Second Primary Lung Cancers Among Breast Cancer Patients Treated with Anti-estrogens Have a Longer Cancer-specific Survival

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Abstract. *Background/Aim: Estrogen is thought to play an important role in lung cancer carcinogenesis and progression. The incidence and survival of second primary lung cancer among breast cancer patients with and without anti-estrogen therapy were evaluated. Patients and Methods: All women diagnosed with breast cancer and treated at the Sun Yat-Sen Cancer Center between January 2000 and December 2009 were included and followed-up for occurrence and/or death from lung cancer until December 2011. Results: Twenty-six women developed second primary lung cancer among 6,361 breast cancer patients. All but one were adenocarcinoma and none had a smoking habit. Seventeen (65.4%) patients had previously received anti-estrogen treatment. The relative risk of developing second primary lung cancer among those who have received anti-estrogens for breast cancer and those who have not was 1.01 (95% confidence interval (CI)=0.45~2.28; p=0.970). Second primary lung cancer patients who have received anti-estrogens had a longer cancer-specific survival (p=0.007). The multivariate Cox proportional hazards analysis showed that anti-estrogen therapy remained an independent prognostic factor with a hazard ratio of 0.11 (95% CI=0.01~0.97, p=0.002) for second primary lung cancer patients. Conclusion: The results of this study further support the fact that estrogen adversely affects the prognosis of patients with lung cancer. However, the role of estrogen in lung cancer carcinogenesis remains to be determined.*

Abbreviations: EGFR, Epidermal growth factor receptor; ER, estrogen receptor; SEER: surveillance, epidemiology and end results; SIR, standardized incidence ratio.

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Estrogen is thought to play an important role in lung cancer carcinogenesis (1, 2). Estrogen receptors (ER) are consistently found in lung cancer tissues and lung cancer cell lines (especially adenocarcinoma) mostly in the form of ERβ. Estrogen has also been reported to adversely affect the prognosis of patients with lung cancer (3-8). The Vitamins and Lifestyle Study evaluated a prospective cohort of 36,588 peri- and post-menopausal women and reported that the use of estrogen-plus-progestin was associated with an increased risk of incident lung cancer and advanced stage at diagnosis in a duration-response manner after adjusting for smoking, age and other potential confounders (9). The Women's Health Initiative randomized controlled trial included 16,608 post-menopausal women and reported a 60% (hazard ratio (HR), 1.59, 95% confidence interval (CI)=1.03-2.46) increased risk of dying from non-small cell lung carcinoma among women in the hormone therapy arm versus women in the placebo arm (10). However, there are also several studies with conflicting results regarding the effect of estrogen on the risk and survival of lung cancer (11-18).

In current clinical practice, women with breast cancer provide a unique opportunity to examine the role of anti-estrogens on lung cancer incidence and survival because many of these women will receive anti-estrogens as part of their multimodality treatments. Bouchardy *et al*. reported a

reduced risk of lung cancer mortality among breast cancer patients treated with anti-estrogens in a population-based study in Geneva (19). In the current study, we evaluated breast cancer patients with second primary lung cancer treated at a 200-bed cancer center between January 2000 and December 2009. The effects of anti-estrogen therapy were examined.

Patients and Methods

Breast cancer patients. All women diagnosed with breast cancer who were registered in the Cancer Information System of Sun Yat-Sen Cancer Center between January 2000 and December 2009 were included. All were followed-up for the occurrence of lung cancer and/or mortality after the date of diagnosis of breast cancer until December 2011. Trained tumor registrars systematically extracted data from medical and laboratory records. Data including demographic information, method of detection, type of confirmation, tumor characteristics (coded according to the International Classification of Diseases for Oncology, ICD-O), hormone receptor status, tobacco smoking history, stage of disease at diagnosis, treatment, survival status and cause of death were recorded. Physicians were asked for missing clinical and therapeutic data. Pathological staging was based on the Union Internationale Contre le Cancer and American Joint Commission on Cancer Tumour, Node, Metastasis staging system. When absent, the clinical staging was used. Hormone receptor status was classified as positive or negative according to the Allred score combining proportional and intensity scores of immunohistochemical findings (20). Treatment was classified as surgery (mastectomy or breast-conserving surgery), radiotherapy (yes, no), chemotherapy (yes, no) and anti-estrogen therapy (yes, no). Tobacco smoking history was classified as never smokers, former smokers (defined as individuals who had stopped smoking for at least 1 year before the diagnosis of breast cancer) or current smokers. The pack-years of cigarette smoking were not routinely expressed.

Second primary lung cancer patients. The cohort of consecutive second primary lung cancer patients were clinically and pathologically staged and underwent homogenous treatment including video-assisted thoracic surgery, new chemotherapeutic agents, targeted-therapy and 3-dimensional conformal radiotherapy, as described previously (21). The index date was defined as the date of confirmation of the diagnosis of lung cancer or the date of hospitalization when it preceded the diagnosis and was related to the disease. Patients were actively followed-up after treatment until the end of the study. A Vital Health Statistics (Department of Health, Executive Yuan, Taiwan) was surveyed for the outcome of patients who were unavailable for follow-up (22). Only deaths attributed to second primary lung cancer were counted as events. Patients who were alive were censored at the date of last appointment. The institutional review board of the Sun Yat-Sen Cancer Center approved this study, as well as the database used to collect the data. All patients gave written informed consent before entering the study. The study was also approved by the local Ethics Committee and it was conducted in accordance with the ethical principles stated in the Declaration of Helsinki or the guidelines on good clinical practice.

Table I. *Patients' characteristics of breast cancer in Cancer Information System registry, 2000-2009*.

Variable	Anti-estrogen (+) (n=4,139)	Anti-estrogen (–) (n=2,222)	*p*-Value
Age, years	49.2±11.2	49.9±10.8	0.014
Stage			<0.001
0	354 (8.6%)	311 (14%)	
I	1335 (32.3%)	530 (23.9%)	
II	1606 (38.8%)	812 (36.5%)	
III	695 (16.8%)	414 (18.6%)	
IV	145 (3.5%)	125 (5.6%)	
History of smoking	192 (4.6%)	117 (5.3%)	0.268
Treatment			
Surgery	3693 (89.2%)	1840 (82.8%)	<0.001
Chemotherapy	2889 (69.8%)	1461 (65.8%)	<0.001
Radiotherapy	2265 (54.7%)	996 (44.8%)	<0.001
Estrogen receptor			<0.001
Positive	3881 (93.8%)	327 (14.7%)	
Negative	193 (4.7%)	1720 (77.4%)	
5-year survival rate	91.92%	80.14%	<0.001

*Data are presented as mean±SD.

Statistical analysis. The breast cancer patients with or without anti-estrogen treatment were compared by their clinical characteristics. The incidence of second primary lung cancer among the breast cancer patients was compared with that expected in the general population in Taiwan (22). The expected number of lung cancer cases was calculated on the basis of the lung cancer incidence in Taiwan for each 5-year age group and calendar year. The standardized incidence ratio (SIR) was then calculated by dividing the observed number by the expected number (23). Continuous data were presented as mean±standard deviation (SD) and categorical data were presented as numbers and percentages. Categorical data were compared by the Pearson's chi-square test. Hazard ratio was used to calculate the relative risk of developing second primary lung cancer among the breast cancer patients with or without anti-estrogen treatment and with or without positive ER immunohistochemistry staining based on the Pike estimate. Kaplan-Meier plots and log-rank tests were used to estimate the cancer-specific survival of breast cancer patients and second primary lung cancer patients. The stratified log-rank test was used to determine whether the use of anti-estrogen provided prognostic information beyond stage. The multivariate Cox proportional hazards analysis was conducted to determine whether the association between anti-estrogen treatment and cancer-specific survival of second primary lung cancer patients was independent of other prognostic factors, including age, stage, smoking history, the use of radiotherapy and chemotherapy for breast cancer, as well as ER status. A two-sided *p*-value of less than 0.05 was considered to be statistically significant. Analysis was performed using the statistical software package SAS, version 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Patients' demographics. The cohort included 6,361 breast cancer patients (Table I). Twenty-six women developed second primary lung cancer (Table II). The median interval

Table II. *Patients' characteristics (in order of the date of the diagnosis of lung cancer).*

No.	Age	Lung cancer pathology	Stage	Interval (months)	Breast cancer stage	R/T	C/T	ER status	Anti-estrogen use
1	47	LELC	IV	1	IV	–	+	(+)	(–)
2	65	Adenocarcinoma	IV	1	III	+	+	(–)	(–)
3	67	Adenocarcinoma	IV	23	I	–	–	(+)	(+)
4	40	Adenocarcinoma	I	43	I	+	+	(+)	(+)
5	58	Adenocarcinoma	I	20	III	+	+	(+)	(+)
6	60	Adenocarcinoma	III	15	II	+	+	(–)	(–)
7	75	Adenocarcinoma	III	2	III	+	+	(–)	(–)
8	63	Adenocarcinoma	III	18	I	+	–	(+)	(+)
9	58	BAC & AAH	I	71	III	+	+	(+)	(+)
10	48	Adenocarcinoma	IV	24	I	+	+	(+)	(+)
11	47	Adenocarcinoma	I	2	II	–	+	(–)	(–)
12	62	Adenocarcinoma	IV	42	II	+	+	(–)	(–)
13	70	Adenocarcinoma	I	3	I	–	–	(+)	(+)
14	53	Adenocarcinoma	I	39	II	–	+	(–)	(–)
15	40	multifocal BAC	IV	34	III	+	+	(+)	(+)
16	52	Adenocarcinoma	I	39	0	–	+	(+)	(+)
17	79	Adenocarcinoma	I	106	II	–	–	(+)	(+)
18	47	Adenocarcinoma	III	86	0	–	–	(+)	(+)
19	57	Adenocarcinoma	II	2	I	–	–	(–)	(–)
20	51	Adenocarcinoma	III	100	II	+	–	(+)	(+)
21	69	Adenocarcinoma	I	43	II	+	+	(+)	(+)
22	55	Adenocarcinoma & BAC	I	7	I	+	+	(+)	(+)
23	58	Adenocarcinoma	II	54	III	+	+	(–)	(–)
24	54	Adenocarcinoma	IV	98	II	+	+	(+)	(+)
25	76	Adenocarcinoma	I	28	0	–	–	(+)	(+)
26	71	Adenocarcinoma	III	46	II	–	+	(+)	(+)

AAH, Atypical adenomatous hyperplasia; BAC, bronchioloalveolar carcinoma; C/T, chemotherapy for breast cancer; ER, estrogen receptor; LELC, lymphoepithelial-like carcinoma; R/T, radiotherapy for breast cancer. *Interval means the time between diagnosis of breast cancer and lung cancer.

between the diagnosis of breast cancer and lung cancer was 2.5 years. Six women had synchronous cancers with an interval of less than 6 months. All lung cancers were detected by regular imaging studies including 22 with chest radiography, 3 with computed tomography and one with integrated positron emission tomography and computed tomography. Two had concurrent cough and 2 had bony pain related to metastasis. All had adenocarcinoma except for one with lymphoepithelial-like carcinoma. None had a history of smoking. The stage distribution appeared to be early migration compared with that reported in the same Cancer Information System lung cancer registry ($p<0.001$). Seventeen (65.4%) patients had previously received anti-estrogens for breast cancer, including 15 with tamoxifen (Nolvadex; AstraZeneca, London, UK) and two with anastrozole (Arimidex; AstraZeneca). The demographics and tumor characteristics were similar between the second primary lung cancer patients with and without previous anti-estrogen therapy. Compared to the general population in Taiwan during the same period, the SIR of developing lung cancer among the breast cancer patients was 1.63 (95% confidence interval (CI), 1.06-2.39).

Incidence of second primary lung cancer and anti-estrogens. The relative risk of developing second primary lung cancer among those who have received anti-estrogens for breast cancer and those who have not was 1.01 (95% CI=0.45-2.28; $p=0.970$). The relative risk of developing second primary lung cancer following ER-positive breast cancer compared with ER-negative breast cancer was 0.91 (95% CI=0.39-2.13; $p=0.831$).

Survival of second primary lung cancer and anti-estrogens. Breast cancer patients who have received anti-estrogens had a longer cancer-specific survival ($p<0.001$) (Figure 1). Second primary lung cancer patients who have received anti-estrogens for breast cancer had a longer cancer-specific survival ($p=0.007$) (Figure 2). The multivariate Cox proportional hazards analysis showed that anti-estrogen therapy remained an independent prognostic factor with a hazard ratio of 0.11 (95% CI=0.01-0.97, $p=0.002$) for second primary lung cancer patients.

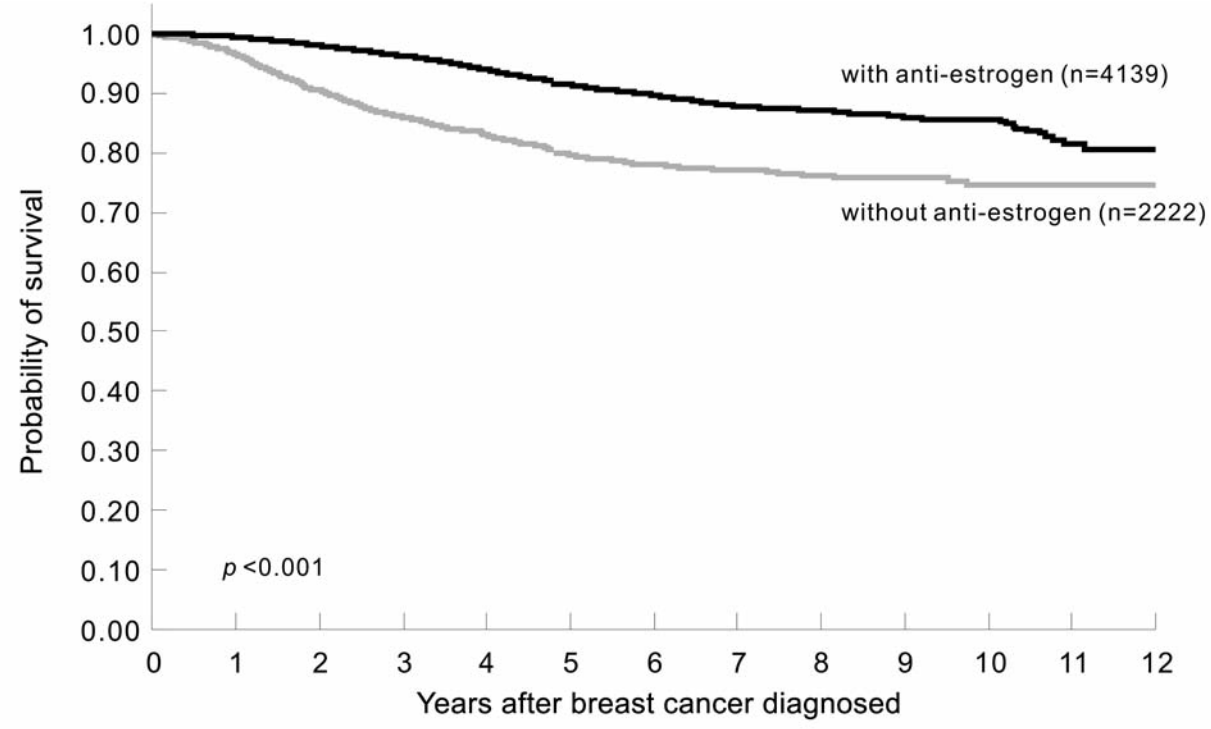

Figure 1. *Kaplan-Meier survival estimates in breast cancer patients with or without anti-estrogen treatment.*

Discussion

This study included 26 consecutive patients with second primary lung cancer among all registered breast cancer patients between January 2000 and December 2009. Detailed clinical and pathological staging were available for the 26 patients. All presented to one referral cancer center from several regions in Taiwan and were treated with homogenous protocols (21). Missing data were avoided by prospective enrollment and only deaths attributed to the second primary lung cancer were counted as events. The type, dosage and duration of anti-estrogen therapy followed a uniform protocol, although lung cancer developed at various times during anti-estrogen therapy. All but one had adenocarcinoma and none of them had a history of smoking, which excluded the confounding effect of histology and tobacco smoking on survival analysis. The distribution of histology and prevalence of smoking history were similar to women with lung cancer in our previous study (21) using the same Cancer Information System lung cancer registry and Taiwan general population. The prevalence of cigarette and other tobacco use of women aged over 18 years in Taiwan were reported to be between 2.3% and 5.3% since 1973.

The breast cancer post-treatment follow-up program included chest radiography that simulated the lung cancer screening protocol. The lead time and length bias may have accounted for the higher incidence of lung cancer compared with the general population in Taiwan and earlier stage compared with the same lung cancer registry. Compared with their Western counterparts, the low prevalence of smoking history and high incidence rate of adenocarcinoma constitute distinctive characteristics of lung cancer in Taiwanese females and suggest non-tobacco related risk factors in the pathogenesis of lung cancer, such as genetic, molecular and hormonal differences (24, 25). Similar to the study of Patel *et al*. (26), we found no significant association between the incidence of lung cancer and anti-estrogen therapy. The use of anti-estrogen is directed by the ER status of breast cancer according to the breast cancer treatment guideline. As expected, we also found that second primary lung cancer risk did not vary by the ER status. However, Schonfeld *et al*. have reported an increased incidence of lung cancer among women with ER-negative breast cancer as compared to ER-positive breast cancer using data from the Surveillance, Epidemiology and End Results (SEER) Program (27). Such difference may be explained by the smaller sample size with a shorter follow-up of our study, different lung cancer patients' characteristics between the Asian and Western populations (higher prevalence of smoking history in the latter) and lack of smoking record in the SEER registries. However, as most ER-

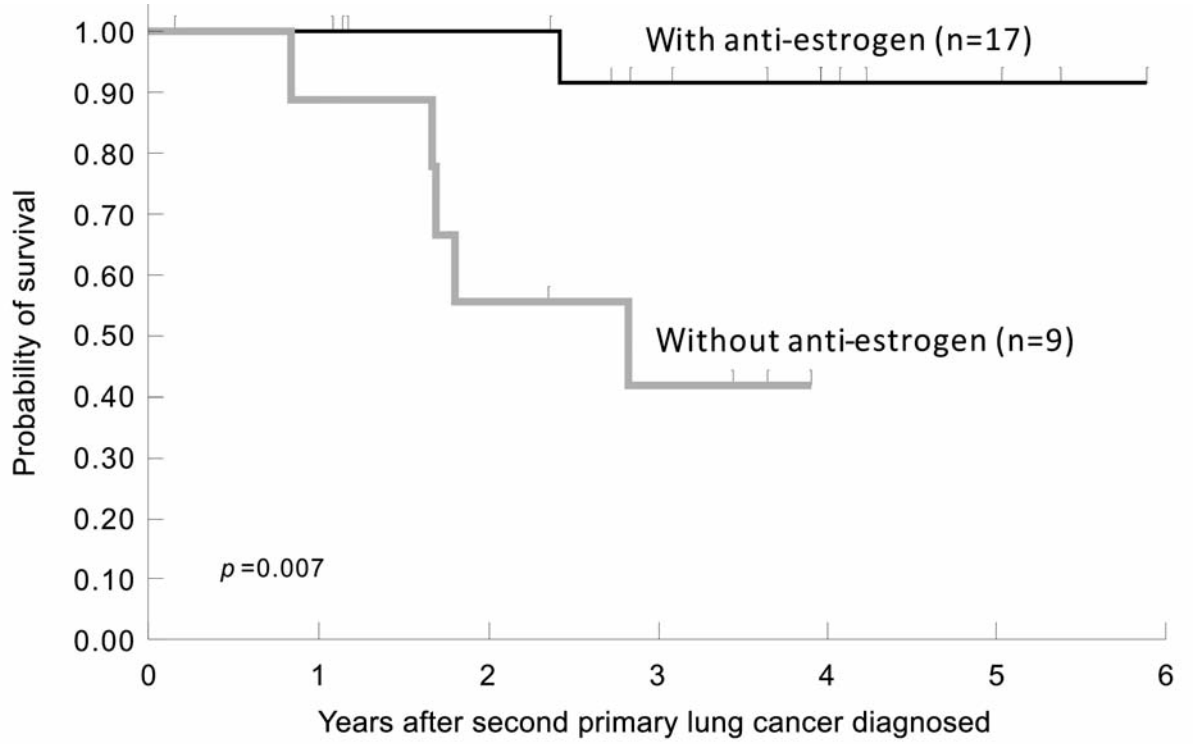

Figure 2. *Kaplan-Meier survival estimates in second primary lung cancer patients with or without anti-estrogen treatment for breast cancer*

positive breast cancer patients will receive anti-estrogen, the study of Schonfeld *et al*. implies some inhibitory effect of anti-estrogen on lung cancer carcinogenesis.

Second primary lung cancer patients who have received anti-estrogens for breast cancer appeared to have a significantly longer cancer-specific survival. Although breast cancer patients treated with anti-estrogen were younger with earlier stage (Table I) and had a longer cancer-specific survival (Figure 1), the multivariate analysis still confirmed that anti-estrogen therapy was an independent prognostic factor for second primary lung cancer patients. The results were consistent with the study of Bouchardy *et al*. (19). Just recently, Lother *et al*. directly compared members of a lung cancer population in the Manitoba Cancer Registry, Canada, based on the use of anti-estrogens not restricted to breast cancer and also demonstrated a strongly protective effect of anti-estrogen (28). To our knowledge, this is the first study to report a similar observation with that in the Asian population from an endemic area of lung adenocarcinoma. These findings reinforced the evidence that estrogen plays a key role in lung cancer progression.

Drugs targeting the estrogen signaling pathway have been shown to suppress the growth of lung cancer cells in both *in vivo* and *in vitro* studies (4, 29, 30). A combination of an ER antagonist and an epidermal growth factor receptor (EGFR) antagonist has been reported to decrease cell proliferation and tumor growth more than individual treatment in both *in vitro* and *in vivo* studies (30-33). We previously examined the epidemiological evidence, explored the characteristics of ER in lung adenocarcinoma and investigated the effects of estrogen in cancer cells migration (34). An estrogen cancer-promoting effect is supposed to be responsible for the more advanced disease and shorter survival in the premenopausal among female never-smoking adenocarcinoma patients. ERβ was found to be the predominant receptor type in lung cancer cell lines. Estrogen up-regulates osteopontin expression and promotes lung cancer cell migration via the MEK-ERK signaling pathway, which is a common downstream pathway with EGFR activation. An additive effect of ER antagonists and EGFR antagonists on the inhibition of lung cancer cell migration was noted. Stabile *et al*. reported that EGFR protein expression was down-regulated in response to estrogen and up-regulated in response to anti-estrogens *in vitro*. Conversely, ERβ expression has been reported to be decreased in response to epidermal growth factor and increased in response to gefitinib (31). A strong association between the expression of *ERβ* and *EGFR* mutations in adenocarcinoma of the lung has also been reported (35, 36). Therefore, there seems to be a

functional interaction between the ER and EGFR pathways providing a rationale to use combined therapy (37, 38). Anti-estrogens may become a new effective treatment modality for patients with lung adenocarcinoma and possibly an alternative treatment for patients with acquired resistance to EGFR antagonists (39, 40).

There are some limitations to this study. The small number of events is subjected to random variation and low statistical power. On the other hand, although we accurately used cancer-specific survival to analyze the 26 second primary lung cancer patients, the impact of heterogeneity between ER-positive and ER-negative breast cancers should be taken into consideration.

Conflicts of Interest

The Authors declare that they have no competing interests.

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