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THE RISK OF A SECOND PRIMARY LUNG CANCER AFTER A FIRST INVASIVE BREAST CANCER ACCORDING TO ESTROGEN RECEPTOR STATUS

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Abstract

Purpose—Lung cancers account for 5% of second primary cancers after breast cancer. The low overall 5-year relative-survival of lung cancer makes it a particularly concerning new malignancy for breast cancer survivors. It is unknown whether second lung cancer risk varies by estrogen receptor (ER) expression of the first breast cancer.

Methods—We evaluated second primary lung cancer risks using standardized incidence ratios (SIRs) (95% Confidence Intervals (CIs)) among 222,148 one-year breast cancer survivors in the NCI-SEER Program registry database (1992–2008). Relative risks (RRs) and (95% CIs) for lung cancer following ER[−] compared with ER⁺ breast cancer were estimated using Poisson regression, adjusted for age-, year-, and stage of breast cancer diagnosis, attained age, latency, and radiotherapy. We also examined the reciprocal association of second ER[−] and ER⁺ breast cancers among 28,107 1-year lung cancer survivors.

Results—There were 418 and 1,444 second lung cancers diagnosed following 50,781 ER[−] and 171,367 ER⁺ breast cancers. Second lung cancer rates were significantly elevated after ER[−] (SIR=1.20 (1.09–1.33)) but not ER⁺ (SIR=0.96 (0.91–1.01)) breast cancer. The adjusted RR for a second lung cancer following ER[−] compared with ER⁺ breast cancer was 1.22 (1.10–1.37). The reciprocal adjusted RR for a second ER[−] compared with ER⁺ breast cancer following lung cancer was 1.29 (0.98–1.70).

Conclusion—The parallel increase for a second lung cancer following an ER[−] first breast cancer and for a second ER[−] breast cancer after a first lung cancer suggests that there may be shared etiologic factors for these cancers. Further evaluation of lung cancer risk after ER[−] breast cancer may identify women at high-risk for this fatal malignancy.

Keywords

breast cancer; lung cancer; estrogen receptor status; second primary

INTRODUCTION

Improvements in the detection and treatment of breast cancer over time have resulted in 5-year relative survival rates exceeding 80% for women diagnosed with localized and regional breast cancer [1]. A corollary of better survival, however, is increased opportunity for the development of second cancers. By ten years after diagnosis, approximately 10% of breast

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cancer survivors have developed a subsequent malignancy [2]. Lung cancer accounts for approximately 5% of second primary cancers among breast cancer survivors [3], and represents a particularly concerning new malignancy given the very low overall 5-year relative-survival rate (<20%) [1].

Although lung cancer rates among breast cancer patients overall in the U.S. are somewhat lower than those observed in the general population, second primary lung cancer rates are significantly elevated among women diagnosed with breast cancer before age 50 years [4]. As the increase is observed as early as one year after breast cancer diagnosis and persists long-term, it seems unlikely to be explained solely by radiotherapy treatment for the breast cancer, which is associated with increased lung cancer rates after a latency period of 5 to 10 years [4–10].

Younger women with breast cancer are more likely to have estrogen receptor negative (ER⁻) tumors than older women [11]. To date, no one has considered the impact of ER expression upon the risk of second lung cancers. We examined the risk of second lung cancer by ER status of the first primary breast cancer using data from the Surveillance, Epidemiology and End Results (SEER) Program. We also assessed the reciprocal association, patterns of second ER⁻ and ER⁺ breast cancers following a first lung cancer. A parallel finding (i.e., mutually elevated risks of two cancers after each other) can be an indication of a shared etiology, particularly when the elevated risk is consistent over time since diagnosis and independent of treatment [12].

METHODS

Population and follow-up

The analysis was based on cancers with diagnoses between January 1, 1992 and December 31, 2008 and reported to the SEER 13 Registries (based on the November 2010 data submission), excluding the Alaska Native Tumor Registry. From the remaining 12 registries, we selected women who were diagnosed with a first primary invasive breast cancer between the ages of 20 and 79 and who survived at least one-year.

The follow-up period for our analysis of second primary lung cancer began 1 year after the date of invasive breast cancer diagnosis and continued until date of diagnosis with a second primary cancer (excluding non-melanoma skin cancer) at any site, death, date of last known vital status, attained age 80, or end of study (December 31, 2008), whichever occurred first. Follow-up was restricted to attained ages <80 years because of concerns of under-ascertainment of second cancers in older patients [12]. Second primary lung cancers diagnosed more than 12 months after the date of invasive breast cancer diagnosis were ascertained from the SEER registries. Exclusion periods vary across studies but the general principle is to minimize the possibility of misdiagnosed metastases and the potential for incidental cancer diagnoses occurring as a result of heightened surveillance during the initial diagnostic and treatment period [12]. Based on International Classification of Diseases for Oncology, third edition (ICD-O-3) morphology codes, lung cancers were further classified as small cell lung cancer (8041–8045) and non-small cell lung cancer (all others) [13].

In addition to age and calendar year of breast cancer diagnosis, we classified women according to whether they received radiotherapy and surgery as part of their initial breast cancer treatment. The SEER Program collects data on first course of therapy in broad categories; however, data on chemotherapy and hormonal therapy are incomplete and therefore not included in the public use SEER database. After excluding (in the following order) women whose breast cancer was not diagnosed at the local or regional stage (n=15,227), women for whom it was unknown whether they received radiotherapy (n=247),

and women with no or unknown breast cancer surgery (n=3909), our analysis of second lung cancer after breast cancer included 50,781 women with ER⁻ breast cancer and 171,367 women with ER⁺ breast cancer. There were an additional 33,841 women with unknown ER status who were excluded from most analyses.

A parallel approach was followed for the reciprocal analysis of second invasive breast cancer after a first primary lung cancer. We excluded women diagnosed with distant (n=12,721) or unstaged (n=2,455) lung cancers and women with unknown radiotherapy status (n=21) resulting in a sample of 28,107 one-year survivors of lung cancer.

Statistical analysis

We calculated standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) based on Poisson exact methods [14]. The SIR is the ratio of the observed (O) number of lung cancers among breast cancer survivors to the number expected (E) among women in the general population. Expected numbers were obtained by multiplying incidence rates specific for race and 5-year attained age and calendar-year intervals by stratum-specific person-years at risk and summing across the strata (Seer*Stat, version 7.0.5) [15].

The relative risks (RRs) and 95% CIs of developing a second primary lung cancer following ER⁻ vs. ER⁺ breast cancer were estimated from Poisson regression with the expected numbers as an offset, which indirectly adjusts for attained calendar year and attained age [16]. The RR estimated from a model with only ER status is equivalent to the ratio of the SIR of lung cancer after ER negative breast cancer to the SIR of lung cancer after ER positive breast cancer. RRs were calculated using epicure software (AMFIT module [17]). In most analyses, we further adjusted for age at breast cancer diagnosis, calendar year of breast cancer diagnosis, time since breast cancer diagnosis, radiotherapy for breast cancer, and stage at breast cancer diagnosis. We also conducted analyses to check whether the RR patterns of developing a second primary lung cancer following ER⁻ vs. ER⁺ breast cancer were consistent across categories of radiotherapy, latency, age, stage and calendar year of breast cancer diagnosis. This was evaluated by comparing model fit with and without the inclusion of an interaction term between a given variable (using ordinal categories as continuous variables) and ER status. P values for the tests of heterogeneity were two-sided and were estimated using the maximum likelihood ratio test. As the risk of lung cancer from radiotherapy has been shown to vary by age at- and time since breast cancer diagnosis [6], a set of analyses stratified by radiotherapy were also conducted to examine this relationship in more detail. Parallel SIR and RR analyses were conducted for the reciprocal analysis of second breast cancers after lung cancer.

To quantify the burden of second lung cancer risk among breast cancer survivors diagnosed in recent calendar years (2000), we estimated second lung cancer incidence rates per 100,000 woman-years by age at breast cancer diagnosis (5-year categories). Rates were estimated from Poisson regression models fitted separately for ER⁺ and ER⁻ breast cancer, adjusted for calendar year (one-year categories) of breast cancer diagnosis and time since breast cancer diagnosis (one-year categories). Our final model, based on assessment of the Akaike's information criteria statistic [18,19], included a categorical function for age at breast cancer diagnosis, a cubic function for year of breast cancer diagnosis, and a linear term for time since breast cancer diagnosis (latency).

RESULTS

There were 222,148 one-year breast cancer survivors followed for an average of 5.6 years. ER⁻ breast cancer accounted for 23% of the breast cancers with known ER status (Table 1). The proportion of women with ER⁻ breast cancer decreased with increasing age at breast

cancer diagnosis. Women with ER⁻ breast cancer were more likely to be diagnosed with regional stage breast cancer and were somewhat less likely to undergo radiotherapy as part of their initial treatment than women with ER⁺ breast cancer. These factors were all statistically significantly associated with ER status ($P < 0.001$) based on multivariable logistic regression adjusted for all variables presented in Table 1.

Among women diagnosed with breast cancer in recent calendar years (between 2000 and 2007), estimated second lung cancer rates per 100,000 person-years were 25 (95% CI 8 to 42), 128 (95% CI: 103 to 153) and 346 (95% CI: 268 to 425) following ER⁻ breast cancer at ages 30–34, 50–54, and 70–74, respectively. After ER⁺ breast cancer, estimated rates for these same three age at diagnosis groups were 13 (95% CI: 4 to 21), 80 (95% CI: 70 to 90) and 278 (95% CI: 247 to 309) per 100,000 person-years.

During the follow-up period, a total of 418 second primary lung cancers developed among women diagnosed with ER⁻ breast cancer which was significantly more than the 346.9 expected based on rates in the general population (SIR 1.20; 95% CI 1.09 to 1.33) (Table 2). After ER⁺ breast cancer, there were 1,444 second primary lung cancers compared with 1501.3 expected overall (SIR 0.96; 95% CI 0.91 to 1.01). The SIRs for lung cancer after breast cancer with unknown ER status fell between those observed after ER⁻ and ER⁺ breast cancer (overall SIR 1.08; 95% CI 0.98 to 1.20). The SIR for lung cancer was elevated for women diagnosed with ER⁺ breast cancer before age 50 years (SIR = 1.32; 95% CI 1.11 to 1.57). Among women diagnosed with ER⁻ breast cancer, the SIR for lung cancer in this age group was 1.63 (95% CI 1.26 to 2.07). The SIR was also elevated at 10 or more years after ER⁺ breast cancer diagnosis (SIR = 1.20; 95% CI 1.05 to 1.37). In analyses stratified by initial treatment with radiotherapy, the SIR after radiotherapy for ER⁺ breast cancer was 1.30 (95% CI 1.08 to 1.55) and 1.09 (95% CI 0.89 to 1.34) after no radiotherapy (Electronic Supplementary Material).

We then compared the risks of lung cancer in ER⁻ compared with ER⁺ breast cancer survivors using Poisson regression models. The RR, adjusted only for attained age and calendar year, was 1.25 (95% CI 1.12 to 1.40). Subsequent RRs were adjusted for the factors in Table 1. The adjusted RR for a second lung cancer following ER⁻ breast cancer vs. ER⁺ breast cancer was 1.22 (95% CI 1.10 to 1.37), and this was consistent across radiotherapy and age at breast cancer diagnosis groups (Table 2). The RRs varied, however, by time since breast cancer diagnosis, calendar year of breast cancer diagnosis, and stage at breast cancer diagnosis. The increased risk of developing a second lung cancer after ER⁻ breast cancer compared with an ER⁺ breast cancer was observed during the first 5 years after breast cancer diagnosis but not thereafter ($P_{\text{heterogeneity}} < 0.001$). Lung cancer risk was significantly greater after ER⁻ breast cancer compared with an ER⁺ breast cancer among women diagnosed with breast cancer after 1997 but not in the period of 1992–1996 ($P_{\text{heterogeneity}} < 0.001$) and was greater among women diagnosed with regional vs. localized stage at diagnosis of breast cancer ($P_{\text{heterogeneity}} < 0.01$) (Table 2). For each of these characteristics, the RR patterns were consistent across groups defined by initial radiotherapy treatment (Electronic Supplementary Material).

We also assessed the risks according to lung cancer histology. For second non-small cell lung cancers, the corresponding SIRs were 1.24 (95% CI 1.12 to 1.37; O=367) in the ER⁻ breast cancer group and 0.97 (95% CI 0.92 to 1.03; O=1,247) in the ER⁺ group. The RR for developing a second non-small cell lung cancers following ER⁻ compared with ER⁺ breast cancer = 1.24 (95% CI 1.10 to 1.40). The SIR for second small cell lung cancer after ER⁻ breast cancer was 1.00 (95% CI 0.74 to 1.31; O=51) and 0.89 (95% CI 0.77 to 1.02; O=197) after ER⁺ breast cancer. The adjusted risk of developing a second primary small cell lung

cancer following ER⁻ breast cancer compared with ER⁺ breast cancer was not statistically significantly increased (RR=1.11; 95% CI 0.81 to 1.52).

Next, we evaluated whether there was a reciprocal association for breast cancer after lung cancer. The SIR for ER⁻ breast cancer after a first primary lung cancer was 1.18 (95% CI 0.91 to 1.51; O=65) and that for ER⁺ breast cancer was 0.92 (95% CI 0.80 to 1.05; O=228) (Table 3). The overall adjusted RR for ER⁻ vs. ER⁺ breast cancer after lung cancer was 1.29 (95% CI 0.98 to 1.70).

DISCUSSION

In this large registry-based study, we found that second primary lung cancer rates were significantly higher following ER⁻ than ER⁺ breast cancer, particularly during the first five years after breast cancer diagnosis, in recent calendar time periods, and among women diagnosed with regional vs. localized breast cancer. In both ER groups, the absolute rate of lung cancer increased with age at breast cancer diagnosis.

The patterns of second primary lung cancer by ER status of a first breast cancer have not been reported previously. Earlier analyses of SEER data from 1973–2000 reported an SIR of 0.94 for lung cancer among breast cancer survivors overall compared with the general population and an increased SIR for lung cancer among women diagnosed with breast cancer before age 50. Several studies of European registry data have reported overall SIRs of 1.2–1.3 [9,20,21]. Many previous studies of lung cancer after breast cancer have examined the role of radiotherapy, demonstrating an increased risk of lung cancer following treatment with radiotherapy after a latency period of at least 5–10 years [10]. In the present study, the absence of an overall elevated SIR among women whose initial treatment for ER⁺ breast cancer included radiotherapy could reflect the concentration of person-years of follow-up in the <10 years after breast cancer diagnosis. Restricting the analysis to 10 years after breast cancer diagnosis, lung cancer rates were significantly higher than those expected based on general population rates. A novel finding of this study is the increased risk of lung cancer after ER⁻ breast cancer both in the absence of radiotherapy and during the latency period before which any radiotherapy effect would be expected.

The mutually increased risk of lung cancer following ER⁻ breast cancer and of ER⁻ breast cancer following lung cancer suggests that there may be shared environmental and/or genetic determinants for these cancers. The over-expression of epidermal growth factor receptor 1 in both a large proportion of lung adenocarcinomas [22] and breast cancers that are ER⁻ as well as progesterone receptor negative and HER2- negative [23,24] may provide one clue for common etiologic pathways. Differential follow-up surveillance according to ER status is unlikely. American Society for Clinical Oncology guidelines for breast cancer follow-up are made irrespective of ER status and do not include recommendations for non-breast imaging studies, which could result in incidental findings of lung cancer (i.e., chest x-ray or computed tomography scans) [25].

We also considered the possibility that misclassification of breast metastases as second primary lung tumors could explain the observed increased risk of lung cancer after ER⁻ breast cancer. Several findings from a recently published pathology review of lung cancers diagnosed 1 year after breast cancer in the Swedish Cancer Registry would suggest that it is unlikely [26]. Our study included breast cancer survivors diagnosed in 1992 or later. In the pathology study, misclassification of lung metastases as new primaries declined significantly with calendar year period, from 20% to less than 5% of cases among women diagnosed with breast cancer in 1980. Further, the majority of misclassified metastases occurred 10 or more years after breast cancer diagnosis. In our study, elevated rates of

second primary lung cancer following ER⁻ were most evident during the 1–5 years after breast cancer diagnosis. Although there have not been, to our knowledge, similar studies based on SEER data, the study of Swedish cases suggests that misclassification is unlikely to explain the increased rates of second primary lung cancers after ER⁻ breast cancer. A related question concerns the possible under-ascertainment of second primary lung cancers after ER⁺ breast cancer due to misclassification of these tumors as breast metastases. Such misclassification could bias the SIR for lung cancer after ER⁺ downward while exaggerating the RR of developing a second primary lung cancer following ER⁻ vs. ER⁺, but would not explain the overall increased SIR of lung cancer after ER⁻ breast cancer [26].

The observed increased risk of lung cancer after ER⁻ vs. ER⁺ breast cancer was not explained by radiotherapy in this study. Lack of detailed treatment data, particularly for chemotherapy and hormonal therapy, is however a recognized limitation of second cancer analyses of SEER. Therefore, we cannot exclude the possibility that other treatment differences between ER⁻ and ER⁺ breast cancers could explain the higher rates of second primary lung cancer following ER⁻ vs. ER⁺ breast cancer. Although neither hormone therapy [9,27–29] nor chemotherapy [10,29] has been significantly associated with second lung cancer risk after breast cancer, lung cancer has been previously related to chemotherapy after Hodgkin lymphoma [30]. As available treatment data in SEER is restricted to the first course of therapy, it is also possible that women who did not initially receive radiotherapy subsequently received radiation treatment or that treatment received outside of a hospital-setting was not captured by the registries [31]. While this misclassification could lead to an underestimate of radiation-related risk of lung cancer, it would not be expected to affect our comparison of lung cancer risk by ER status.

The absence of individual risk factor data is another limitation of registry-based studies such as this one. In particular, is the lack of smoking given the strong association between cigarette smoking and lung cancer [32]. The evidence for an association between smoking and breast cancer is mixed but early age at initiation and long-term duration of smoking may increase breast cancer risk [33]. Mixed results have been reported in studies that further stratified by ER status, with some showing a stronger association for either ER positive or negative tumors and others finding no evidence of heterogeneity [34–40]. Nonetheless, we cannot exclude the possibility that our results are driven by underlying differences in the smoking histories between ER⁻ and ER⁺ breast cancer. Further analyses with data on treatment and smoking are warranted.

Strengths of the study include the large sample size, including 418 second lung cancers after ER⁻ breast cancer and 1,444 lung cancers after ER⁺ breast cancer. We had sufficient case numbers to estimate not only the overall RR of lung cancer following ER⁻ vs. ER⁺ breast cancer but also across latency, age at diagnosis, radiotherapy and stage categories to better characterize the patterns.

In summary, the results from this large, registry-based study suggest a higher overall risk of second lung cancer after ER⁻ breast cancer compared with rates after ER⁺ breast cancer and those in the general population. Radiotherapy, an established risk factor for second lung cancers among breast cancer survivors, does not appear to explain this observed risk. As this is the first study, to our knowledge, to report this observation, replication of this finding in other large, registry-based studies is necessary. Analytic studies with detailed tumor characteristics and lifestyle risk factor information are also needed to help better understand this association and elucidate whether there could be potential shared etiology between ER⁻ breast cancers and lung cancers. Further evaluation of lung cancer risk after ER⁻ breast cancer may identify high-risk women for this fatal malignancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Selected characteristics of 222,148 women surviving at least one year after diagnosis of a first primary ER negative or ER positive invasive breast cancer in 12 SEER registries, 1992–2008.

Characteristic ^a	ER Negative		ER Positive		Total	
	No. women	%	No. women	%	No. women	%
All women	50 781	100%	171 367	100%	222 148	
Initial radiotherapy for breast cancer						
No	23 414	46%	71 985	42%	95 399	
Yes	27 367	54%	99 382	58%	126 749	
Age at breast cancer diagnosis						
< 50 y	19 766	39%	45 859	27%	65 625	
50–59 y	14 656	29%	46 388	27%	61 044	
60–69 y	9 992	20%	43 950	26%	53 942	
70 y	6 367	13%	35 170	21%	41 537	
Year of breast cancer diagnosis						
1992–1996	15 209	30%	43 948	26%	59 157	
1997–2001	15 766	31%	56 141	33%	71 907	
2002–2007	19 806	39%	71 278	42%	91 084	
Stage at breast cancer diagnosis						
Localized	31 869	63%	114 836	67%	146 705	
Regional	18 912	37%	56 531	33%	75 443	

Abbreviations: SEER = Surveillance, Epidemiology and End Results; ER = Estrogen receptor

^a All variables listed in this table associated with ER negative breast cancer status at P < 0.001 based on logistic regression model mutually adjusted for the variables presented in the table.

Table 2

Relative risk of developing a second primary lung cancer among women surviving at least one year after diagnosis of ER negative vs. ER positive breast cancer in 12 SEER registries, 1992–2008.

	ER Negative				ER Positive				ER Negative vs. ER positive		
	O	E	SIR	95% CI	O	E	SIR	95% CI	RR ^a	95% CI	P ^b _{heterogeneity}
Overall	418	346.9	1.20	1.09 to 1.33	1,444	1501.3	0.96	0.91 to 1.01	1.22	1.10 to 1.37	
Initial radiotherapy for breast cancer											
No	194	172.1	1.13	0.97 to 1.30	627	653.7	0.96	0.89 to 1.04	1.16	0.98 to 1.36	
Yes	224	174.9	1.28	1.12 to 1.46	817	847.6	0.96	0.90 to 1.03	1.28	1.11 to 1.49	0.28
Time since breast cancer diagnosis											
1-<5 y	244	169.0	1.44	1.27 to 1.64	672	781.8	0.86	0.80 to 0.93	1.61	1.39 to 1.86	
5-9 y	122	122.2	1.00	0.83 to 1.19	550	534.9	1.03	0.94 to 1.12	0.97	0.80 to 1.18	
10 y	52	55.7	0.93	0.70 to 1.22	222	184.6	1.20	1.05 to 1.37	0.80	0.59 to 1.08	< 0.001
Age at breast cancer diagnosis											
<50 y	66	40.5	1.63	1.26 to 2.07	134	101.2	1.32	1.11 to 1.57	1.28	0.95 to 1.72	
50-59 y	129	104.5	1.23	1.03 to 1.47	341	349.2	0.98	0.88 to 1.09	1.28	1.04 to 1.57	
60-69 y	157	139.5	1.13	0.96 to 1.32	661	676.1	0.98	0.90 to 1.06	1.15	0.96 to 1.37	
70 y	66	62.4	1.06	0.82 to 1.35	308	374.8	0.82	0.73 to 0.92	1.29	0.99 to 1.69	> 0.50
Year of breast cancer diagnosis											
1992-1996	176	175.1	1.00	0.86 to 1.16	670	664.6	1.01	0.93 to 1.09	0.99	0.83 to 1.17	
1997-2001	153	116.8	1.31	1.11 to 1.54	520	578.1	0.90	0.82 to 0.98	1.40	1.17 to 1.68	
2002-2007	89	55.0	1.62	1.30 to 1.99	254	258.7	0.98	0.86 to 1.11	1.59	1.25 to 2.03	< 0.001
Stage at breast cancer diagnosis											
Localized	271	246.6	1.10	0.97 to 1.24	1,076	1092.2	0.99	0.93 to 1.05	1.10	0.96 to 1.25	
Regional	147	100.3	1.47	1.24 to 1.72	368	409.1	0.90	0.81 to 1.00	1.57	1.29 to 1.90	< 0.01

Abbreviations: SEER = Surveillance, Epidemiology and End Results; ER = Estrogen receptor; O = Observed; E = Expected; SIR = standardized incidence ratio = ratio of observed to expected cases; 95% CI = 95% confidence intervals; RR = relative risk

^aRRs calculated using Poisson regression with expected cases as an offset with stratification by radiation (no/yes), age at breast cancer diagnosis (20–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79), calendar year of breast cancer diagnosis (1992–1996, 1997–2001, 2002–2007), time since breast cancer diagnosis (1–<5 years, 5–9 years, 10 years), and stage at breast cancer diagnosis (localized, regional)

^bTests for heterogeneity evaluated by comparing model fit with and without the inclusion of an interaction term between a given variable (using ordinal categories as continuous variables) and ER status.

Table 3

Relative risk of developing a second primary ER negative vs. ER positive breast cancer among women surviving at least one year after diagnosis of a first lung cancer in 12 SEER registries, 1992–2008

ER Negative													ER Positive				ER negative vs. ER positive		
	No. women	O	E	SIR	95% CI	O	E	SIR	95% CI	RR ^a	95% CI	P ^b _{heterogeneity}							
Overall	28,107	65	55.0	1.18	0.91 to 1.51	228	248.3	0.92	0.80 to 1.05	1.29	0.98 to 1.70								
Initial radiotherapy for lung cancer																			
No	17,892	51	40.8	1.25	0.93 to 1.64	177	186.2	0.95	0.82 to 1.10	1.32	0.97 to 1.80								
Yes	10,215	14	14.2	0.99	0.54 to 1.66	51	62.1	0.82	0.61 to 1.08	1.19	0.66 to 2.16	> 0.50							
Time since lung cancer diagnosis																			
<5 y		49	36.4	1.35	1.00 to 1.78	141	162.4	0.87	0.73 to 1.02	1.55	1.12 to 2.14								
5 y		16	18.6	0.86	0.49 to 1.39	87	85.9	1.01	0.81 to 1.25	0.86	0.51 to 1.47	0.05							
Age at lung cancer diagnosis																			
<60 y	8,177	18	19.9	0.90	0.54 to 1.43	68	70.8	0.96	0.75 to 1.22	0.93	0.55 to 1.57								
60 y	19,930	47	35.1	1.34	0.98 to 1.78	160	177.5	0.90	0.77 to 1.05	1.49	1.08 to 2.06	0.14							
Year of lung cancer diagnosis																			
1992 – 1996	8,428	31	22.5	1.38	0.94 to 1.95	87	100.6	0.86	0.69 to 1.07	1.61	1.06 to 2.42								
1997 – 2001	9,062	26	20.0	1.30	0.85 to 1.90	95	91.4	1.04	0.84 to 1.27	1.25	0.81 to 1.93								
2002 – 2007	10,617	8	12.5	0.64	0.28 to 1.26	46	56.3	0.82	0.60 to 1.09	0.78	0.37 to 1.65	0.11							
Stage at lung cancer diagnosis																			
Localized	13,674	40	32.4	1.24	0.88 to 1.68	154	148.0	1.04	0.88 to 1.22	1.19	0.84 to 1.69								
Regional	14,433	25	22.7	1.10	0.71 to 1.63	74	100.3	0.74	0.58 to 0.93	1.48	0.94 to 2.34	0.45							

Abbreviations: SEER = Surveillance, Epidemiology and End Results; ER = Estrogen receptor; O = Observed; E = Expected; SIR = standardized incidence ratio = ratio of observed to expected cases; 95% CI = 95% confidence intervals; RR = relative risk

^aRRs calculated using Poisson regression with expected cases as an offset with stratification by radiation (no/yes), age at lung cancer diagnosis (20–59, 60–79), calendar year of lung cancer diagnosis (1992–1996, 1997–2001, 2002–2007), time since lung cancer diagnosis (1–5 years and 5 years), and stage at lung cancer diagnosis (localized, regional)

^bTests for heterogeneity evaluated by comparing model fit with and without the inclusion of an interaction term between a given variable (using ordinal categories as continuous variables) and ER status.