

Differences in Histology between First and Second Primary Lung Cancer¹

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Abstract

Data from the Surveillance, Epidemiology, and End Results (SEER) Program were used to compare the histological distribution of second lung cancer following an initial cancer of the lung, head and neck, and breast to primary lung carcinoma occurring as a first cancer.

Following initial head and neck cancer or initial squamous cell carcinoma of the lung, the proportion of second primary lung cancer which was of squamous cell histology rose dramatically, while the proportion of pulmonary adenocarcinomas rose following initial adenocarcinoma of the lung. The histological distribution of lung cancer following an initial breast cancer in women was similar to the distribution of *de novo* lung cancer in women. These results persisted as the time interval between diagnosis of the two primaries was increased from 12 to 48 months.

We conclude that the histology of a second primary lung cancer following an initial cancer of the lung or head and neck tends to repeat the histology of the initial cancer (field effect), and this observation is not likely to be due to misdiagnosis of a recurrence of the initial cancer.

Introduction

Lung cancer typically occurs in one of three major histological subtypes or one of several minor subtypes. In most series, adenocarcinoma constitutes 22–28% of all lung cancers, squamous cell carcinoma comprises 28–34%, and small cell carcinoma comprises 15–22% (1–3). The natural history of the disease, its response to treatment, and the survival of the patient are strongly dependent on the histology of the malignancy (4).

Following a first primary carcinoma which is associated with cigarette smoking, there is known to be a higher than expected incidence of lung cancer occurring as a second neoplasm, in particular following a carcinoma of the head and neck (5–8) or of the lung (9–12). This study seeks to explore whether lung carcinoma occurring as a second primary neoplasm has the same histological distribution as lung cancer occurring as a first primary neoplasm.

Materials and Methods

The Surveillance, Epidemiology, and End Results Program (SEER)³ of the National Cancer Institute collects clinical, demographic, and outcome information on all neoplasms in ten tumor registries from various defined areas around the United States, comprising approximately 10% of the U.S. population. This database has been previously described in detail (13). We analyzed SEER data for a time interval starting January 1, 1973 and ending December 31, 1986.

Our analysis focused on patients with two primary cancers, the second of which was primary in the lung, and the first of which was a primary breast cancer, a head and neck cancer, or a primary lung cancer. Any second neoplasm in an individual for which data on the first neoplasm were not in the registry was excluded, as were all third or later neoplasms. When the first primary cancer was metastatic or of unknown stage, the individual's second tumor was excluded from analysis in order to decrease the likelihood that a second neoplasm was, in fact, a recurrence of the first tumor.

Lung cancer was identified by an International Classification of Disease-Oncology site code of 162.1–162.9. Head and neck cancer included malignancies of the oral cavity, lip, pharynx, hypopharynx, larynx and nasopharynx (site codes 140, 141, 143–149, and 161), excluding salivary gland cancer. More than 95% of the head and neck cancers were squamous cell in type. Female breast cancer cases were defined by a site code of 174.0–174.9. For information on the histology of the lung cancer, we relied on the registry's coding. Lung cancer histology was classified as squamous cell, adenocarcinoma (excluding bronchoalveolar), small cell carcinoma, and all other carcinoma types. Because we were primarily interested in metachronous tumors, we excluded second lung cancers occurring within the first 12 months after diagnosis of the first primary tumor. Cancers which were diagnosed by autopsy or death certificate were also excluded.

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³ The abbreviation used is: SEER, Surveillance, Epidemiology, and End Results Program.

Table 1 Histological classification of primary lung carcinoma occurring as a first cancer in women and as a second cancer following initial primary carcinoma of the breast, SEER database (numbers in parentheses)

Histological classification	First primary carcinoma of the lung	Carcinoma of the lung as second primary cancer following initial primary carcinoma of the breast		
		>12 months between diagnoses	>24 months between diagnoses	>48 months between diagnoses
Squamous cell carcinoma	20.0% (6,687)	25.1% (100)	23.8% (77)	22.3% (43)
Adenocarcinoma	36.6% (12,270)	31.7% (126)	33.8% (109)	32.6% (63)
Small cell carcinoma	19.3% (6,477)	16.8% (67)	16.7% (54)	18.7% (36)
Other and carcinoma not otherwise specified	24.1% (8,062)	26.4% (105)	25.7% (83)	26.4% (51)
Total	100.0% (33,496)	100.0% (398)	100.0% (323)	100.0% (193)
χ^2		10.043	4.618	1.838
P		0.018	NS ^a	NS

^a NS, not significant.

Table 2 Histological classification of primary lung carcinoma occurring as a first tumor and as a second primary carcinoma following initial primary carcinoma of the head and neck, SEER database (numbers in parentheses)

Histological classification	First primary carcinoma of the lung	Carcinoma of the lung as second primary cancer following initial primary carcinoma of the head and neck		
		>12 months between diagnoses	>24 months between diagnoses	>48 months between diagnoses
Squamous cell carcinoma	30.9% (34,449)	50.8% (371)	49.7% (288)	44.8% (146)
Adenocarcinoma	28.4% (31,738)	17.8% (130)	18.0% (104)	20.9% (68)
Small cell carcinoma	17.1% (19,102)	14.3% (104)	14.9% (86)	15.3% (50)
Other and carcinoma not otherwise specified	23.6% (26,327)	17.1% (125)	17.4% (101)	19.0% (62)
Total	100.0% (111,616)	100.0% (730)	100.0% (579)	100.0% (326)
χ^2		138.440	99.506	30.429
P		<0.0001	<0.0001	<0.0001

Tables were prepared using the SAS statistical package (14). Statistical significance was assessed by χ^2 testing, comparing the histological distribution among second primary cancers to that of *de novo* lung cancer, as appropriate.

Results

In the SEER database, 111,616 first lung cancers were classified by histology to compare to the second primary lung cancers. There were 398 second primary lung cancers following 114,199 breast cancers, 730 second primary lung cancers following 31,612 head and neck can-

cers, and 405 second primary lung cancers following 62,829 nonmetastatic primary lung cancers.

Table 1 shows the histological breakdown of the second lung cancers following an initial nonmetastatic breast cancer, as compared to the histological breakdown of *de novo* primary lung cancer in women. The histological distribution does not appear to change dramatically.

In Table 2, the histological breakdown of second primary lung cancer following an initial nonmetastatic cancer of the head and neck is compared to *de novo* lung cancer. It is striking that the percentage of squamous cell malignancies has increased from 30.9% of the first

Table 3 Histological classification of primary lung carcinoma occurring as a first tumor and as a second primary carcinoma following initial primary squamous cell carcinoma of the lung, SEER database (numbers in parentheses)

Histological classification	First primary carcinoma of the lung	Carcinoma of the lung as second primary cancer following initial squamous cell carcinoma of the lung		
		>12 months between diagnoses	>24 months between diagnoses	>48 months between diagnoses
Squamous cell carcinoma	30.9% (34,449)	50.0% (80)	50.4% (68)	51.2% (44)
Adenocarcinoma	28.4% (31,738)	15.0% (24)	15.6% (21)	15.1% (13)
Small cell carcinoma	17.1% (19,102)	20.0% (32)	18.5% (25)	18.6% (16)
Other and carcinoma not otherwise specified	23.6% (26,327)	15.0% (24)	15.6% (21)	15.1% (13)
Total	100.0% (111,616)	100.0% (160)	100.0% (135)	100.0% (86)
χ^2		34.863	28.325	19.556
P		<0.0001	<0.0001	<0.0001

Table 4 Histological classification of primary lung carcinoma occurring as a first tumor and as a second primary carcinoma following initial primary adenocarcinoma of the lung, SEER database (numbers in parentheses)

Histological classification	First primary carcinoma of the lung	Carcinoma of the lung as second primary cancer following initial primary adenocarcinoma of the lung		
		>12 months between diagnoses	>24 months between diagnoses	>48 months between diagnoses
Squamous cell carcinoma	30.9% (34,449)	19.0% (31)	20.6% (27)	25.6% (20)
Adenocarcinoma	28.4% (31,738)	52.2% (85)	53.4% (70)	51.3% (40)
Small cell carcinoma	17.1% (19,102)	10.4% (17)	8.4% (11)	7.7% (6)
Other and carcinoma not otherwise specified	23.6% (26,327)	18.4% (30)	17.6% (23)	15.4% (12)
Total	100.0% (111,616)	100.0% (163)	100.0% (131)	100.0% (78)
χ^2		45.655	41.020	21.258
P		<0.0001	<0.0001	<0.0001

lung cancers to 50.8% of the second lung cancers following head and neck cancers.

The histological breakdown of the 160 second primary lung cancers following an initial squamous cell cancer of the lung is given in Table 3. Again it can be observed that the percentage of squamous cell carcinoma has increased markedly to 50.0%. It can also be seen in Table 4 that for the 163 lung cancers which follow a first primary adenocarcinoma of the lung, 52.2% of the second lung cancers were adenocarcinoma as well.

There were too few cases of second primary lung cancer following an initial small cell lung cancer to undertake a similar analysis because of its high mortality.

A possible problem in the interpretation of these results is that the second primary lung cancer may really

represent a recurrence of the first tumor. Therefore, we looked at second primary lung cancers which occur after 2 years and 4 years, and reasoned that we should observe the disappearance of the increases in squamous cell and adeno histologies following the first squamous cell and adeno histologies if, in fact, the increases were the result of a misdiagnosed recurrence. However, if the second neoplasm were, in fact, a new primary, then the increases following squamous cell malignancies and of adenocarcinomas following adenocarcinomas should persist.

When the histology of metachronous lung cancer following 24-month and 48-month time intervals is examined, the histological distribution is similar to that observed following a 12-month time delay (Tables 1–4). Recurrences of head and neck cancer or lung cancer will

almost always do so by 3 years following diagnosis (4, 15). Therefore, our observations cannot be explained as purely misdiagnosis of a recurrence.

Discussion

Multiple primary neoplasms constitute almost 10% of all tumors collected in the SEER database (13). Careful study of multiple primary neoplasms can be utilized to shed light on the etiology, natural history, and biology of cancer. An earlier case series from Japan (16) found an increase in the percentage of second lung cancers which are squamous cell in type following first squamous cell cancers of the lung.

Using population-based data, with much larger sample sizes, we have confirmed that finding and shown that the proportion of second primary squamous cell lung cancers is increased following head and neck cancers. In addition, following a first adenocarcinoma of the lung, there is a much greater likelihood that a second primary lung cancer will also be adenocarcinoma in type.

These results suggest that the histology of the second primary lung cancer tends to repeat the histology of the initial respiratory tract malignancy. One possible explanation is that there is a bias on the part of the pathologist to repeat the histology of the initial malignancy. However, the results following female breast cancer do not support this conclusion.

A second possibility is that these second lung cancers are in fact recurrences of the initial tumor. To minimize this, we excluded second cancers in the first year and excluded metastatic first primary cancer. Our results with initial breast cancer (Table 1) suggest that there was no confusion with recurrent breast cancer, since the proportion of adenocarcinoma of the lung was not elevated. Furthermore, almost all recurrences occur within 3 years (4, 15), and the observed proportions persisted after 4 years (Tables 1–4). Thus we do not feel that recurrences played a major role in our findings.

The results suggest that those who form a first squamous cell malignancy within the respiratory tract are predisposed to develop a second primary squamous cell malignancy, while those who develop an adenocarcinoma will likewise be predisposed to develop a second adenocarcinoma within the respiratory tree. This may reflect the impact of cigarette smoking or other carcinogens on the mucosa of the respiratory tract (17). This "field effect" has long been recognized in lung and other cancers (18, 19).

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