Bronchioloalveolar carcinoma is not associated with younger age at diagnosis: An analysis of the SEER database

Dan J. Raz, MD, and David M. Jablons, MD

**Introduction:** Bronchioloalveolar carcinoma (BAC) is a unique subtype of non-small cell lung cancer (NSCLC) that is associated with female gender, Asian ethnicity, and never-smoking status. Although BAC is commonly reported to occur more frequently in young people with lung cancer, there is a lack of evidence to support this association.

**Methods:** We analyzed the association between age at diagnosis and NSCLC histology among 293,417 incident cases of NSCLC in the Surveillance, Epidemiology, and End Results (SEER) database during the years 1973 to 2002.

**Results:** The mean age of patients with BAC (66.99 years) was similar to the mean age of all patients with NSCLC (66.44 years). The proportion of patients younger than 50 years of age was significantly smaller among patients with BAC than the overall cohort (6.06% compared with 6.90%). Although a greater percentage of women and Asian patients with lung cancer were younger than 50 years old, the proportion of patients with BAC was similar to the proportion of men and non-Asians with BAC. Finally, the prevalence of BAC histology among patients younger than 50 years did not change significantly after revision of the 1999 World Health Organization pathologic criteria for the diagnosis of BAC (risk ratio 0.93 versus 0.87, \( p = 0.31 \)).

**Conclusion:** BAC is not associated with a younger mean age at diagnosis, nor is it associated with an age of less than 50 years at diagnosis. Patients with mixed BAC probably have similar age characteristics compared with patients with pure BAC.

**Key Words:** Bronchioloalveolar carcinoma, Epidemiology, Age, Lung cancer.

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Bronchioloalveolar carcinoma (BAC) is a subtype of non-small cell lung carcinoma (NSCLC) with a unique histopathology, tumor biology, clinical course, and response to treatment. Interest in BAC has grown amid reports that the incidence of BAC may be rising\(^1\)\(^2\) and that BAC histology may predict response to the epidermal growth factor tyrosine kinase inhibitors gefitinib (Iressa; AstraZeneca Pharmaceuticals, Wilmington, DE) and erlotinib (Tarceva; OSI Pharmaceuticals, Melville, NY).\(^3\)--\(^5\) Patients with BAC are more likely to be women, Asians, and never-smokers compared with patients with other subtypes of NSCLC.\(^3\)--\(^8\)

There is a prevailing notion that BAC disproportionately affects younger patients; however, there is no strong evidence that patients with BAC are younger than those with other subtypes of NSCLC, nor is there evidence that younger patients with lung cancer are more likely to have BAC. Whereas several single-institution series have reported a younger mean age for BAC compared with other NSCLC histologies,\(^2\)--\(^9\),\(^10\) other series have shown no difference in mean age.\(^11\)--\(^12\) In one of the most widely cited studies on the epidemiology of BAC, Barsky et al.\(^2\) reported a mean age of 59 years among 187 patients with BAC, which was significantly lower than the mean age of 64 years for patients with non-BAC adenocarcinomas. Meanwhile, Read et al.\(^13\) found no difference between the mean age of patients with BAC compared with all patients with lung cancer in the Surveillance Epidemiology and End Results (SEER) database through 1998. Data from another population-based study of patients in a large cancer registry also suggest that the mean age among patients with BAC is similar to the mean age of patients with other subtypes of NSCLC.\(^14\) No large series specifically examining the possible association between patient age and lung cancer histology has been recently published.

We used the SEER database to determine whether patients with BAC were younger than other patients with lung cancer and whether young people with lung cancer were more likely to have BAC. Because BAC is associated with female gender and Asian ethnicity, we also wanted to determine whether women and Asians were more likely to be younger than men and non-Asians and whether there was any interaction with gender or ethnicity in the possible association between BAC and younger age. Finally, we examined whether there were temporal trends in the age at diagnosis of patients with BAC during the almost 30-year period captured in the SEER database. Specifically, we wanted to determine whether age characteristics changed in 1999, when the World Health Organization revised the criteria for the diagnosis of
BAC, restricting the diagnosis to tumors without any histologic invasion.15

MATERIALS AND METHODS

We used SEER public-use data (1973–2002), released April 2005, and downloaded from http://seer.cancer.gov. The database is maintained by the National Cancer Institute, and the catchment areas for the database have been expanded successively since 1972. More information on the geographic areas included in the database can be found on the SEER website.

Tumor histology in the database are classified by International Classification of Disease 0-3 codes. Histology codes were categorized by major NSCLC histology subgroup as follows: BAC (8250-8255), adenocarcinoma (non-BAC: 8140-8141, 8143, 8147, 8250-8255, 8260, 8480-8481, 8550-8551, 8560, 8562), squamous cell carcinoma (8050-8052, 8070-8078), and other NSCLC (8012, 8013, 8020-8022, 8030, 8031, 8046). The vast majority of tumors in the “other NSCLC” category were large cell carcinoma and undifferentiated NSCLC. Based on these histologic diagnoses, we identified 293,417 patients with NSCLC, of whom 13,859 had BAC. Patients were categorized as Asian or non-Asian based on ethnicity information in the SEER database.

Data were analyzed using STATA version 9.1. Mean age of diagnosis was determined for the entire cohort and for each major histology group. Mean age for each major histology group was determined for female NSCLC patients and Asian NSCLC patients. Mean ages were compared using an analysis of variance followed by the Holmes-Sidak t-test to isolate differences.

The incidence of BAC and the other major histologic subtypes of NSCLC was stratified by decade of age for comparison. Patients were then stratified by age younger than 50 years to look for a difference in incidence among histologic subtypes and by race and gender. A cutoff of 50 years was used after consensus with lung cancer practitioners at our institution as best describing the age at which patients with lung cancer are considered young. Risk ratios for the major histologic subtypes of NSCLC were calculated and compared with the reference risk ratio (all cases of NSCLC) using the Pearson $\chi^2$ test.

The incidence of BAC among women and Asians was stratified by age younger than 50 years. The Pearson $\chi^2$ test was used to compare incidence between men and women, and Asians and non-Asians. A multiple logistic regression was performed to model predictors of BAC incorporating available variables in the database, including age younger than 50 years, gender, and Asian ethnicity. Odds ratios and 95% confidence intervals (CIs) were calculated.

The incidence of BAC among all patients, as well as patients younger than 50 years, during each year for which the SEER database reported data (1973–2002) was calculated to assess for temporal trends. Data were then stratified by years 1973–1998 and 1999–2002 to determine whether there were changes in the age distribution of patients with BAC before and after the World Health Organization revised its diagnostic criteria in 1999. Overall and NSCLC subtype-specific mean ages were calculated and compared between the two time periods using a paired t-test. The proportion of patients younger than 50 years was calculated in the entire cohort and among the histologic subtypes and compared between the two time periods using the Pearson $\chi^2$ test. Risk ratios for age younger than 50 years were determined for each histology subtype and stratified by time period. Strata-specific risk ratios were compared using the Mantel-Hanzel test of homogeneity.

RESULTS

The mean ($\pm$SD) age of the 293,417 patients with NSCLC was 66.44 $\pm$ 10.77 years; it was 66.99 $\pm$ 10.66 for the 13,859 patients with BAC. Mean ages for the other major histologic subtypes are listed in Table 1. The mean ages were not meaningfully different, although they were statistically significantly different because of the large sample size.

The percentage of patients younger than 50 years of age was determined in the entire cohort and among each major histology group and is summarized in Table 1. Overall,

<table>
<thead>
<tr>
<th>Age at diagnosis (years)</th>
<th>All NSCLC</th>
<th>BAC</th>
<th>Adenocarcinoma</th>
<th>Squamous cell</th>
<th>Other NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>All NSCLC</td>
<td>66.44 $\pm$ 10.77</td>
<td>66.99 $\pm$ 10.66</td>
<td>65.59 $\pm$ 11.26</td>
<td>67.63 $\pm$ 9.96</td>
<td>65.77 $\pm$ 11.05</td>
</tr>
<tr>
<td>Patients &lt;50 years of age (%)</td>
<td>All NSCLC</td>
<td>BAC</td>
<td>Adenocarcinoma</td>
<td>Squamous cell</td>
<td>Other NSCLC</td>
</tr>
<tr>
<td>6.90</td>
<td>6.06</td>
<td>8.64</td>
<td>4.45</td>
<td>8.26</td>
<td></td>
</tr>
<tr>
<td>Risk ratio (95% CI)*</td>
<td>1.00</td>
<td>0.88 (0.82–0.94)</td>
<td>1.28 (1.26–1.29)</td>
<td>0.63 (0.61–0.64)</td>
<td>1.21 (1.18–1.25)</td>
</tr>
<tr>
<td>p value*</td>
<td>0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

NSCLC, non-small cell lung cancer; BAC, bronchioloalveolar carcinoma. * Risk of NSCLC among patients younger than 50 years of age compared with all patients with NSCLC. *p value is for the $\chi^2$ test for which the calculated risk ratio differs from 1.0.
6.90% of patients with NSCLC were younger than 50 years, compared with 6.06% of patients with BAC and 8.64% of patients with adenocarcinoma. Among patients with NSCLC, those with BAC were less likely to be younger than 50 years (RR 0.88, 95% CI 0.82–0.94; p = 0.0001), whereas those with adenocarcinoma were more likely to be younger than 50 years (RR 1.28, 95% CI 1.26–1.29; p < 0.0001).

Next we analyzed the age at diagnosis of women and Asians with lung cancer, because these characteristics are known to be associated with BAC histology (Table 2). The mean age of the 108,482 women in the cohort was 66.33 ± 11.27, and the mean age of the 7,445 women with BAC was 66.86 ± 10.94. The mean age of the 15,908 Asians in the cohort was 66.74 ± 11.61, and the mean age of the 1,215 Asians with BAC was 66.47 ± 11.29. Women and Asians with lung cancer were more likely to be younger than 50 years at diagnosis. Of the women with NSCLC, 8.04% were younger than 50 years, while 6.81% of women with BAC were younger than 50 years, and 9.51% of women with adenocarcinoma were younger than 50 years. Of Asians with NSCLC, 8.33% were younger than 50 years, while 7.82% of Asians with BAC were younger than 50 years, and 9.71% of Asians with adenocarcinoma were younger than 50 years. However, race and gender did not modify the risk of being younger than 50 years among patients with BAC. In other words, women and Asians younger than 50 years were no more likely to have BAC than men or non-Asians (test of homogeneity: p = 0.47 for Asian ethnicity, p = 0.95 for female gender).

We performed multivariate analysis of the risk of BAC histology, adjusting for female gender, Asian race, and age younger than 50 years (Table 3). Patients with BAC were more likely to be female (adjusted odds ratio [OR] 2.06, 95% CI 1.99–2.14) and Asian (adjusted OR 1.76, 95% CI 1.66–1.97) but actually less likely to be younger than 50 years (OR 0.82, 95% CI 0.77–0.88).

The incidence of the major histologic subtypes of NSCLC was further stratified by decade of age (Figure 1).

The proportion of patients with BAC and the proportion of patients with BAC younger than 50 years of age were determined yearly from 1973 to 2002 (Figure 2). Data were then stratified by histologic subtype and by years 1973–1998 (n = 238,313) and 1999–2002 (n = 55,104) to examine for any effect of the revised World Health Organization histologic criteria for BAC in 1999 (Table 4). The overall and histologic subtype specific mean ages were slightly higher during 1999–2002 (68.39 versus 65.99 years among all patients with NSCLC and 68.64 versus 66.52 years among patients with BAC). The percentage of patients younger than 50 years during 1999–2002 was lower in the entire cohort and for each histologic subtype (5.82% versus 7.15% among all patients with NSCLC; 5.53% versus 6.27% among patients with BAC). When stratified by time period, the RR of BAC among patients younger than 50 years was not significantly different: 0.87 (95% CI 0.80–0.94) for 1973–1998 compared with 0.95 (95% CI 0.81–1.10) for 1999-2002 (p = 0.31). The RR of adenocarcinoma among patients younger than 50 years was also not significantly different (1.28 versus 1.27, p = 0.50).

**DISCUSSION**

Our findings, using a very large multi-institutional cohort of patients with lung cancer, provide strong evidence that BAC is not associated with younger age at diagnosis. The mean age of patients with BAC was not meaningfully different from other subtypes of lung cancers, confirming data from Read et al. and Zell et al. The proportion of patients with BAC who were younger than 50 years of age at diagnosis was slightly less than the proportion of patients younger than 50 years of age with all types of NSCLC. Similarly, when we stratified the patients by gender and Asian ethnicity, we found no difference in the mean age or in the proportion of patients younger than 50 years of age with all types of NSCLC. In a multivariate model of BAC incorporating gender, ethnicity, and age, age younger than 50 years was not significantly associated with increased risk of BAC histology among patients with lung cancer. Whereas women and Asians are more likely to have BAC, young patients with lung cancer actually have a slightly decreased chance of having BAC and have a higher chance of having non-BAC adenocarcinoma.
There was also no meaningful change in the percentage of patients with BAC younger than 50 years between 1973 and 2002. There has actually been a slight decrease in the rate of lung cancers in patients younger than 50 years reported in the SEER database since 1998.

An important limitation of the SEER database is that histologic diagnoses cannot be confirmed by independent pathologists. Because patients are entered into the database based on histology diagnosis code, we would expect that the diagnosis of BAC applies only to patients with pure BAC, as opposed to mixed BAC and adenocarcinoma. This classification scheme accounts for the relatively low proportion of

<table>
<thead>
<tr>
<th>TABLE 3. Multivariate model of predictors of BAC histology</th>
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<tr>
<td>Odds ratio (95% CI)</td>
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<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Age &lt;50 years</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Asian ethnicity</td>
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</tbody>
</table>

CI, confidence interval.

| FIGURE 1. Percentage of NSCLC major histologic subtypes within each age group. A total of 293,417 patients with non-small cell lung cancer from the SEER database were included. |

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<table>
<thead>
<tr>
<th>TABLE 4. Comparison of data by time period</th>
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<tr>
<td>Mean Age (±SD)</td>
</tr>
<tr>
<td>All NSCLC</td>
</tr>
<tr>
<td>BAC</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
</tr>
</tbody>
</table>

| Patients <50 years (%)                   | 1973–1998 (n = 17,042) | 1999–2001 (n = 3,207) | \( p \) value† |
| All NSCLC                                | 7.15                   | 5.82                   | <0.001 |
| BAC                                      | 6.27                   | 5.53                   | <0.001 |
| Adenocarcinoma                           | 8.98                   | 7.25                   | <0.001 |

| RR among patients <50 years              | (RR [95% CI]) §        | 1973–1998               | 1999–2001               | \( p \) value‡ |
| BAC                                      | 0.87 (0.80–0.94)       | 0.95 (0.81–1.10)        | 0.31                   |
| Adenocarcinoma                           | 1.28 (1.26–1.30)       | 1.27 (1.22–1.31)        | 0.5                    |

NSCLC, non-small cell lung cancer; BAC, BAC, bronchioloalveolar carcinoma; CI, confidence intervals. *\( p \) value is for a paired \( t \)-test that tests the hypothesis that mean age was the same within groups. †\( p \) value is for a \( \chi^2 \)-test that tests the hypothesis that the percentage of patients younger than 50 years was the same within groups. ‡\( p \) value is for the Mantel-Haenszel test of homogeneity comparing time-specific risk ratios. §Risk ratios (RR) compare incidence among patients younger than 50 years compared with patients older than 50 years.
patients with BAC compared with several small published series that estimate the incidence of BAC, both pure and mixed, to be closer to 20%.1,2,7 Our results are valid for patients with pure BAC. Although it does not seem plausible that patients with mixed BAC and adenocarcinoma would be younger than patients with pure BAC, patients with adenocarcinoma in this study were more likely to be younger than 50 years old at diagnosis than any other histology group. The age breakdown of patients with mixed BAC histology who were classified as having adenocarcinoma is unknown.

To determine whether patients with mixed BAC (classified as adenocarcinoma) differed in age from patients with pure BAC (classified as BAC), we stratified patients according to diagnosis before and after 1999, the year that the World Health Organization criteria for BAC were revised to exclude patients with an invasive component from being diagnosed with BAC. We would expect that more patients diagnosed before 1999 would have histologically mixed BAC. Thus, if mixed BAC was associated with age younger than 50 years, we would expect that the risk of BAC among patients younger than 50 years in this very large cohort would be greater before 1999. This was a strategy similar to that used by Zell et al.14 in their population-based study examining the survival of patients with BAC before and after the revision of World Health Organization pathologic criterion for BAC in 1999. We found that there was no significant difference in risk of BAC among patients with lung cancer younger than 50 years before and after 1999; in fact, there was a trend toward a greater risk of BAC after 1999.

The lack of a World Health Organization-sanctioned pathologic diagnosis for mixed BAC and adenocarcinoma has resulted in non-uniform classification schemes in the literature as well as in cancer registries and the SEER database.16–18 As a result, it is difficult to conduct multi-institutional epidemiologic research into the apparent increase in incidence of BAC, clinical research about the response of patients with BAC to treatment, and basic science research about the unique biology of BAC without a universally accepted classification scheme for both pure and mixed BAC.

Although our data suggest that BAC is not associated with younger age at diagnosis, patients with adenocarcinoma were more likely to be younger than 50 years compared with patients with other histologic subtypes (RR 1.28, p < 0.0001), and women and Asians with adenocarcinoma were more likely to be younger than 50 years than men and non-Asians. The etiology of the predisposition of younger patients, especially women and Asians, to develop adenocarcinoma rather than squamous cell carcinoma is unknown and warrants further investigation.

REFERENCES