |       |       |       |
| > 2005 | 141 | 55  | 37   | 93   | 96  | 19  | 12   | 28   | 36  | 85  | 54  | -   | 22  | -   | -   |
| 1995–2005 | 83  | 154 | 77   | -   | 40  | 12  | 6    | 26   | 33  | 151 | 47  | -   | 47  | -   | -   |
| < 1995 | 46  | 169 | 75   | 335  | 22  | 30  | 8    | 71   | 13  | 173 | 25  | -   | 33  | 335 | 176  |
| Overall | 270 | 99  | 59   | 155  | 158 | 20  | 12   | 27   | 102 | 151 | 59  | -   | 102 | 335 | 240  |
| **SBC** |       |       |       |       |       |       |       |       |       |       |       |       |       |
| > 2005 | 180 | -   | 54   | -   | 147 | 114 | 82   | -   | 105 | 68  | 47  | -   | 84  | 88  | 39  |
| 1995–2005 | 82  | -   | -   | -   | 25  | -   | 70   | -   | 54  | 178 | 143 | -   | 33  | -   | 87  |
| < 1995 | 52  | 139 | 60   | 5    | 67  | 9    | -   | 28   | -   | 106 | -   | 22  | -   | 38  |
| Overall | 314 | -   | 139  | -   | 177 | -   | 82   | -   | 187 | -   | 117 | -   | 139 | -   | -   |
| **LABC** |       |       |       |       |       |       |       |       |       |       |       |       |       |
| > 2005 | 184 | 39  | 23   | 91   | 104 | 17  | 10   | 25   | 107 | 46  | 18  | -   | 87  | -   | 83  |
| 1995–2005 | 80  | 37  | 24   | 127  | 46  | 10  | 5    | 19   | 54  | 51  | 27  | -   | 33  | 180 | 83  |
| < 1995 | 50  | 32  | 25   | 66   | 22  | 32  | 7    | 87   | 26  | 60  | 12  | 90  | 21  | 100 | 30  |
| Overall | 314 | 36  | 27   | 54   | 172 | 17  | 10   | 23   | 187 | 47  | 27  | 90  | 141 | 180 | 100  |

Table 3. Overall-survival analysis between patients with LABC and matched single breast/lung cancer. LABC breast cancer with prior primary lung cancer; SBC Single breast cancer; SLA Single lung cancer, – not reached; Overall survival was determined by median survival time (month).
Several studies depicted the survival of patients with lung cancer and prior cancer. Prior head and neck cancer history was reported to be associated with compromised survival of lung cancer patients, whereas gastrointestinal tract and colorectal cancer history were not relevant to the prognosis\textsuperscript{21–23}. These results supported the argument from another report that the prognosis of lung cancer with prior cancer was heterogeneous among types and stages\textsuperscript{24}. For lung cancer and prior breast malignancy, Zhou et al. reported that patients with prior breast cancer generally experienced survival inferior to that of patients without prior cancer\textsuperscript{16}. Laccetti et al. and Martin et al. revealed that patients with lung cancer and prior breast cancer generally had no worse survival compared with patients without prior cancer history\textsuperscript{7, 25}, and a synchronous breast malignancy may be associated with improved survival\textsuperscript{26}. These results are conflicting; the higher number of patients involved in Laccetti’s report (patients diagnosed between 2004 and 2008 versus 1992 and 2009) and the bias involved in PSM program may be part of the underlying reasons. In the present study, entire records with a complete history of breast and lung cancers linked in the SEER database were included, and potential biases, such as medical progress accompanying time of treatment, were excluded at the beginning of the PSM program. The results suggested that the overall and cancer-specific survival of patients with lung cancer and prior breast cancer (interval time between two cancers of over 18 months) was generally similar to those without prior cancer. However, more studies are required because these patients with lung cancer (interval time of less than 6 months) may have a survival advantage, which may interfere with the trial results.

Information about the prognosis of lung cancer with subsequent breast cancer is lacking, which could be considerably attributed to its rareness. Zhou et al. reported that patients with prior lung cancer experienced survival similar to those without prior cancer. Caijin Lin et al. demonstrated that patients with prior cancer experienced worse overall survival and improved cancer-specific survival\textsuperscript{27}. Both studies were based on limited clinical observations. The present study suggested that the survival of metachronous LABC since secondary cancer was improved relative to that of synchronous LABC and single lung cancer. Potential explanations included an advantageous cancer survivor phenotype in patients with metachronous LABC and more frequent, intensive care–associated lead- and length–time biases\textsuperscript{8, 28, 29}. Another possible reason was the unexpected effect of drugs targeting hormonal pathways in breast cancer treatment. Estrogen receptor \(\alpha\) is highly expressed in women suffering from lung adenocarcinoma, which is associated with poor prognosis\textsuperscript{30–32}. In-vitro experiments and animals suggested that targeting estrogen receptor signaling leads to proliferation inhibition and increased response to chemotherapy in lung adenocarcinoma\textsuperscript{31, 33}. Finally, inappropriate treatment may be referred to synchronous two primary cancers due to the misjudged stage. For patients with synchronous primary breast and lung cancers, chemoradiotherapy may be referred due to the difficulty in distinguishing lung cancer invasion-related satellite nodules from breast cancer metastasis. However, the survival rate of T4 satellite lung cancer treated with radical resection was better than that of patients treated with chemoradiotherapy\textsuperscript{34}. These hypotheses may partly

### Table 4. Overall-survival analysis since secondary diagnosis in patients with BCLA/LABC. Group sTPC, mTPC1 and mTPC2 were categorized by first cancer stage; Overall survival was determined by median survival time (month). – not reached.

|             | BCLA | LABC | BCLA | LABC |
|-------------|------|------|------|------|
|             | NO   | 50%  | 95% CI | NO   | 50%  | 95% CI |
| sTPC        |      |      |       |      |      |       |
| First cancer stage |      |      |       |      |      |       |
| Localize    | 290  | 41   | 31    | 49   | 46   | 48    | 28   | 65 |
| Regional    | 144  | 89   | 56    | 105  | 39   | 32    | 18   | 87 |
| Distant     | 35   | 14   | 5     | 29   | 90   | 8     | 5    | 10 |
| Unknown     | 49   | 19   | 8     | 33   | 25   | 26    | 9    | 44 |
| Subtotal    | 518  | 42   | 34    | 53   | 200  | 18    | 12   | 25 |
| mTPC1       |      |      |       |      |      |       |
| First cancer stage |      |      |       |      |      |       |
| Localize    | 721  | 22   | 20    | 26   | 126  | 169   | 60   | –  |
| Regional    | 243  | 25   | 20    | 31   | 78   | 60    | 27   | 139 |
| Distant     | 28   | 25   | 12    | 37   | 41   | 17    | 8    | 32  |
| Unknown     | 6    | 11   | 1     | 26   | 49   | 14    | 68   |     |
| Subtotal    | 998  | 23   | 20    | 26   | 271  | 60    | 35   | 96  |
| mTPC2       |      |      |       |      |      |       |
| First cancer stage |      |      |       |      |      |       |
| Localize    | 1242 | 20   | 18    | 22   | 81   | 180   | 83   | –  |
| Regional    | 503  | 21   | 17    | 24   | 42   | 164   | 164  | –  |
| Distant     | 17   | 14   | 8     | 50   | 7    | –     | 2    | –  |
| Unknown     | 14   | 18   | 5     | 46   | 32   | 100   | 30   | –  |
| Subtotal    | 1776 | 20   | 18    | 22   | 162  | 180   | 100  | –  |
| Overall     | 3292 | 23   | 21    | 25   | 633  | 52    | 39   | 68  |
Figure 1. (A) Survival estimates of BCLA since secondary diagnosis stratified by group sTPC, mTPC1 and mTPC2; (B) Survival estimates of LABC since secondary diagnosis stratified by group sTPC, mTPC1 and mTPC2; (C–E) Survival estimates of BCLA in respective group sTPC, mTPC1 and mTPC2 since secondary diagnosis stratified by breast cancer stage; (F–H) Survival estimates of LABC in respective group sTPC, mTPC1 and mTPC2 since secondary diagnosis stratified by breast cancer stage.

Figure 2. For breast cancer with subsequent lung cancer, adjusted cumulative hazard of all-cause mortality since secondary cancer was classified into group sTPC, mTPC1 and mTPC2.
explain the survival advantage of patients with simultaneous BCLA and metachronous LABC. However, further studies are still required to reveal the underlying mechanisms.

The limitation of this study included several dimensions. First, the information on chemotherapy, targeted therapy, and other covariates associated with lung cancer prognosis was inaccessible, whereas that on radiotherapy and insurance was limited in the SEER database, which may affect the results of PSM and Cox analysis. Second, the information on patients’ psychological status was missing. The ratios of lung surgery performed in the sTPC group were higher than those in the mTPC group for BCLA but lower for LABC, suggesting that the number of patients inclined to abandon treatment varied among groups. Third, given the large scale of patients included in the SEER database, the number of patients qualified in this study was still low, particularly those categorized for analysis. Patients from other countries are necessary for further study. Finally, bias was inevitable due to the properties of a prospective epidemiological study.

In conclusion, this study depicted the prognosis of patients with BCLA and LABC. Compared with patients with single breast cancer, those with BCLA and LABC generally experienced poor survival. Patients with metachronous LABC and synchronous BCLA experienced better prognosis than those with single lung cancer, and the survival of the remaining patients statistically differed. Although the surgery for breast and lung cancer was associated with improved survival, its rate was lower in the sTPC group. Further study is required to clarify the mechanisms mediating survival advantage in BCLA/LABC relative to single lung cancer and increase the rate of surgery performed for breast and lung cancers.

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References
1. Kuhn, E. et al. Adenocarcinoma classification: Patterns and prognosis. Pathologica 110, 5–11 (2018).
2. Badve, S. S. & Gökmen-Polar, Y. Ductal carcinoma in situ of breast: Update 2019. Pathology 51, 563–569. https://doi.org/10.1016/j.pathol.2019.07.005 (2019).
3. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. SEER Cancer Statistics Review 2009–2015, https://seer.cancer.gov/statfacts/html/breast.html (2020).
4. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. SEER Cancer Statistics Review 2009–2015, https://seer.cancer.gov/statfacts/html/lungb.html (2020).
5. Ye, Y., Neil, A. L., Wills, K. E. & Venn, A. J. Temporal trends in the risk of developing multiple primary cancers: A systematic review. BMC Cancer 16, 849. https://doi.org/10.1186/s12885-016-2876-y (2016).
6. Pruitt, S. L., Laccetti, A. L., Xuan, L., Halm, E. A. & Gerber, D. E. Revisiting a longstanding clinical trial exclusion criterion: Implications for clinical trial eligibility and accrual. J. Natl. Cancer Inst. https://doi.org/10.1093/jnci/dju302 (2015).
7. Laccetti, A. L., Pruitt, S. L., Xuan, L., Halm, E. A. & Gerber, D. E. Effect of prior cancer on outcomes in advanced lung cancer: Implications for clinical trial eligibility and accrual. J. Natl. Cancer Inst. https://doi.org/10.1093/jnci/dju302 (2015).
8. Gerber, D. E., Laccetti, A. L., Xuan, L., Halm, E. A. & Pruitt, S. L. Impact of prior cancer on eligibility for lung cancer clinical trials. J. Natl. Cancer Inst. https://doi.org/10.1093/jnci/dju302 (2014).
9. Weiler, J. & Dittmar, T. Cell fusion in human cancer: The dark matter hypothesis. Cells https://doi.org/10.3390/cells8020132 (2019).
10. Bastos, N., Ruivo, C. F., da Silva, S. & Melo, S. A. Exosomes in cancer: Use them or target them?. Semin. Cell Dev. Biol. 78, 13–21. https://doi.org/10.1016/j.secmdb.2017.08.009 (2018).
11. Shan, S. et al. Clinical characteristics and survival of lung cancer patients associated with multiple primary malignancies. PLoS ONE 12, e0185485–e0185485. https://doi.org/10.1371/journal.pone.0185485 (2017).
12. Aguilo, R. et al. Multiple independent primary cancers do not adversely affect survival of the lung cancer patient. Eur. J. Cardio-Thorac. Surg. 34, 1075–1080. https://doi.org/10.1016/j.ejcts.2008.08.004 (2008).
13. Baba, Y. et al. Clinical and prognostic features of patients with esophageal cancer and multiple primary cancers: A retrospective single-institution study. Ann. Surg. 267, 478–483. https://doi.org/10.1097/SLA.0000000000002118 (2018).
14. Etiz, D., Metcalfe, E. & Akcay, M. Multiple primary malignant neoplasms: A 10-year experience at a single institution from Turkey. J. Cancer Res. Ther. 13, 16–20. https://doi.org/10.4103/0973-1482.183219 (2017).
| Group | H. R | P   | 95% CI | SHR | P   | 95% CI |
|-------|------|-----|--------|-----|-----|--------|
| tTPC  | 1.00 | 1.00 |        | 1.00 | 1.00 |        |
| mTPC1 | 1.21 | 0.01 | 1.04   | 1.41 | 1.14 | 0.07   | 0.99 | 1.31 |
| mTPC2 | 1.08 | 0.33 | 0.92   | 1.28 | 1.00 | 0.99   | 0.86 | 1.16 |
| Category |        |        |        |        |        |        |
| >2005 | 1.00 | 1.00 |        | 1.00 | 1.00 |        |
| 1995–2005 | 1.22 | 0.07 | 0.99   | 1.50 | 1.18 | 0.13   | 0.95 | 1.47 |
| <1995 | 1.55 | <0.01 | 1.22   | 1.98 | 1.47 | <0.01  | 1.14 | 1.90 |
| Race |        |        |        |        |        |        |
| NHW  | 1.00 | 1.00 |        | 1.00 | 1.00 |        |
| NHB  | 1.01 | 0.95 | 0.86   | 1.18 | 0.97 | 0.72   | 0.82 | 1.14 |
| NHA  | 0.77 | 0.01 | 0.63   | 0.94 | 0.83 | 0.06   | 0.69 | 1.01 |
| Hispanic | 1.13 | 0.29 | 0.91   | 1.40 | 1.02 | 0.86   | 0.79 | 1.32 |
| Others | 0.96 | 0.90 | 0.51   | 1.80 | 1.09 | 0.76   | 0.63 | 1.88 |
| Sex |        |        |        |        |        |        |
| Male | 1.00 | 1.00 |        | 1.00 | 1.00 |        |
| Female | 0.72 | 0.18 | 0.44   | 1.17 | 0.95 | 0.86   | 0.53 | 1.69 |
| Insurance1 |        |        |        |        |        |        |
| Uninsured | 1.00 | 1.00 |        | 1.00 | 1.00 |        |
| Insured | 0.54 | 0.11 | 0.25   | 1.14 | 0.51 | 0.04   | 0.27 | 0.96 |
| Unknown | 0.62 | 0.21 | 0.29   | 1.31 | 0.60 | 0.12   | 0.32 | 1.14 |
| Marital1 |        |        |        |        |        |        |
| Single | 1.00 | 1.00 |        | 1.00 | 1.00 |        |
| Married | 0.84 | 0.01 | 0.74   | 0.96 | 0.89 | 0.09   | 0.78 | 1.02 |
| Unknown | 0.87 | 0.29 | 0.67   | 1.13 | 0.84 | 0.18   | 0.65 | 1.09 |
| Seerstage1 |        |        |        |        |        |        |
| Localized | 1.00 | 1.00 |        | 1.00 | 1.00 |        |
| Regional | 1.01 | 0.77 | 0.92   | 1.12 | 1.00 | 0.95   | 0.90 | 1.11 |
| Distant | 1.38 | 0.03 | 1.04   | 1.82 | 1.34 | 0.04   | 1.01 | 1.79 |
| Unknown | 1.28 | 0.19 | 0.89   | 1.85 | 1.18 | 0.38   | 0.81 | 1.70 |
| Surgery1 |        |        |        |        |        |        |
| No | 1.00 | 1.00 |        | 1.00 | 1.00 |        |
| Yes | 0.91 | 0.47 | 0.70   | 1.18 | 1.09 | 0.56   | 0.82 | 1.43 |
| Unknown | 1.83 | 0.08 | 0.94   | 3.55 | 2.20 | 0.01   | 1.26 | 3.86 |
| Radiation1 |        |        |        |        |        |        |
| No | 1.00 | 1.00 |        | 1.00 | 1.00 |        |
| Yes | 0.92 | 0.87 | 0.34   | 2.49 | 0.85 | 0.66   | 0.41 | 1.76 |
| Unknown | 0.99 | 0.99 | 0.36   | 2.70 | 0.91 | 0.80   | 0.44 | 1.89 |
| Age |        |        |        |        |        |        |
| <55 | 1.00 | 1.00 |        | 1.00 | 1.00 |        |
| 55–75 | 1.26 | 0.01 | 1.06   | 1.49 | 1.19 | 0.05   | 1.00 | 1.41 |
| >75 | 1.59 | <0.01 | 1.32   | 1.91 | 1.37 | <0.01  | 1.13 | 1.65 |
| Marital2 |        |        |        |        |        |        |
| Single | 1.00 | 1.00 |        | 1.00 | 1.00 |        |
| Married | 1.03 | 0.67 | 0.90   | 1.18 | 1.02 | 0.81   | 0.88 | 1.17 |
| Unknown | 0.86 | 0.19 | 0.69   | 1.08 | 0.91 | 0.39   | 0.74 | 1.12 |
| Insurance2 |        |        |        |        |        |        |
| Uninsured | 1.00 | 1.00 |        | 1.00 | 1.00 |        |
| Insured | 0.74 | 0.37 | 0.39   | 1.42 | 0.69 | 0.20   | 0.39 | 1.22 |
| Unknown | 0.74 | 0.38 | 0.38   | 1.45 | 0.70 | 0.24   | 0.38 | 1.27 |
| Seerstage2 |        |        |        |        |        |        |
| Localized | 1.00 | 1.00 |        | 1.00 | 1.00 |        |
| Regional | 2.08 | <0.01 | 1.81   | 2.40 | 1.98 | <0.01  | 1.74 | 2.26 |
| Distant | 4.15 | <0.01 | 3.61   | 4.77 | 3.77 | <0.01  | 3.29 | 4.32 |
| Unknown | 2.24 | <0.01 | 1.87   | 2.69 | 2.08 | <0.01  | 1.75 | 2.48 |

| Continued |        |        |        |        |        |        |
|                    | H. R | P   | 95% CI  | SHR | P   | 95% CI  |
|--------------------|------|------|---------|-----|------|---------|
| No                 | 1.00 |      |         | 1.00|      |         |
| Yes                | 0.45 | <0.01| 0.40    | 0.51| 0.52 | <0.01   |
| Unknown            | 0.65 | 0.24 | 0.32    | 1.33| 0.69 | 0.49    |

Table 5. Covariates associated with all-cause and cancer-specific death in patients with BCLA. All variables were used in multivariate analysis. Insuarance1 first insurance status; Marital1 first marital status; Seerstage1 first cancer stage; Surgery1 first surgery; Radiation1 first radiation; Insuarance2 secondary insurance status; Marital2 secondy marital status; Seerstage2 secondary cancer stage; Surgery2 secondary surgery; Radiation2 secondary radiation; H.R risk of all-cause death; SHR risk of cancer-specific death.

Figure 4. For breast cancer with prior lung cancer, adjusted cumulative hazard of all-cause mortality since secondary cancer was classified into group sTPC, mTPC1 and mTPC2.

Figure 5. For breast cancer with prior lung cancer, adjusted cumulative hazard of cancer-specific mortality since secondary cancer was classified into group sTPC, mTPC1 and mTPC2.

15. Akbani, R. et al. A pan-cancer proteomic perspective on The Cancer Genome Atlas. Nat. Commun. 5, 3887. https://doi.org/10.1038/ncomms4887 (2014).
16. Zhou, H. et al. Impact of prior cancer history on the overall survival of patients newly diagnosed with cancer: A pan-cancer analysis of the SEER database. Int. J. Cancer 143, 1569–1577. https://doi.org/10.1002/ijc.31543 (2018).
17. Copur, M. S. & Manapuram, S. multiple primary tumors over a lifetime. Oncology (Williston Park) 33 (2019).
| Group     | H.R | P   | 95% CI    | SHR | P   | 95% CI    |
|-----------|-----|-----|-----------|-----|-----|-----------|
| sTPC      | 1.00|      |           |     |     |           |
| mTPC1     | 0.87| 0.34| 0.66      | 1.15| 0.79| 0.59      |
| mTPC2     | 0.52| <0.01| 0.34    | 0.80| 0.51| <0.01    |
| Category  |      |      |           |     |     |           |
| >2005     | 1.00|      |           |     |     |           |
| 1995–2005 | 1.63| 0.02| 1.09      | 2.44| 1.51| 0.04      |
| <1995     | 2.63| <0.01| 1.51    | 4.60| 2.84| <0.01    |
| Race      |      |      |           |     |     |           |
| NHW       | 1.00|      |           |     |     |           |
| NHB       | 1.01| 0.98| 0.67      | 1.50| 0.79| 0.35      |
| NHA       | 0.76| 0.36| 0.42      | 1.37| 0.86| 0.61      |
| Hispanic  | 0.65| 0.19| 0.34      | 1.24| 0.67| 0.20      |
| Others    | <0.01| 1.00| <0.01    | -   |     | <0.01    |
| Age       |      |      |           |     |     |           |
| <55       | 1.00|      |           |     |     |           |
| 55–75     | 1.10| 0.64| 0.73      | 1.68| 0.90| 0.64      |
| >75       | 1.23| 0.40| 0.76      | 1.99| 0.86| 0.52      |
| Insurance1|      |      |           |     |     |           |
| Uninsure  | 1.00|      |           |     |     |           |
| Insure    | 0.97| 0.97| 0.27      | 3.54| 0.65| 0.57      |
| Unknown   | 0.79| 0.73| 0.21      | 2.97| 0.52| 0.38      |
| Seerstage1|      |      |           |     |     |           |
| Localized | 1.00|      |           |     |     |           |
| Regional  | 1.25| 0.18| 0.90      | 1.72| 1.22| 0.21      |
| Distant   | 1.93| <0.01| 1.35    | 2.76| 1.84| <0.01    |
| Unknown   | 0.97| 0.91| 0.59      | 1.59| 0.91| 0.70      |
| Marital1  |      |      |           |     |     |           |
| Single    | 1.00|      |           |     |     |           |
| Married   | 0.93| 0.58| 0.73      | 1.19| 0.97| 0.83      |
| Unknown   | 0.63| 0.12| 0.35      | 1.12| 0.75| 0.34      |
| Surgery1  |      |      |           |     |     |           |
| No        | 1.00|      |           |     |     |           |
| Yes       | 0.48| <0.01| 0.34    | 0.67| 0.55| <0.01    |
| Unknown   | 0.74| 0.77| 0.10      | 5.66| 0.67| 0.74      |
| Radiation1|      |      |           |     |     |           |
| No        | 1.00|      |           |     |     |           |
| Yes       | 1.31| 0.70| 0.32      | 5.39| 1.32| 0.59      |
| Unknown   | 1.19| 0.81| 0.29      | 4.95| 1.11| 0.84      |
| Seerstage2|      |      |           |     |     |           |
| Localized | 1.00|      |           |     |     |           |
| Regional  | 1.21| 0.22| 0.89      | 1.66| 1.25| 0.14      |
| Distant   | 2.52| <0.01| 1.72    | 3.70| 2.46| <0.01    |
| Unknown   | 1.73| 0.07| 0.95      | 3.13| 1.28| 0.44      |
| Surgery2  |      |      |           |     |     |           |
| No        | 1.00|      |           |     |     |           |
| Yes       | 0.57| <0.01| 0.40    | 0.80| 0.59| <0.01    |
| Unknown   | 2.48| 0.14| 0.75      | 8.27| 2.63| <0.01    |
| Radiation2|      |      |           |     |     |           |
| No        | 1.00|      |           |     |     |           |
| Yes       | 0.64| 0.54| 0.15      | 2.66| 0.70| 0.66      |
| Unknown   | 0.91| 0.89| 0.22      | 3.76| 0.96| 0.20      |

Table 6. Covariates associated with all-cause and cancer-specific death in patients with LABC. All variables were used in multivariate analysis. Insurance1 first insurance status; Seerstage1 first cancer stage; Surgery1 first surgery; Radiation1 first radiation; Seerstage2 secondary cancer stage; Surgery2 secondary surgery; Radiation2 secondary radiation; H.R risk of all-cause death; SHR risk of cancer-specific death.
18. Amer, M. H. Multiple neoplasms, single primaries, and patient survival. *Cancer Manag. Res.* **6**, 119–134. https://doi.org/10.2147/cmrr.57378 (2014).
19. Imbens, G. W. Matching methods in practice: Three examples. *J. Hum. Resour.* **50**, 373–419 (2015).
20. Afifi, A. M. *et al.* Causes of death after breast cancer diagnosis: A US population-based analysis. *Cancer* **126**, 1559–1567. https://doi.org/10.1002/cncr.32648 (2020).
21. Aokage, K. *et al.* Is cancer history really an exclusion criterion for clinical trial of lung cancer? Influence of gastrointestinal tract cancer history on the outcomes of lung cancer surgery. *Jpn. J. Clin. Oncol.* **47**, 145–156. https://doi.org/10.1093/jjco/hyw157 (2017).
22. Pagedar, N. A., Jayawardena, A., Charlton, M. E. & Hoffman, H. T. Second primary lung cancer after head and neck cancer: implications for screening computed tomography. *Ann. Otol. Rhinol. Laryngol.* **124**, 765–769. https://doi.org/10.1177/0003484115582259 (2015).
23. Hattori, A. *et al.* Prognosis of lung cancer patients with a past history of colorectal cancer. *Jpn. J. Clin. Oncol.* **44**, 1088–1095. https://doi.org/10.1093/jjco/hyu122 (2014).
24. Monsalve, A. F. *et al.* Variable impact of prior cancer history on the survival of lung cancer patients. *Lung Cancer* **127**, 130–137. https://doi.org/10.1016/j.lungcan.2018.11.040 (2019).
25. Laccetti, A. L., Pruitt, S. L., Xuan, L., Halm, E. A. & Gerber, D. E. Prior cancer does not adversely affect survival in locally advanced lung cancer: A national SEER-Medicare analysis. *Lung Cancer* **98**, 106–113. https://doi.org/10.1016/j.lungcan.2016.05.029 (2016).
26. Fuchling, M. *et al.* Second malignancy in non-small cell lung cancer (NSCLC): Prevalence and overall survival (OS) in routine clinical practice. *J. Cancer Res. Clin. Oncol.* **144**, 2059–2066. https://doi.org/10.1007/s00432-018-2714-5 (2018).
27. Lin, C. *et al.* Impact of prior cancer history on the clinical outcomes in advanced breast cancer: A propensity score-adjusted, population-based study. *Cancer Res. Treat.* **52**, 552–562. https://doi.org/10.4143/crt.2019.210 (2020).
28. Massard, G. *et al.* Lung cancer following previous extrapulmonary malignancy. *Eur. J. Cardiothorac. Surg.* **18**, 524–528. https://doi.org/10.1016/s1010-7940(00)00571-6 (2000).
29. Sankila, R. & Hakulinen, T. Survival of patients with colorectal carcinoma: Effect of prior breast cancer. *J. Natl. Cancer Inst.* **90**, 63–65. https://doi.org/10.1093/jnci/90.1.63 (1998).
30. Hsu, L.-H., Chiu, N.-M. & Kao, S.-H. Estrogen, estrogen receptor and lung cancer. *Int. J. Mol. Sci.* **18**, 1713. https://doi.org/10.3390/ijms18081713 (2017).
31. Hamilton, D. H. *et al.* Targeting estrogen receptor signaling with fulvestrant enhances immune and chemotherapy-mediated cytotoxicity of human lung cancer. *Cancer Res.* **22**, 6204–6216. https://doi.org/10.1158/0003-482X.CAN-15-3059 (2016).
32. Honma, N., Hosoi, T., Arai, T. & Takubo, K. Estrogen and cancers of the colorectum, breast, and lung in postmenopausal women. *Pathol. Int.* **65**, 451–459. https://doi.org/10.1111/pin.12326 (2015).
33. Marquez-Garban, D. C., Chen, H. W., Goodglick, L., Fishbein, M. C. & Pietras, R. J. Targeting aromatase and estrogen signaling in human non-small cell lung cancer. *Ann. N. Y. Acad. Sci.* **1155**, 194–205. https://doi.org/10.1111/j.1749-6632.2009.04116.x (2009).
34. Loukeri, A. A., Kampolis, C. F., Ntokou, A., Tsoukalas, G. & Syrigos, K. Metachronous and synchronous primary lung cancers: Diagnostic aspects, surgical treatment, and prognosis. *Clin. Lung Cancer* **16**, 15–23. https://doi.org/10.1016/j.cllc.2014.07.001 (2015).

**Author contributions**
X.Z.: study design, data analysis, results discussion and manuscript preparation. F.L.: data extraction and analysis, manuscript preparation; M.C.: data analysis, results discussion and manuscript preparation; L.J.: data extraction and results discussion.

**Competing interests**
The authors declare no competing interests.

**Additional information**

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