Distinctive Characteristics of Non-small Cell Lung Cancer (NSCLC) in the Young

A Surveillance, Epidemiology, and End Results (SEER) Analysis

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Background: The median age of patients with newly diagnosed non-small cell lung cancer (NSCLC) at presentation is 71 years. We conducted an analysis of Surveillance, Epidemiology, and End Results data to assess whether the presentation and outcomes of NSCLC in younger patients (age ≤40 years) are different from that in older patients (age >40 years).

Methods: We obtained the demographic, clinical, and outcomes data for all patients diagnosed with NSCLC from 1988 to 2003 in the Surveillance, Epidemiology, and End Results registry. Patients were grouped by age at diagnosis into younger than or equal to 40 years (younger cohort) or older than 40 years (older cohort).

Results: During the period analyzed, we identified 2775 patients with NSCLC in the younger cohort and 236,313 patients in the older cohort. Compared with the older group, the younger group had greater proportion of African Americans (19.2% versus 10.9%; $p < 0.0001$), Asian or Pacific Islander (10.3% versus 5.9%; $p < 0.0001$), women (48.7% versus 41.9%; $p < 0.0001$), and patients with stage IV disease (57.4% versus 43.0%; $p < 0.0001$). Adenocarcinoma was more common in younger patients than in the older patients (57.5% versus 45.2%; $p < 0.0001$). Squamous cell carcinoma was less prevalent in the younger cohort than in older cohort (12.5% versus 26.4%; $p < 0.0001$). Five-year overall survival and cancer specific survival were significantly better for younger patients than for older patients across all stages.

Conclusions: There is a greater representation of African Americans, Asians or Pacific Islanders, women, and adenocarcinoma histology in the younger cohort of patients with NSCLC compared with the older cohort. Despite presenting with stage IV disease more often, the overall and cancer-specific survivals are better in younger cohort than in the older cohort.

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Lung cancer is estimated to affect 215,020 persons in the year 2008 in United States.[1] It is the most commonly diagnosed malignancy in the United States. The clinical presentation and outcomes for lung cancer in the young have not been described well. The majority of published data regarding lung cancer in the young have originated from single institutional retrospective studies with their attendant drawbacks. These studies have almost uniformly reported a higher incidence of adenocarcinoma and greater representation of women in younger patients with lung cancer.[2–13] However, there are conflicting data on whether younger patients with lung cancer have better or worse outcomes compared with the older population.[2–6,8,9,11–13] Lung cancer usually affects patients in their 60s and 70s and is not common in younger patients (age ≤40 years). A large population study is required to describe the characteristics and outcomes of lung cancer in the younger patients.

To the best of our knowledge, only one large population-based study has addressed the issue of lung cancer in the young using the Metropolitan Detroit Cancer Surveillance System (part of the Surveillance, Epidemiology, and End Results [SEER] database).[3] Since that publication more than 10 years ago, the SEER database has grown to include several more cancer registries. Moreover, there have been significant changes in the diagnosis and management of non-small cell lung cancer (NSCLC). In addition, the Metropolitan Detroit Cancer Surveillance System study included a significant proportion of patients with small cell lung cancer. Therefore, we analyzed the SEER database to identify the differences in presentation and outcomes between younger and older patients with NSCLC.

MATERIALS AND METHODS

Database

In this study, we analyzed the SEER Cancer Incidence Public Use Database 1988 to 2003 that was submit-

ted in November 2006 and issued in April 2007. (http://seer.cancer.gov). Lung tumors (site codes, C34.0-C34.9) were extracted from the SEER database for the years 1988 to 2003. The following histologic codes were designated as NSCLC: 8010, 8012, 8013, 8020, 8046, 8050–8052, 8070–8078, 8140, 8141, 8143, 8147, 8250–8255, 8260, 8310, 8430, 8480, 8481, 8490, 8560, and 8570–8575. We excluded patients diagnosed to have small cell lung cancer (ICD-0-3 histology code 8041–8045). In addition, patients without pathologic diagnosis of NSCLC and American Joint Committee on Cancer staging information were excluded. Only patients aged 18 years or older were included. Previously published studies have variably chosen ages ranging from 40 to 50 years to define their "younger" cohorts of patients with lung cancer. We chose the cutoff age of 40 years or less at presentation to define the "younger" cohort.

Statistical Analysis

Overall survival was defined as the time from diagnosis to death from any cause, and patients alive were censored at the time of last recording. Based on the cause of death information provided by the SEER database, cancer-specific survival was defined as the time from diagnosis to death from lung cancer only, and patients who died of other causes were censored. χ^2 test was used to test the statistical significance of difference in frequencies of gender, histology, race, and stage between the two age groups. Overall survival and cancer-specific survival were estimated using the Kaplan-Meier product-limit method and compared by log-rank test. Multivariate Cox models were also fitted to assess the differences among age groups, while adjusting for other known risk factors including gender, race, histologic subtypes, stage, and treatment modalities. Statistical analyses were performed using the standard package SAS version 9 (SAS Institute, Cary, NC). A p value less than 0.05 was considered significant, and all statistical tests were two sided.

RESULTS

The SEER database included 239,088 patients with NSCLC diagnosed from 1988 to 2003 with the median age of 68 years (range, 18–105 years) at diagnosis. The younger group (age ≤40 years at diagnosis) included 2775 patients and the older group (age >40 years at diagnosis) had 236,313 patients (Table 1). The median age for the younger group was 38 years (range, 18–40 years) and it was 69 years (range, 41–105 years) for the older group. The proportion of women with NSCLC was significantly higher in the younger group than in the older group (48.7% versus 41.9%; $p < 0.0001$). There were a higher proportion of African Americans in the younger group when compared with the older patients (19.2% versus 10.9%; $p < 0.0001$). The proportion of Asian or Pacific Islanders was higher in younger patients compared with older patients (10.3% versus 5.9%; $p < 0.0001$).

There were significant differences in the distribution of tumor histology between the two groups. Adenocarcinoma was the most common histology in both groups. However, the younger group had a higher proportion of patients with adenocarcinoma (57.5% versus 45.2%; $p < 0.0001$) than the older group, whereas squamous cell carcinoma was more common in the older group (12.5% versus 26.4%; $p < 0.0001$). The staging distribution for the two groups was also significantly different. The younger group had a higher proportion of patients with stage IV disease at presentation than the older group (57.4% versus 43.0%; $p < 0.0001$). Fewer patients in the younger group presented with stage I disease as compared with the older group (11.7% versus 20.9%; $p < 0.0001$).

TABLE 1. Description of the SEER Population of Patients with NSCLC by Age at Diagnosis

	Age ≤40 yr, *N* (%)	Age >40 yr, *N* (%)	*p*
N		2775 (1.2)	236,313 (98.8)
Gender			
Men	1424 (51.3)	137,270 (58.1)	<0.0001
Women	1351 (48.7)	99,043 (41.9)	
Race			
White	1942 (70.0)	195,349 (82.7)	<0.0001
African American	534 (19.2)	25,878 (10.9)	
Asian or Pacific Islander	285 (10.3)	13,880 (5.9)	
Other	14 (0.5)	1206 (0.5)	
Histology			
Adeno	1596 (57.5)	106,773 (45.2)	<0.0001
Squamous	346 (12.5)	62,487 (26.4)	
Adenosquamous	51 (1.8)	3894 (1.6)	
Large cell	285 (10.3)	17,956 (7.6)	
Carcinoma NOS	475 (17.1)	43,986 (18.6)	
Undifferentiated	22 (0.8)	1217 (0.5)	
Staging			
Stage I	324 (11.7)	49,377 (20.9)	<0.0001
Stage II	72 (2.6)	8929 (3.8)	
Stage III	786 (28.3)	76,442 (32.3)	
Stage IV	1593 (57.4)	101,565 (43.0)	

NOS, not otherwise specified.

Information on surgery and radiation therapy is available in the SEER database, and there was no significant difference in the proportion of patients undergoing surgery between the younger and older age groups (33.6% versus 32.5%; $p = 0.24$). The proportion of patients undergoing radiation was significantly higher in the younger patients than older patients (60.0% versus 45.9%; $p < 0.00001$).

The stage-wise overall and cancer-specific 5-year survival was higher for younger patients in comparison with the older patients (Figures 1 and 2). We conducted a multivariate analysis to control for the effect of gender, histology, race, tumor stage, treatment modality, and year of diagnosis on survival (Table 2). We divided the entire population studied into subgroups with age ranges of 10 years. Patients aged 61 to 70 years were used as the reference group, because most patients with NSCLC are diagnosed at this age range. The results of the multivariate analysis indicated that the risk of mortality with NSCLC increases with age and is significantly less in the youngest group. In addition, the multivariate analysis indicated that male gender, large cell carcinoma, adenosquamous, undifferentiated histology, and African

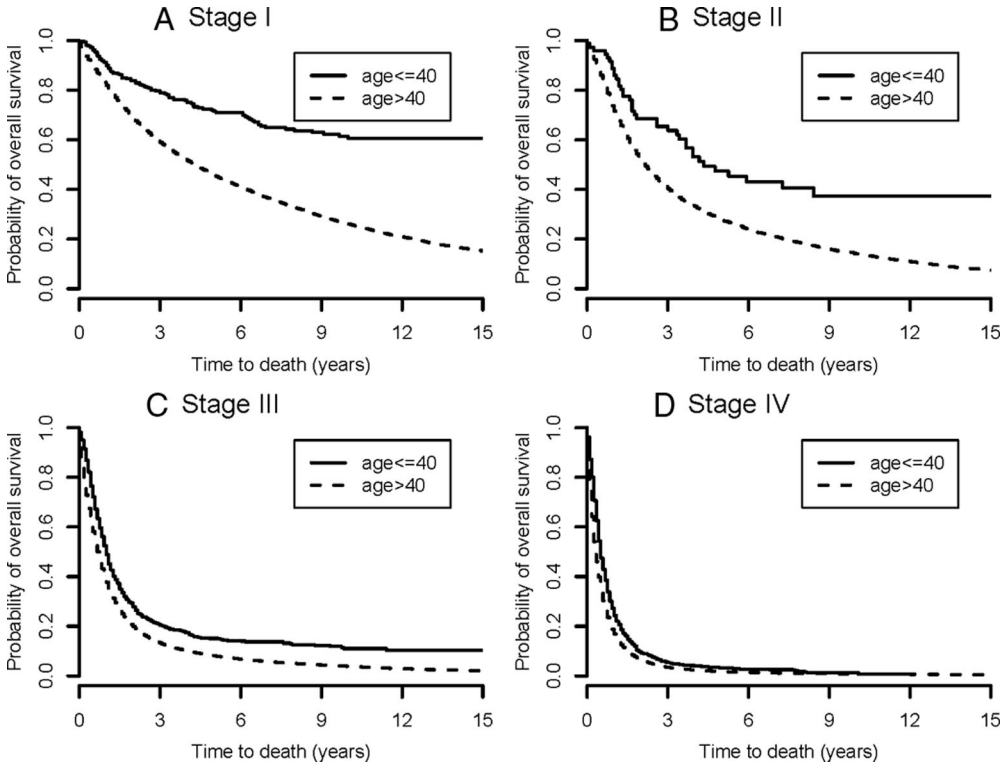

FIGURE 1. Kaplan-Meier curves comparing stage-wise overall survival between age younger than or equal to 40 years and age older than 40 years.

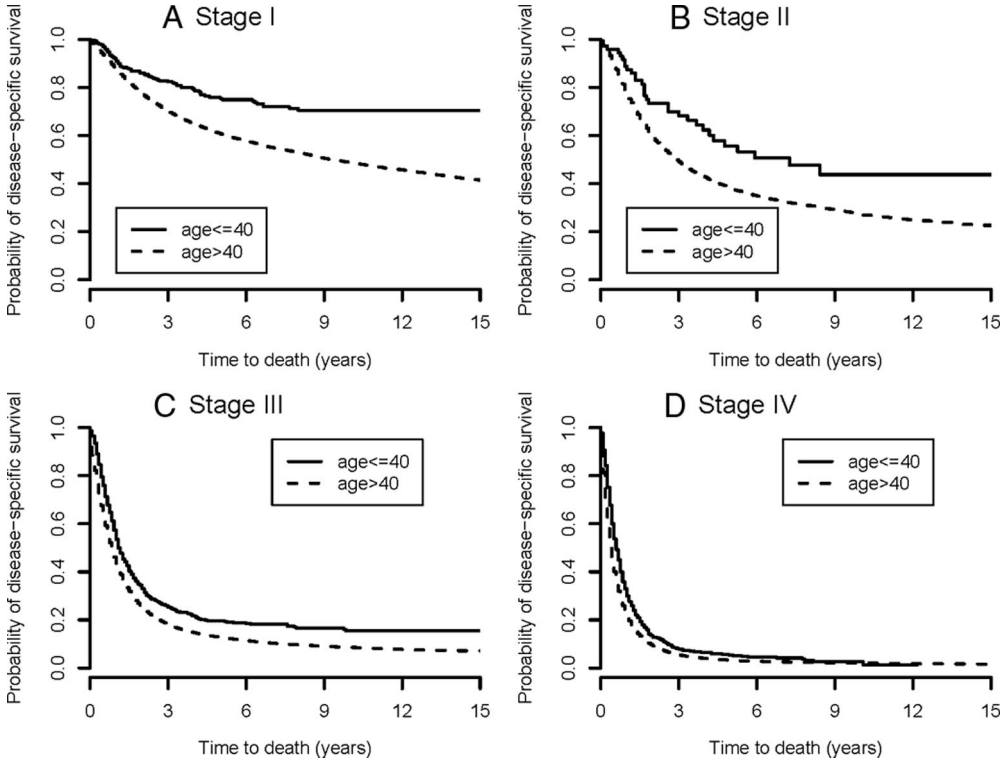

FIGURE 2. Kaplan-Meier curves comparing stage-wise cancer-specific survival between age younger than or equal to 40 years and age older than 40 years.

TABLE 2. Multivariate Analysis of Survival in SEER Population of Patients with NSCLC

Variable	Hazard Ratio	95% Confidence Interval	*p*
Age (yr)			
18–30	0.793	0.668–0.942	0.008
31–40	0.815	0.780–0.851	<0.0001
41–50	0.847	0.831–0.864	<0.0001
51–60	0.895	0.883–0.907	<0.0001
61–70	1.0		<0.0001
71–80	1.193	1.179–1.206	<0.0001
81–90	1.462	1.439–1.486	<0.0001
>91	1.837	1.734–1.946	<0.0001
Sex			
Female	1.0		<0.0001
Male	1.17	1.160–1.181	<0.0001
Race			
Caucasian	1.0		<0.0001
Asian or Pacific Islander	0.857	0.841–0.873	<0.0001
Black	1.048	1.034–1.063	<0.0001
Others	1.008	0.946–1.073	0.81
Stage			
I	0.25	0.246–0.255	<0.0001
II	0.427	0.415–0.439	<0.0001
III	0.614	0.608–0.621	<0.0001
IV	1.0		<0.0001
Histology			
Adenocarcinoma	1.0		<0.0001
Carcinoma NOS	1.089	1.076–1.103	<0.0001
Adenosquamous	1.136	1.096–1.178	<0.0001
Large cell	1.133	1.114–1.152	<0.0001
Squamous	1.044	1.032–1.056	<0.0001
Undifferentiated	1.146	1.081–1.215	<0.0001
Radiation therapy			
Yes	1.0		<0.0001
No	1.194	1.183–1.205	<0.0001
Surgery			
Yes	1.0		<0.0001
No	2.225	2.195–2.256	<0.0001
Year of diagnosis			
1988–1998	1.0		<0.0001
1999–2003	0.875	0.867–0.883	<0.0001

NOS, not otherwise specified.

American race were independent negative prognostic factors for NSCLC.

DISCUSSION

Our analysis of the SEER database confirms the previous observations that NSCLC in young patients is characterized by a higher proportion of women, adenocarcinoma, and stage IV disease than the older population with NSCLC.[2–13] Interestingly, there was no difference in the number of patients undergoing surgery between the two groups, although a greater proportion of younger patients received radiation therapy than the older patients. In the multivariate analysis, younger age was clearly associated with reduced risk for death due to NSCLC. The analysis also identified male gender, African American race, adenosquamous, year of diagnosis before 1999, and undifferentiated and large-cell histologies to be associated with a higher risk for lung cancer mortality. Younger patients had better stage-wise overall and disease-specific survival than older patients with NSCLC, and the difference in survival was statistically significant for all stages ($p < 0.0001$). There was no difference in the proportion of patients undergoing surgery between the two groups. The younger group had a higher proportion of patients undergoing radiation therapy. However, age was a statistically significant prognostic factor after including the treatment information to the multivariate analysis.

Our study has the usual limitations that are typically associated with any retrospective analysis of registry-based data involving a group of patients not treated uniformly. In addition, we could not evaluate the influence of tobacco use, presence or absence of comorbidities, and treatment-related toxicities because they are not captured in the SEER database. It is likely that the comorbidities associated with increasing age accounted for poor outcomes in the older population.

In this study, African Americans with NSCLC had worse survival compared with non-African American patients. Similar findings have been reported previously.[14–20] The inferior survival in patients with NSCLC of African American descent has been attributed to socioeconomic differences rather than intrinsic biologic variation.[19,20] We observed a higher proportion of African Americans in the younger age group than Caucasians in our study. This could be due to African Americans starting to smoke tobacco at an earlier age or there may be biologic differences that predispose to develop NSCLC at a younger age. In a case-control study, 216 patients with NSCLC and population controls were investigated to identify whether inefficient G_2-M checkpoint arrest was associated with increased risk for developing lung cancer. The association was not statistically significant with an OR of 1.17 (95% confidence interval [CI]: 0.73–1.88).[21] When stratified by race, inefficient G_2-M checkpoint arrest was associated with increased risk for lung cancer in African Americans ($n = 62$) but not in Caucasians, OR 2.25 (95% CI: 0.97–5.20). The G_2-M checkpoint is activated by DNA damage and prevents cells with chromosomal aberrations from going through the cell cycle. Inefficient G_2-M checkpoint arrest results in accumulation of DNA damage, and replication of cells with DNA damage could lead to malignant transformation. The presence of such biologic variations in African Americans could predispose to develop lung cancer at an earlier age.

Our study also identified a higher proportion of younger patients with lung cancer in the Asian or Pacific Islander ethnic population compared with the Caucasian population. Asian Americans have a higher proportion of never smokers with lung cancer than Caucasian or African Americans.[22] Because the SEER registry does not have data on tobacco smoking, we do not know whether there is a higher proportion of never smokers in the younger Asian or Pacific Islander

group. However, retrospective studies from the Pacific Rim countries have reported that never smokers with lung cancer present at an earlier age than tobacco smokers. In addition, never smokers with lung cancer from Pacific Rim countries have unique risk factors for lung cancer such as exposure to cooking fumes and polymorphisms of genes involved in xenobiotic metabolism.[23,24] It is not known whether these same risk factors play a role in the early development of lung cancer in Asian or Pacific Islander population living in the United States. The Asian or Pacific Islander group in the United States is a large and diverse population, and risk factors identified in Asians from Pacific Rim countries may be applicable to people of similar origin living in the United States. The reason for the higher proportion of younger patients with lung cancer in the Asian or Pacific Islander ethnic group may be due to multiple reasons including cultural and biologic differences, which require further investigation.

Patients diagnosed with NSCLC before 1999 had increased hazard of death compared with patients diagnosed between 1999 and 2003. This improvement in outcomes may be related to advances in diagnostic imaging, the availability of newer treatment options, such as second line chemotherapy, and less toxic treatment regimens. In addition, we have made progress in the arena of supportive care for cancer patients and the management of treatment complications. The multivariate analysis also identified large cell and adenosquamous histologies to be adverse prognostic factors in keeping with findings from previous studies on the prognostic role of histology in patients with NSCLC.[25,26]

It is unclear whether patients who develop lung cancer at an early age have intrinsic susceptibility to develop lung cancer or have inordinate sensitivity to tobacco-related carcinogenesis. The proportion of smokers appears to be similar in younger and older patients with NSCLC, although there are only limited data on the cumulative tobacco exposure between the two groups.[2,4,9,27] Kreuzer et al.[7] reported that the number of cigarettes smoked per day was higher in younger patients (age ≤45 years) than in the older ones with NSCLC.

It is conceivable that younger patients developing NSCLC are more susceptible to tobacco-related carcinogens than their older counterparts. It has been hypothesized that younger patients with genetic polymorphisms of glutathione *S*-transferases resulting in loss of or reduced enzymatic activity for detoxifying reactive metabolites of tobacco smoke procarcinogens might be at a higher risk for developing cancer.[28,29] Some of the genetic polymorphisms of glutathione *S*-transferases such as GSTP1 AG or GG genotype, GSTM1 null genotype, and GSTT1 null genotype are associated with reduced or loss of enzymatic activity. In a large case-control study, GSTP1 GG and GSTM1 null genotypes were not associated with increased risk for lung cancer.[30] However, when the analysis was restricted to patients younger than or equal to 55 years with both GSTP1 GG and GSTM1 null genotype, the risk for lung cancer was significantly increased; adjusted OR 4.03 (95% CI: 1.47–11.1). Similar findings were reported in another case-control study on patients diagnosed with early onset lung cancer (age <50 years), and the *GSTT1* null genotype was associated with higher risk for lung cancer; OR 3.1 (95% CI: 1.1–8.4) in heavy smoking (>23 pack-years) Caucasians.[29] In addition, the combination of *GSTM1* and *GSTT1* null genotypes were associated with a greater risk for lung cancer in the same group; OR 5.0 (95% CI: 1.1–23.6).

More recently, case-control studies have specifically examined the role of polymorphisms of genes involved in DNA repair pathways and xenobiotic metabolism in younger patients. Polymorphisms of 34 well-known cell cycle control and DNA repair genes were compared between 299 patients with lung cancer younger than 50 years and 377 age- and gender-matched healthy controls.[31] Polymorphism of the mismatch repair gene (DNA ligase 1) LIG1 -7C>T (OR 1.7; 95% CI: 1.13–2.64) and LIG3 rs 1052536 (OR 2.05; 95% CI: 1.25–3.38) were associated with increased risk for developing lung cancer in younger patients. Polymorphisms of genes involved in xenobiotic metabolism and the risk of lung cancer were studied in the same population.[32] The following polymorphisms were associated with increased risk for developing lung cancer in younger patients: heterozygote CYP1A2 (1545TàC) (OR 1.5; 95% CI: 1.02–2.21), CYP1A2 (-164CàA) (OR 1.58; CI: 1.09–2.27), and homozygous GSTA2 (OR 1.88; 95% CI: 1.11–3.17). Further work is required to identify other potential risk factors that may play a more significant role in the development of lung cancer.

In summary, NSCLC in the young is characterized by higher frequency of African American, Asian or Pacific Islander race, female gender, and adenocarcinoma histology than the older population with NSCLC. Patients who develop NSCLC at a young age could have inherited risk factors, which in combination with tobacco smoking increase their risk for NSCLC. These patients may be more "sensitive" to the carcinogenic effects of tobacco smoke. Further studies are required to better understand the molecular mechanisms predisposing younger patients to develop lung cancer and also identify potential targets to develop new treatment modalities.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin* 2008;58:71–96.
2. Sekine I, Nishiwaki Y, Yokose T, Nagai K, Suzuki K, Kodama T. Young lung cancer patients in Japan: different characteristics between the sexes. *Ann Thorac Surg* 1999;67:1451–1455.
3. Ramalingam S, Pawlish K, Gadgeel S, Demers R, Kalemkerian GP. Lung cancer in young patients: analysis of a surveillance, epidemiology, and end results database. *J Clin Oncol* 1998;16:651–657.
4. Gadgeel SM, Ramalingam S, Cummings G, et al. Lung cancer in patients <50 years of age: the experience of an academic multidisciplinary program. *Chest* 1999;115:1232–1236.
5. Skarin AT, Herbst RS, Leong TL, Bailey A, Sugarbaker D. Lung cancer in patients under age 40. *Lung Cancer* 2001;32:255–264.
6. Kuo CW, Chen YM, Chao JY, Tsai CM, Perng RP. Non-small cell lung cancer in very young and very old patients. *Chest* 2000;117:354–357.
7. Kreuzer M, Kreienbrock L, Gerken M, et al. Risk factors for lung cancer in young adults. *Am J Epidemiol* 1998;147:1028–1037.
8. Mauri D, Pentheroudakis G, Bafaloukos D, et al. Non-small cell lung cancer in the young: a retrospective analysis of diagnosis, management and outcome data. *Anticancer Res* 2006;26:3175–3181.
9. Radzikowska E, Roszkowski K, Glaz P. Lung cancer in patients under 50 years old. *Lung Cancer* 2001;33:203–211.
10. Chen KY, Chang CH, Yu CJ, Kuo SH, Yang PC. Distribution according

to histologic type and outcome by gender and age group in taiwanese patients with lung carcinoma. *Cancer* 2005;103:2566–2574.
11. Subramanian J, Velcheti V, Goodgame B, Gao F, Baggstrom M, Govindan R. Distinctive characteristics of non-small cell lung cancer (NSCLC) in the young: Washington university experience. *J Thorac Oncol* 2007;2:S563.
12. Roviaro GC, Varoli F, Zannini P, Fascianella A, Pezzuoli G. Lung cancer in the young. *Chest* 1985;87:456–459.
13. Whooley BP, Urschel JD, Antkowiak JG, Takita H. Bronchogenic carcinoma in young patients. *J Surg Oncol* 1999;71:29–31.
14. Bach PB, Cramer LD, Warren JL, Begg CB. Racial differences in the treatment of early-stage lung cancer. *N Engl J Med* 1999;341:1198–1205.
15. Graham MV, Geitz LM, Byhardt R, et al. Comparison of prognostic factors and survival among black patients and white patients treated with irradiation for non-small-cell lung cancer. *J Natl Cancer Inst* 1992;84:1731–1735.
16. Wingo PA, Bolden S, Tong T, Parker SL, Martin LM, Heath CW Jr. Cancer statistics for African Americans, 1996. *CA Cancer J Clin* 1996;46:113–125.
17. Wingo PA, Ries LA, Giovino GA, et al. Annual report to the nation on the status of cancer, 1973–1996, with a special section on lung cancer and tobacco smoking. *J Natl Cancer Inst* 1999;91:675–690.
18. Young JL Jr, Ries LG, Pollack ES. Cancer patient survival among ethnic groups in the United States. *J Natl Cancer Inst* 1984;73:341–352.
19. Blackstock AW, Herndon JE II, Paskett ED, et al. Outcomes among African-American/non-African-American patients with advanced non-small-cell lung carcinoma: Report from the Cancer and Leukemia Group B. *J Natl Cancer Inst* 2002;94:284–290.
20. Bryant AS, Cerfolio RJ. Impact of race on outcomes of patients with non-small cell lung cancer. *J Thorac Oncol* 2008;3:711–715.
21. Zheng YL, Loffredo CA, Alberg AJ, et al. Less efficient g2-m checkpoint is associated with an increased risk of lung cancer in African Americans. *Cancer Res* 2005;65:9566–9573.
22. Raz DJ, Gomez SL, Chang ET, et al. Epidemiology of non-small cell lung cancer in Asian Americans: incidence patterns among six subgroups by nativity. *J Thorac Oncol* 2008;3:1391–1397.
23. Subramanian J, Govindan R. Lung cancer in never smokers: a review. *J Clin Oncol* 2007;25:561–570.
24. Kato S, Shields PG, Caporaso NE, et al. Analysis of cytochrome p450 2e1 genetic polymorphisms in relation to human lung cancer. *Cancer Epidemiol Biomarkers Prev* 1994;3:515–518.
25. Battafarano RJ, Fernandez FG, Ritter J, et al. Large cell neuroendocrine carcinoma: an aggressive form of non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2005;130:166–172.
26. Okamoto T, Maruyama R, Suemitsu R, et al. Prognostic value of the histological subtype in completely resected non-small cell lung cancer. *Interact Cardiovasc Thorac Surg* 2006;5:362–366.
27. Liam CK, Lim KH, Wong CM. Non-small cell lung cancer in very young and very old Malaysian patients. *Chest* 2002;121:309–310.
28. Butkiewicz D, Grzybowska E, Phillips DH, Hemminki K, Chorazy M. Polymorphisms of the GSTP1 and GSTM1 genes and PAH-DNA adducts in human mononuclear white blood cells. *Environ Mol Mutagen* 2000;35:99–105.
29. Cote ML, Kardia SL, Wenzlaff AS, Land SJ, Schwartz AG. Combinations of glutathione s-transferase genotypes and risk of early-onset lung cancer in Caucasians and African Americans: a population-based study. *Carcinogenesis* 2005;26:811–819.
30. Miller DP, Liu G, De Vivo I, et al. Combinations of the variant genotypes of GSTP1, GSTM1, and p53 are associated with an increased lung cancer risk. *Cancer Res* 2002;62:2819–2823.
31. Landi S, Gemignani F, Canzian F, et al. DNA repair and cell cycle control genes and the risk of young-onset lung cancer. *Cancer Res* 2006;66:11062–11069.
32. Gemignani F, Landi S, Szeszenia-Dabrowska N, et al. Development of lung cancer before the age of 50: the role of xenobiotic metabolizing genes. *Carcinogenesis* 2007;28:1287–1293.