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ORIGINAL REPORT

Incidence of *EGFR* Exon 19 Deletions and L858R in Tumor Specimens From Men and Cigarette Smokers With Lung Adenocarcinomas

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
EGFR mutations underlie the sensitivity of lung cancers to erlotinib and gefitinib and can occur in any patient with this illness. Here we examine the frequency of *EGFR* mutations in smokers and men.

Methods
We determined the frequency of *EGFR* mutations and characterized their association with cigarette smoking status and male sex.

Results
We tested 2,142 lung adenocarcinoma specimens for the presence of *EGFR* exon 19 deletions and L858R. *EGFR* mutations were found in 15% of tumors from former smokers (181 of 1,218; 95% CI, 13% to 17%), 6% from current smokers (20 of 344; 95% CI, 4% to 9%), and 52% from never smokers (302 of 580; 95% CI, 48% to 56%; $P < .001$ for ever *v* never smokers). *EGFR* mutations in former or current smokers represented 40% of all those detected (201 of 503; 95% CI, 36% to 44%). *EGFR* mutations were found in 19% (157 of 827; 95% CI, 16% to 22%) of tumors from men and 26% (346 of 1,315; 95% CI, 24% to 29%) of tumors from women ($P < .001$). *EGFR* mutations in men represented 31% (157 of 503; 95% CI, 27% to 35%) of all those detected.

Conclusion
A large number of *EGFR* mutations are found in adenocarcinoma tumor specimens from men and people who smoked cigarettes. If only women who were never smokers were tested, 57% of all *EGFR* mutations would be missed. Testing for *EGFR* mutations should be considered for all patients with adenocarcinoma of the lung at diagnosis, regardless of clinical characteristics. This strategy can extend the use of *EGFR* tyrosine kinase inhibitors to the greatest number individuals with the potential for substantial benefit.

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INTRODUCTION

Ninety percent of clinically relevant *EGFR* (epidermal growth factor receptor) mutations are either missense mutations in exon 21 or deletions in exon 19.[1] Patients with lung adenocarcinomas and *EGFR* exon 19 or 21 mutations have high rates of radiologic response to gefitinib and erlotinib.[2-4] In the Iressa Pan-Asia Study (IPASS), individuals with *EGFR* mutations treated with gefitinib had a 69% absolute improvement in objective response rate and a longer progression-free survival when compared with those without *EGFR* mutations.[5]

Randomized phase III studies of patients with metastatic non–small-cell lung cancer (NSCLC) and *EGFR* mutations have demonstrated improved progression-free survival and response rates for treatment with gefitinib compared with conventional doublet chemotherapy. On the basis of these data, *EGFR* tyrosine kinase inhibitors (TKIs) have emerged as a recommended first-line therapy in patients with *EGFR*-sensitizing mutations.[6-9]

Many clinicians have adopted a strategy to either treat all never smokers with lung adenocarcinoma with gefitinib or erlotinib or to only order mutation testing on tumor specimens from women who have never smoked. Although *EGFR* mutations are more common in tumors from patients with these characteristics, they can be found in men and in those who smoked cigarettes. In a multiinstitutional study conducted in Spain, 2,105 patients were screened for the presence of *EGFR*

Table 1. Incidence of *EGFR* Mutations by Cigarette Smoking History

Smoking History	Stage I-IIIA			Stage IIIB/IV			All Stages				
	No. with Mutations	Total No. of Tumors	%	No. with Mutations	Total No. of Tumors	%	No. with Mutations	Total No. of Tumors	%	95% CI	*P*
Never	131	228	57	171	352	49	302	580	52	48 to 56	$< .001$ $\chi^2_{(df = 2)} = 314$
Former	83	714	12	98	504	19	181	1,218	15	13 to 17	
Current	4	143	3	16	201	8	20	344	6	4 to 9	

mutations. *EGFR* mutations were found in 350 patients (17%). The incidence of *EGFR* mutations was 8%, 10%, and 6% in men, former smokers, and current smokers, respectively.[10] Pham et al[11] found *EGFR* mutations in 51% of patients with lung adenocarcinoma who were never smokers, with a similar incidence of mutations in men (27%) and women (23%; $P = .55$). *EGFR* mutations also were found in the tumors of former and current smokers. Patients who smoked from 16 to 75 pack-years had a 10% incidence of *EGFR* mutations as compared with 46% among those with 15 or fewer pack-years ($P < .001$). We have now expanded this effort to examine the frequency of *EGFR* mutations in men and cigarette smokers with lung adenocarcinomas in a cohort of 2,142 patients with stage I to IV lung adenocarcinoma. We hypothesized that, although less frequent than in women and never smokers, a significant proportion of lung adenocarcinomas with *EGFR* mutations occur in men and current/former smokers.

METHODS

Patients and Data Collection

Lung adenocarcinomas from consecutive patients evaluated at Memorial Sloan-Kettering Cancer Center between January 2002 and November 2009 with available tumor tissue underwent analysis for *EGFR* mutations. After microscopic examination confirmed the diagnosis of lung adenocarcinoma, DNA was extracted. *EGFR* exon 19 deletions and exon 21 L858R mutations were identified as previously described.[12]

With a waiver of authorization from the Memorial Sloan-Kettering Cancer Center institutional review board, we collected age, sex, smoking history, and stage of disease for all patients. Patients were categorized as never smokers ($<$ 100 lifetime cigarettes), former smokers (quit $\geq$ 1 year ago), or current smokers (quit $<$ 1 year ago).[13]

Statistical Analysis

The association between *EGFR* mutation status, sex, and amount of cigarettes smoked were evaluated using a χ^2 test. We tested for the presence of a trend in the association between *EGFR* mutation status and the number of pack-years smoked (grouped in categories: 0, 1 to 5, 6 to 10, 11 to 15, 16 to 25, 26 to 50, 51 to 75, and $>$ 75) using univariate logistic regression in which pack-year categories were treated in a continuous fashion, with the median number of pack-years assigned as the corresponding score. These cut points have been used in earlier studies.[11,13,14] Overall survival was estimated from time of surgery (for stage I to IIIA patients) or diagnosis with advanced cancer (for stage IIIB to IV patients) until death or last available follow-up using Kaplan-Meier method. The log-rank test was used to detect differences in survival by sex and smoking history.

RESULTS

The presence of *EGFR* exon 19 deletions or L858R was determined in 2,142 lung adenocarcinomas, 1,085 with stage I to IIIA and 1,057 with stage IIIB to IV disease. There were 218 *EGFR* mutations (20%) detected in patients with early-stage lung adenocarcinoma and 285 (27%) in those with advanced stage disease. Among early-stage patients with *EGFR* mutations, 53% had exon 19 deletions and 47% had L858R. Of the advanced-stage patients with *EGFR* mutations, 61% had exon 19 deletions and 39% had L858R.

EGFR mutations were found in 15% of tumors from former smokers (181 of 1,218; 95% CI, 13% to 17%) and 6% of tumors from current smokers (20 of 344; 95% CI, 4% to 9%), compared with 52% of tumors from never smokers (302 of 580; 95% CI, 48% to 56%; $P < .001$ for ever *v* never smokers; Table 1). *EGFR* mutations in former and current smokers represented 40% of all mutations detected (201 of 503; 95% CI, 36% to 44%; Fig 1A). There was an inverse relationship between the incidence of *EGFR* mutations and the number of pack-years of cigarette smoking, with fewer mutations found in patients with greater smoking histories (P for trend $< .001$ for patients with early-stage disease, with advanced-stage disease, and for all patients; Table 2).

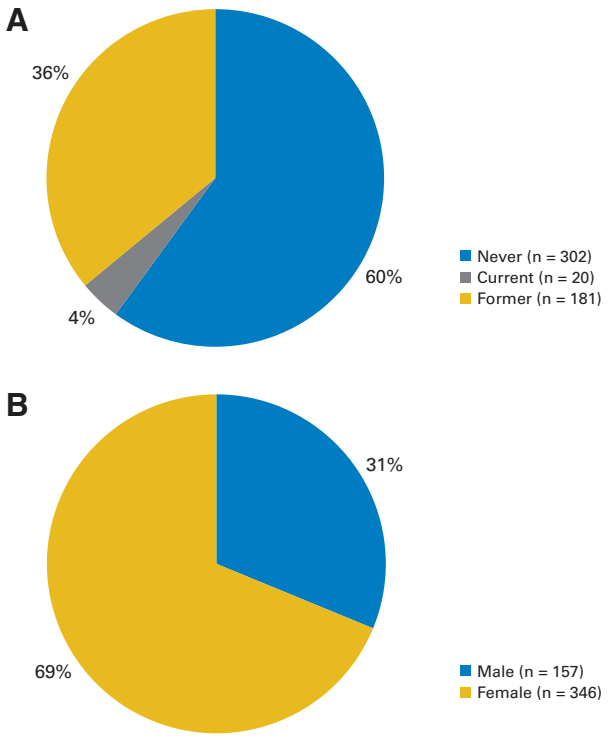

Fig 1. *EGFR* mutation by (A) smoking status and (B) sex.

Table 2. Incidence of *EGFR* Mutations by Pack-Years of Cigarettes Smoked

	Stage I-IIIA			Stage IIIB/IV			All Stages			
Pack-Years	No. With Mutations	Total No. of Tumors	%	No. With Mutations	Total No. of Tumors	%	No. With Mutations	Total No. of Tumors	%	95% CI
Never smokers	131	228	57	171	352	49	302	580	52	48 to 56
1 to 5	22	57	39	20	68	29	42	125	34	25 to 43
6 to 10	11	47	23	29	69	42	40	116	34	26 to 44
11 to 15	10	59	17	9	49	18	19	108	18	11 to 26
16-25	13	129	10	13	110	12	26	239	11	7 to 16
26 to 50	16	294	5	27	246	11	43	540	8	6 to 11
51 to 75	10	148	7	11	95	12	21	243	9	5 to 13
> 75	3	116	3	4	66	6	7	183	4	2 to 8
P (trend test)	< .001 $\chi^2_{(df = 1)} = 129$			< .001 $\chi^2_{(df = 1)} = 90.2$			< .001 $\chi^2_{(df = 1)} = 224$			

The incidence of *EGFR* mutations among all patients decreases from 52% in never smokers to 29% in patients with smoking histories of 1 to 15 pack-years to 8% in patients who reported 16 or more pack-years of cigarette smoke ($P < .001$). However, *EGFR* mutations were found even in those patients with a greater than 75 pack-year smoking history, with a 3% and 6% incidence in those with early-stage and in those with advanced adenocarcinoma, respectively.

EGFR mutations were found in 19% (157 of 827; 95% CI, 16% to 22%) of tumors from men and 26% (346 of 1,315; 95% CI, 24% to 29%) of tumors from women ($P < .001$; Table 3), with mutations in men representing 31% (157 of 503; 95% CI, 27% to 35%) of all those detected (Fig 1B). The smoking status was analyzed separately for males and females. We found that the incidence of mutations in female smokers and male smokers was 14% and 11%, respectively ($P = .073$), whereas in female never smokers and male never smokers, it was 55% and 47%, respectively ($P = .15$, Table 4).

The median overall survival in former/current smokers with stage I to III disease whose tumors harbor an *EGFR* mutation has not yet been reached, whereas in never smokers it is 6.9 years ($P = .36$). For those with stage IIIB/IV disease harboring *EGFR* mutations, the median overall survival in never smokers is 2.8 years and in former/current smokers is 3.5 years ($P = .09$).

The median overall survival for patients whose tumors harbor *EGFR* mutations with stage I to III disease has not yet been reached in men and is 6.9 years in women ($P = .30$). There is no difference in median overall survival by sex in individuals with stage IIIB/IV disease with *EGFR* mutations ($P = .96$).

DISCUSSION

Before the discovery of *EGFR* mutations in the tumors of patients with dramatic responses to gefitinib and erlotinib, clinical characteristics were the only way to predict response. Since 2004, multiple prospective studies have proven that mutations in the *EGFR* tyrosine kinase domain are the best predictors of response and progression-free survival benefit with *EGFR* TKI.[5,7,8]

Although mutations are clearly more common in adenocarcinomas from women and never smokers, a substantial proportion of these specimens do not harbor mutations, and patients with these characteristics derive little or no benefit from gefitinib (a 1% partial response rate and lower progression-free survival, hazard ratio of 2.93 in IPASS). Many studies have attempted to select patients likely to respond to gefitinib and erlotinib (and with *EGFR* mutations) using established clinical characteristics such as female sex, never or "light" smoking history, and bronchioloalveolar features in tumor specimens.[5,15,16] When mutation testing was done, the proportion of patients with *EGFR* mutations ranged from 42% to 60%. Even in IPASS, in which nearly all patients were female never smokers from East Asia, just 60% had *EGFR* mutations. Mutations were less frequent (40% and 42%) in the two North American series.

In this analysis, *EGFR* mutations occur with an incidence of 23% in 2,142 patients with stage I through IV lung adenocarcinoma, similar to our previous findings. Tumors from 19% of men and 13% of current/former smokers harbor *EGFR* sensitizing mutations. Although there is a decrease in the incidence of mutations with increased number of pack-years smoked, a substantial number of *EGFR* mutations were found in patients with a significant history of smoking. *EGFR* mutations in men and former/current smokers represent 31% and 40% of all mutations, respectively. Further demonstrating that it is the mutation and not the clinical characteristic that underlies the clinical outcomes seen after *EGFR* TKI treatment, the overall survival of men and former/current smokers with *EGFR* mutations was similar to that seen in women and never smokers. The results in these North

Table 3. Incidence of *EGFR* Mutations by Sex

	Stage I-IIIA			Stage IIIB/IV			All Stages				
Sex	No. With Mutations	Total No. of Tumors	%	No. With Mutations	Total No. of Tumors	%	No. With Mutations	Total No. of Tumors	%	95% CI	*P*
Female	161	690	23	185	625	30	346	1,315	26	24 to 29	< .001 $\chi^2_{(df = 1)} = 15.2$
Male	57	395	14	100	432	23	157	827	19	16 to 22	
Total	218	1,085	20	285	1,057	27	503	2,142	23	22 to 25	

Table 4. Incidence of *EGFR* Mutations by Cigarette Smoking History and Sex

Smoking History and Sex	Stage I-IIIA			Stage IIIB/IV			All Stages				
	No. With Mutations	Total No. of Tumors	%	No. With Mutations	Total No. of Tumors	%	No. With Mutations	Total No. of Tumors	%	95% CI	*P**
Never smokers											
Female	101	176	57	116	222	52	217	398	55	49 to 59	.15
Male	30	52	57	55	130	42	85	182	47	39 to 54	$\chi^2_{(df\ =\ 1)} = 2.12$
Total	131	228	57	171	322	53	302	580	52	48 to 56	
Smokers											
Female	60	514	12	69	403	17	129	917	14	12 to 16	.073
Male	27	343	8	45	302	15	72	645	11	9 to 14	$\chi^2_{(df\ =\ 1)} = 3.21$
Total	87	857	10	114	705	16	201	1,562	13	11 to 15	

*P value was adjusted for stage.

American patients (predominantly of European heritage) are comparable to the results reported among patients from East Asia.[5,7,8] Similar findings were reported in a multi-institutional study conducted in Spain where *EGFR* mutations were found 350 (17%) of 2,105 patients. The incidence of *EGFR* mutations was 8%, 10%, and 6% in men, former, and current smokers, respectively.[10]

Limitations in this analysis are that this is a single-institution series and we did not test for the L861Q and G719A/S, which may be sensitive to *EGFR* TKI treatment during the time period of this study. We now routinely assay for these less common *EGFR* sensitivity mutations, and their incidence remains quite rare. Of 119 *EGFR* mutations, we discovered only five (4%). The exon 19 deletions and L858R point mutations we assayed in all patients represent 90% of *EGFR* sensitizing mutations. This is the largest series reported, and the analytic methods used have been consistent and reproducible over this time period.[11,12] The methods used to collect tobacco exposure and the documentation of never smoking status have been standardized.[11,13]

With the "proof of principle" experience with *EGFR* mutations and *EGFR* TKIs in lung adenocarcinomas, since January 1, 2009, we have tested the tumors of all patients diagnosed with lung adenocarcinoma tumors and adequate tissue for the presence of driver mutations (*KRAS*, *EGFR*, *BRAF*, *HER2*, *PIK3CA*, *AKTI*, *MEKI* [*MAP2K1*], *NRAS*, and *EML4-ALK*). We have also joined with 13 other US institutions to form the Lung Cancer Mutation Consortium to test 1,000 adenocarcinoma specimens for the presence of the driver mutations listed above, in an attempt to link patients with "actionable" mutations to clinical trials of targeted agents.

Although clinical selection factors to choose *EGFR* TKIs have guided the care of individual patients and facilitated research for a decade, this strategy has been eclipsed by our ability to use the presence of *EGFR* sensitizing mutations as the basis for treatment. If we only perform mutation testing in selected patients based on clinical features, we will fail to detect a substantial number of mutations in smokers and men, denying them the benefits of gefitinib or erlotinib at diagnosis. Thirty-one percent of all *EGFR* mutations would be missed if testing were restricted to women, 40% would be missed if testing were restricted to never smokers, and 57% would be missed if testing were restricted to women who never smoked cigarettes (Table 5). Our findings in men and smokers add evidence to support the growing consensus that all patients with adenocarcinoma and large-cell carcinoma of the lung and NSCLC not otherwise specified should undergo mutation testing at diagnosis if tissue is available, now part of the National Comprehensive Cancer Network guidelines for the treatment of NSCLC.[6] *EGFR* mutations can be accurately and quickly determined by widely available tests. Although these analyses now require the availability of sufficient tumor, new approaches hold promise to permit the detection of *EGFR* mutations on cytology specimens[17,18] and circulating tumor cells.[19]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Gregory J. Riely, AstraZeneca (C), Boehringer Ingelheim (C); Vincent A. Miller,

Table 5. Patients Tested and *EGFR* Mutations Missed Under Different Testing Strategies

Population Tested	Patients Tested		*EGFR* Mutations Detected		*EGFR* Mutations Missed	
	No.	%	No.	%	No.	%
Women only	1,315	61	346	69	157	31
Never smokers only	580	27	302	60	201	40
Never smoking women	398	19	217	43	286	57
All patients	2,142	100	503	100	0	0

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Glossary Terms

Driver mutations: Driver mutations are those that are causally implicated in oncogenesis or tumor survival. Such mutations have been positively selected during carcinogenesis and often show a recurrent pattern within or across tumor types. This is in contrast with passenger events, which arise from the background mutation rate and do not contribute to oncogenesis.

EGFR (epidermal growth factor receptor): Also known as HER-1, EGFR belongs to a family of receptors (HER-2, HER-3, HER-4 are other members of the family) and binds to the EGF, TGF-α, and other related proteins, leading to the generation of proliferative and survival signals within the cell. It also belongs to the larger family of tyrosine kinase receptors and is generally overexpressed in several solid tumors of epithelial origin.

Erlotinib: Also known as Tarceva, erlotinib is a small molecule that inhibits the tyrosine kinase activity of EGFR/HER-1 and has been evaluated extensively in clinical trials in patients with non-small-cell lung cancer, pancreatic cancer, and glioblastoma multiforme.

Gefitinib: Belonging to the class of tyrosine kinase inhibitors, gefitinib (also known as Iressa) binds to the cytoplasmic region of the EGFR that also binds ATP. By competing with ATP binding that is essential for tyrosine phosphorylation, gefitinib inhibits activation of EGFR and blocks the cascade of reactions leading to cellular proliferation.

