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Original Article

EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII)

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Abstract: Mutations in the epidermal growth factor receptor (*EGFR*) gene are commonly observed in non-small-cell lung cancer (NSCLC), particularly in tumors of adenocarcinoma (ADC) histology (NSCLC/ADC). Robust data exist regarding the prevalence of *EGFR* mutations in Western and Asian patients with NSCLC/ADC, yet there is a lack of data for patients of other ethnicities. This review collated available data with the aim of creating a complete, global picture of *EGFR* mutation frequency in patients with NSCLC/ADC by ethnicity. Worldwide literature reporting *EGFR* mutation frequency in patients with NSCLC/ADC was reviewed, to create a map of the world populated with *EGFR* mutation frequency by country (a 'global *EGFR* mutMap'). A total of 151 worldwide studies (*n*=33162 patients with NSCLC/ADC, of which 9749 patients had *EGFR* mutation-positive NSCLC/ADC) were included. There was substantial variation in *EGFR* mutation frequency between studies, even when grouped by geographic region or individual country. As expected, the Asia-Pacific NSCLC/ADC subgroup had the highest *EGFR* mutation frequency (47% [5958/12819; 87 studies; range 20%-76%]) and the lowest *EGFR* mutation frequency occurred in the Oceania NSCLC/ADC subgroup (12% [69/570; 4 studies; range 7%-36%]); however, comparisons between regions were limited due to the varying sizes of the patient populations studied. In all regional (geographic) subgroups where data were available, *EGFR* mutation frequency in NSCLC/ADC was higher in women compared with men, and in never- compared with ever-smokers. This review provides the foundation for a global map of *EGFR* mutation frequency in patients with NSCLC/ADC. The substantial lack of data from several large geographic regions of the world, notably Africa, the Middle East, Central Asia, and Central and South America, highlights a potential lack of routine mutation testing and the need for further investigations in these regions.

Keywords: Adenocarcinoma, *EGFR* mutation frequency, non-small-cell lung cancer

Introduction

Lung cancer represents a significant clinical burden worldwide. Recent statistics (WHO 2012) have indicated that lung cancer is the most common cancer in men globally, with an age-standardised rate (ASR; per 100,000) of 34.2 and an incidence of 1.2 million, and the fourth most common cancer in women (ASR 13.6; incidence 0.6 million) after cancer of the breast, colorectum, and cervix [1]. Consequently, lung cancer is the leading cause of cancer-related mortality worldwide, accounting for 19.4% of all cancer-related deaths [1].

Non-small-cell lung cancer (NSCLC) accounts for ~85% of primary lung cancers, and the majority of patients present with advanced or metastatic disease at diagnosis [2]. Adenocarcinoma (ADC) is one of the most common histological subtypes of NSCLC [3, 4]. Molecular profiling of tumor samples from patients with NSCLC has identified driver mutations that may contribute to early carcinogenesis in more than 80% of ADC cases, including epidermal growth factor receptor (*EGFR*) mutations [5], which are now considered to be commonly associated with NSCLC tumors [5-13].

Mutation status improves predictions of the behavior and characterization of tumors of ADC histology when compared with the use of prognostic factors, such as tumor node metastasis stage [14]. Mutation testing has enabled many

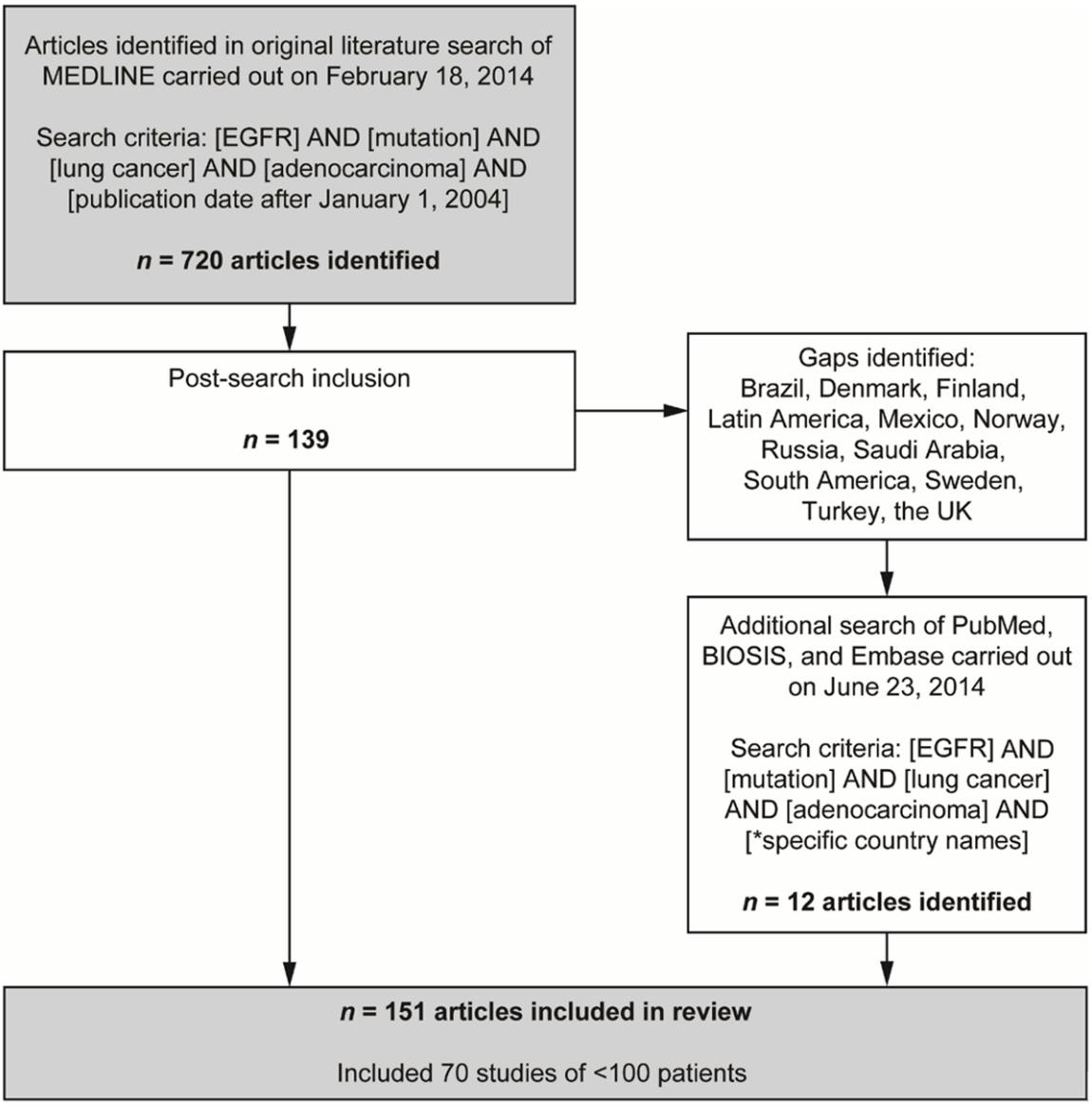

Figure 1. Flow of studies identified and included in the meta-analyses.

patients with *EGFR* mutation-positive NSCLC of ADC histology (referred to as NSCLC/ADC throughout) to receive personalized treatment with EGFR tyrosine kinase inhibitors (TKIs), which specifically target *EGFR* oncogenes [9-12], based on the molecular characteristics of their tumor, with the result that treatment outcomes are optimized in these patients [15, 16]. It is now widely accepted that response to EGFR TKIs is greater in patients with tumors harboring *EGFR* mutations compared with patients without *EGFR* mutations; results from several clinical trials have demonstrated the successful use of mutation testing to ascertain the mutation status of the tumors of patients with NSCLC [16-18], and superior response to EGFR TKIs in patients with *EGFR* mutation-positive NSCLC compared with patients with *EGFR* mutation-negative NSCLC [16, 17, 19].

Current clinical guidelines now advocate the role of tumor *EGFR* mutation testing for patients with NSCLC during initial diagnosis [20, 21], as do several working groups [22-24]. More clinicians are requesting *EGFR* mutation tests for their patients with NSCLC/ADC, and the number of facilities that conduct the tests has increased [25, 26]. However, adoption of test-

Table 1. Frequency of *EGFR* mutations in patients with NSCLC of ADC histology by country

Country	No. studies	*EGFR* mutation frequency		
		No. patients with an *EGFR* mutation/ total no. patients	Overall *EGFR* mutation frequency (%)	*EGFR* mutation frequency range (%)
Asia-Pacific				
Overall	87	5958/12819	47	20-76
China	18 [27, 34-50]	1403/2949	48	27-66
Hong Kong	3 [27, 51, 52]	312/585	53	47-58
Japan	33 [53-84]	2069/4619	45	21-68
Malaysia	2 [85, 86]	272/599	45	39-47
Philippines	1 [27]	34/65	52	N/A
Republic of Korea	17 [87-103]	1248/2884	43	20-56
Singapore	2 [104, 105]	57/142	40	39-43
Taiwan	9 [27, 75, 106-112]	423/739	57	36-76
Thailand	1 [27]	63/117	54	N/A
Vietnam	1 [27]	77/120	64	N/A
Europe				
Overall	39	1527/10464	15	6-41
Austria	1 [113]	7/96	7	N/A
Czech Republic	1 [114]	21/101	21	N/A
Finland	1 [115]	58/398	10	N/A
France	2 [116, 117]	193/1289	15	15-17
Germany	7 [118-124]	175/1573	11	6-41
Greece	2 [125, 126]	30/137	22	20-22
Italy	9 [127-135]	306/2223	14	10-33
Lithuania	1 [136]	8/65	12	N/A
The Netherlands	2 [13, 137]	162/1110	15	11-20
Norway	1 [138]	16/141	11	N/A
Poland	3 [139-141]	88/678	13	11-14
Portugal	1 [142]	29/216	13	N/A
Russia	2 [143, 144]	53/240	22	20-31
Slovakia	1 [145]	56/285	20	N/A
Spain	1 [146]	283/1634	17	N/A
Sweden	1 [147]	16/148	11	N/A
Turkey	2 [148, 149]	15/41	37	22-41
UK	1 [150]	11/89	12	N/A
North America				
Overall	19	1638/7396	22	3-42
Canada	2 [151, 152]	84/612	14	14
USA	16 [7, 75, 153-165]	1531/6663	23	3-42
USA (African Americans)	1 [166]	23/121	19	N/A
Indian subcontinent				
Overall	5	278/1090	26	22-27
Bangladesh	1 [167]	14/61	23	N/A
India	3 [27, 168, 169]	261/1018	26	22-26
Pakistan	1 [170]	3/11	27	N/A
South America				
Overall	5	250/686	36	9-67

Argentina	1 [30]	47/244	19	N/A
Brazil	3 [171-173]	67/239	28	9-34
Peru	1 [30]	136/203	67	N/A
Oceania				
Overall	4	69/570	12	7-36
Australia	4 [75, 174-176]	69/570	12	7-36
Africa				
Overall	1	29/137	21	N/A
Morocco	1 [177]	29/137	21	N/A

ADC adenocarcinoma, *EGFR* epidermal growth factor receptor, *N/A* not available, *NSCLC* non-small-cell lung cancer.

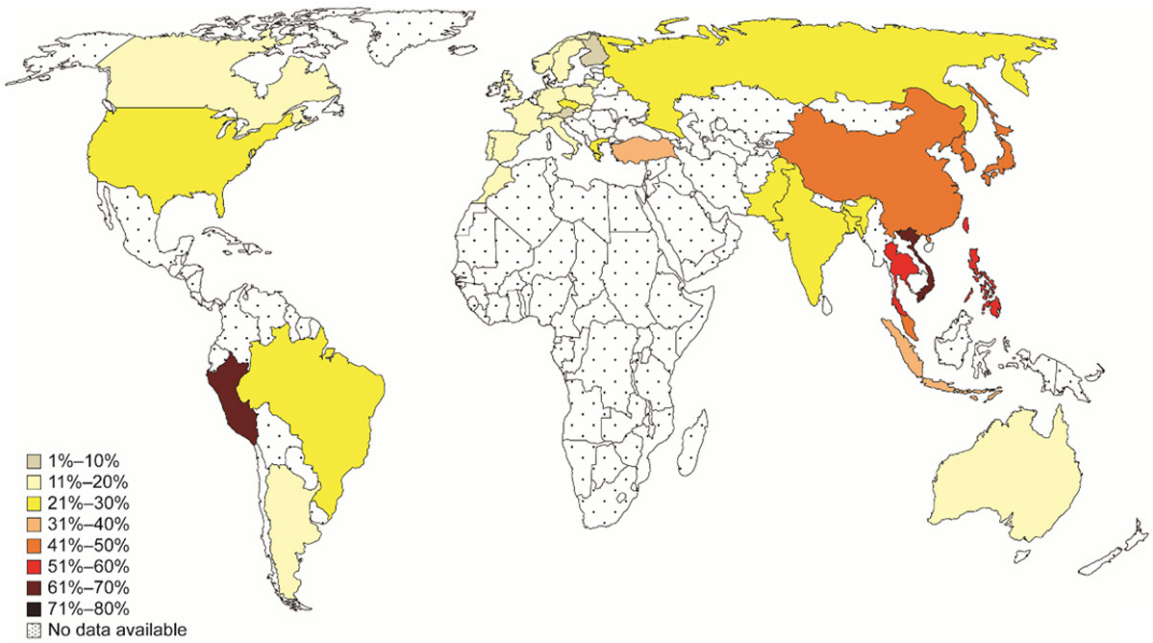

Figure 2. Global *EGFR* mutMap: *EGFR* mutation frequency in patients with NSCLC of ADC histology by country (where data available). See **Table 1** for study and patient numbers for each country. *ADC* adenocarcinoma, *EGFR* epidermal growth factor receptor, *NSCLC* non-small-cell lung cancer.

ing may be influenced by differences both within and between geographic regions/countries. It is important to understand where *EGFR* mutation testing is less routinely carried out, and why, to facilitate routes for clinicians/patients to access tests and have the opportunity to receive personalized therapy.

Studies of patients with NSCLC/ADC have provided robust data demonstrating the frequency of *EGFR* mutations in Western and Asian populations only [5, 27]. There is limited understanding of the availability of mutation-status data indicating the presence of testing, and the prevalence and distribution of *EGFR* mutations in tumors of patients with NSCLC/ADC globally; further to this, the potential environmental [28] and genetic [29] influences on population differences in *EGFR* mutation status are yet to be fully elucidated. The aim of this systematic review is to describe the *EGFR* mutation frequency in patients with NSCLC/ADC from multiple ethnic backgrounds and create a global map of *EGFR* mutation prevalence (a 'global *EGFR* mutMap').

Methods

Literature search

A literature search of the MEDLINE database was carried out on February 18, 2014, to identify journal articles reporting studies of *EGFR*

Table 2. Frequency of *EGFR* mutations in patients with NSCLC of ADC histology by gender and country

Country	No. studies	*EGFR* mutation frequency					
		Males			Females		
		No. patients with an *EGFR* mutation/ total no. patients	Overall *EGFR* mutation frequency (%)	*EGFR* mutation frequency range (%)	No. patients with an *EGFR* mutation/ total no. patients	Overall *EGFR* mutation frequency (%)	*EGFR* mutation frequency range (%)
Asia-Pacific							
Overall	20	473/1250	37	20-80	763/1263	60	0-83
China	4 [36, 40, 46, 49]	41/86	48	25-80	43/62	69	29-83
Hong Kong	1 [51]	28/84	33	N/A	87/131	66	N/A
Japan	10 [60, 61, 65, 68, 69, 74, 76, 77, 80, 82]	345/893	39	34-67	534/866	62	0-76
Republic of Korea	4 [87, 89, 94, 95]	41/152	27	20-36	75/162	46	38-80
Taiwan	1 [111]	18/35	51	N/A	24/42	57	N/A
Europe							
Overall	9	88/1035	9	4-18	133/616	22	3-35
Austria	1 [113]	3/58	5	N/A	4/38	11	N/A
Germany	2 [118, 120]	15/211	7	4-12	27/163	17	14-23
Greece	1 [125]	3/17	18	N/A	1/3	33	N/A
Italy	3 [127, 133, 135]	26/323	8	6-13	49/215	23	13-35
Poland	1 [140]	25/310	8	N/A	30/121	25	N/A
Russia	1 [143]	16/116	14	N/A	22/76	29	N/A
North America							
Overall	2	175/923	19	8-20	459/1656	28	21-28
USA	2 [7, 157]	175/923	19	8-20	459/1656	28	21-28
Indian subcontinent							
Overall	3	160/689	23	23-26	99/318	31	14-33
Bangladesh	1 [167]	12/47	26	N/A	2/14	14	N/A
India	2 [168, 169]	148/642	23	23	97/304	32	32-33
Africa							
Overall	1	7/91	8	N/A	22/46	48	N/A
Morocco	1 [177]	7/91	8	N/A	22/46	48	N/A

ADC adenocarcinoma, *EGFR* epidermal growth factor receptor, *N/A* not available, *NSCLC* non-small-cell lung cancer.

Table 3. Frequency of *EGFR* mutations in patients with NSCLC of ADC histology by smoking status and country

Country	No. studies	*EGFR* mutation frequency					
		Never-smokers*			Ever-smokers*		
		No. patients with an *EGFR* mutation/ total no. patients	Overall *EGFR* mutation frequency (%)	*EGFR* mutation frequency range (%)	No. patients with an *EGFR* mutation/total no. patients	Overall *EGFR* mutation frequency (%)	*EGFR* mutation frequency range (%)
North America							
Overall	6[a]	680/1433	47	38-56	433/3151	14	6-16
USA	6[a] [7, 155, 157, 159, 161, 178]	680/1433	47	38-56	433/3151	14	6-16
Asia-Pacific							
Overall	20	847/1312	64	40-83	426/1242	33	11-100
China	4 [36, 40, 46, 49]	97/134	72	50-79	28/66	42	11-100
Hong Kong	1 [51]	94/129	73	N/A	21/86	24	N/A
Japan	9 [60, 61, 68, 69, 74, 76, 77, 80, 82]	549/829	66	57-83	326/919	35	26-54
Republic of Korea	4 [87, 89, 94, 95]	81/171	47	40-62	35/143	24	21-29
Taiwan	1 [111]	26/49	53	N/A	16/28	57	N/A
Europe							
Overall	6	61/176	35	23-50	31/373	8	3-17
Austria	1 [113]	5/22	23	N/A	2/74	3	N/A
Germany	1 [120]	12/24	50	N/A	8/90	9	N/A
Greece	1 [125]	1/2	50	N/A	3/18	17	N/A
Italy	2 [133, 135]	13/34	38	37-50	10/93	11	5-13
Russia	1 [143]	30/94	32	N/A	8/98	8	N/A
Indian subcontinent							
Overall	2	38/118	32	22-35	19/109	17	14-24
Bangladesh	1 [167]	5/23	22	N/A	9/38	24	N/A
India	1 [169]	33/95	35	N/A	10/71	14	N/A
Africa							
Overall	1	24/58	41	N/A	5/79	6	N/A
Morocco	1 [177]	24/58	41	N/A	5/79	6	N/A

*As defined by original study criteria. [a]Ever-smokers category had 5 studies. *ADC* adenocarcinoma, *EGFR* epidermal growth factor receptor, *N/A* not available, *NSCLC* non-small-cell lung cancer.

mutation frequency/incidence in patients with NSCLC/ADC. The following search criteria were used: [EGFR] AND [mutation] AND [lung cancer] AND [adenocarcinoma] AND [publication date after January 1, 2004]. The following were excluded: [non-English language papers] AND [Review] AND [Comment] AND [Editorial] AND [Letter].

Publications yielded in this initial search were reviewed and shortlisted; studies were only included if they had a population of ≥ 100 patients, although this criterion was waived in countries where data were sparse.

Where the initial search yielded no data from certain countries, additional literature searches of PubMed, BIOSIS, and Embase were carried out on June 23, 2014, using the previous search criteria with the addition of specific country names, to identify any additional relevant publications.

Analysis of EGFR mutation frequency

EGFR mutation frequency data were analyzed by country, gender, and smoking status (never- or ever-smokers, according to the definitions of the original studies). A map of the world was populated with available *EGFR* mutation frequency data by country (a 'global *EGFR* mutMap').

Results

Included studies

The initial literature search yielded 720 publications, from which 139 were selected, based upon the criteria that they contained relevant *EGFR* mutation frequency data in patients with NSCLC/ADC. Gaps were identified in Brazil, Denmark, Finland, Latin America, Mexico, Norway, Russia, Saudi Arabia, South America, Sweden, Turkey, and the UK; therefore, an additional literature search of PubMed, BIOSIS, and Embase was carried out on June 23, 2014, which yielded an additional 12 publications. This resulted in a total of 151 studies included in this review (*n*=33162 patients with NSCLC, of which *n*=9749 had *EGFR* mutation-positive NSCLC/ADC) (**Figure 1**; Supplementary Table 1). This included 70 smaller studies of < 100 patients with NSCLC/ADC (19/70 studies, *n* ≥ 70 patients; 40/70, *n* ≥ 50 patients), in the interest of providing as comprehensive a review as possible (Supplementary Table 1) from the following countries: Australia, Bangladesh, Brazil, China, Germany, Greece, Italy, Japan, Lithuania, Taiwan, Turkey, the UK, the USA, the Philippines, Pakistan, Republic of Korea, and Singapore.

As expected from previous reports [5] and consistent with NSCLC incidence figures [1], there were more data available for NSCLC/ADC patient populations in the Asia-Pacific and European geographic regions (87 studies, 12819 patients; 39 studies, 10464 patients, respectively). Data available for patient populations of the other geographic regions included were as follows (in decreasing order): North America (19 studies, 7396 patients; including one study in US African-Americans [121 patients]); Indian subcontinent (5 studies, 1090 patients); South America (5 studies, 686 patients); Oceania (4 studies, 570 patients); and Africa (1 study, 137 patients) (**Table 1**).

EGFR mutation frequency in patients with NSCLC/ADC by geographic region

EGFR mutation frequency in patients with NSCLC/ADC is summarized in **Table 1** and is represented as a 'global *EGFR* mutMap' in **Figure 2**.

When analyzed by geographic region, the Asia-Pacific NSCLC/ADC subgroup had the highest *EGFR* mutation frequency at 47% (*n*=5958/12819; 87 studies; range 20%-76%). Within this region, Taiwan had the highest *EGFR* mutation frequency in patients with NSCLC/ADC (57% [*n*=423/739; 9 studies; range 36%-76%]), while Singapore had the lowest (40% [*n*=57/142; 2 studies; range 39%-43%]), although comparisons between these countries were limited due to the differing patient population sizes (**Table 1**).

Of all the geographic regions included, the Oceania NSCLC/ADC subgroup, which only included data from Australia, had the lowest *EGFR* mutation frequency at 12% [*n*=69/570; 4 studies; range 7%-36%]) (**Table 1**; **Figure 2**).

The South American NSCLC/ADC subgroup had the widest *EGFR* mutation frequency range and second highest *EGFR* mutation frequency (36% [*n*=250/686; 5 studies; range 9%-67%]);

although this result was skewed by data from one study of patients from Peru (*EGFR* mutation frequency, 67% [*n*=136/203]). The narrowest *EGFR* mutation frequency range was observed in the Indian subcontinent NSCLC/ADC subgroup (*EGFR* mutation frequency, 26% [*n*=278/1090; 5 studies; range 22%-27%]) (**Table 1**; **Figure 2**).

EGFR mutation frequency in patients with NSCLC/ADC by geographic region and gender

In all regions where data were available, *EGFR* mutation frequency in patients with NSCLC/ADC was higher in women compared with men: Europe, 22% versus 9%; Asia-Pacific 60% versus 37%; Indian subcontinent, 31% versus 23%; Africa, 48% versus 8%; and North America 28% versus 19% (**Table 2**). All country-specific NSCLC/ADC subgroups followed this pattern, apart from Bangladesh, where the *EGFR* mutation frequency was higher in men than in women (26% versus 14%, respectively) (**Table 2**).

EGFR mutation frequency in patients with NSCLC/ADC by geographic region and smoking status

In all regions where data were available, *EGFR* mutation frequency in NSCLC/ADC was higher in never-smokers compared with ever-smokers: Europe, 35% versus 8%; Asia-Pacific, 64% versus 33%; Indian subcontinent, 32% versus 17%; Africa, 41% versus 6%; and North America, 47% versus 14% (**Table 3**). Similar to *EGFR* mutation prevalence by gender, this pattern was followed by all country-specific subgroups apart from Bangladesh and Taiwan, where *EGFR* mutation frequency was higher in ever-smokers compared with never-smokers (24% versus 22% for Bangladesh; 57% versus 53% for Taiwan, respectively) (**Table 3**).

Discussion

This review investigated *EGFR* mutation frequency in patients with NSCLC/ADC to create a 'global *EGFR* mutMap' to visually represent *EGFR* mutation frequency in countries where data were available, and to identify where there is still a need for more studies to be carried out.

Results of this review reflected the robust data available for *EGFR* mutation frequency in Western/Asian populations, building upon and supporting the results of previous studies and meta-analyses in these ethnicities. In the first 'mutMap' study of the incidence and coincidence of genetic mutations associated with NSCLC, *EGFR* mutation frequency was 47.9% in Asian patients with NSCLC/ADC, compared with 19.2% in Western patients with NSCLC/ADC [5]. These data are similar to our findings in related patient populations: Asia-Pacific subgroup, 47%; and European subgroup, 15%. The slight decrease in *EGFR* mutation frequency in the European subgroup of this study compared with the first mutMap study may be due to differing studies/patient populations used in the analyses. In addition, *EGFR* mutations in patients with NSCLC/ADC were more prevalent in, but not exclusive to, Asian patients compared with patients of other ethnicities included in this study; and across most countries where data were available, *EGFR* mutations in patients with NSCLC/ADC were more prevalent in, but not exclusive to, females and never-smokers, with only data from patients in Bangladesh and Taiwan differing from this pattern. Results of the first mutMap study similarly indicated that although *EGFR* mutations occurred more frequently in females, Asians, and never-/light-smokers, mutations were also found outside of these three subgroups [5]. Likewise, results of the PIONEER molecular epidemiology study across seven Asian countries/regions also found that although *EGFR* mutations occurred more frequently in females, Asians, and never-smokers, *EGFR* mutations were not restricted to patients with these clinical characteristics. In fact, more than 50% of patients with *EGFR* mutations in the PIONEER study were *not* female non-smokers [27]. These findings, therefore, support *EGFR* mutation testing in all patients with NSCLC/ADC.

The review also highlighted that despite the burden of NSCLC reported to exist in these large geographic regions by global registries [1], a substantial lack of data was observed from Africa, the Middle East, Central Asia, and Central and South America; with no data available at all for several countries within these regions (**Figure 2**). The importance of determining the prevalence of *EGFR* mutations in these regions/countries is emphasized by the interesting result that *EGFR* mutation frequency in NSCLC/ADC was particularly high in patients

from Peru (67% [*n*=136/203]) [30], with the population of this study taken almost exclusively from the indigenous ('Mestizo'), not historically Caucasian, population (68% versus 32% of the study sample, respectively). While only limited conclusions can be drawn from this single study, it does suggest NSCLC patient populations around the world may yet yield important findings. The paucity of published data in these regions/countries may reflect a lack of routine mutation testing in the clinical management of patients with NSCLC, which may be due to various factors, including tumor sampling practices, patients' ability/willingness to undergo sampling, and availability/use of mutation tests. More global research into the infrastructure around diagnosis and management of NSCLC, and *EGFR* mutation frequencies, in regions outside of Europe and Asia will further understanding of this, and facilitate development of local clinical guidelines.

Where data were available, there was substantial variation in *EGFR* mutation frequency between studies, even when grouped by geographic region and country, which may be explained by several factors - for example, preselection of patients, differing patient baseline characteristics, underlying genetic differences between populations, variations in mutation-testing practices, and environmental factors-which are yet to be fully understood [28]. Considering genetic differences between populations, as well as different *EGFR* mutation subtypes existing [31], *EGFR* amplification and regulation of protein expression may also differ between patients [29]; a number of studies have identified polymorphisms in the *EGFR* promoter region and demonstrated that these polymorphisms have a functional impact on *EGFR* protein transcription or expression in non-cancerous tissues [32, 33]. Furthermore, a study by Nomura et al. [29] has demonstrated that differences in prevalence of three of these polymorphisms exist between Asian and Western patients. This review found that *EGFR* mutation prevalence in the Indian subcontinent and South American populations lies between the prevalence in Asian and Western populations. One hypothesis may be that this intermediate *EGFR* mutation expression pattern may be explained, in part, by differences in *EGFR* promoter polymorphisms. Therefore, a study is potentially warranted that examines reasons for differences in prevalence of *EGFR* mutations and the link with, for example, environmental factors or *EGFR* promoter polymorphisms, and potentially EGFR expression in non-cancerous tissues.

This review comprises the most comprehensive summary to date of the global *EGFR* mutation frequency in patients with NSCLC/ADC. However, it has to be considered that the results presented here reflect only the available and relevant published data and, therefore, comprise a small sample size relative to the global population. This is especially relevant for this study, where data from 70 small studies (in Australia, Bangladesh, Brazil, China, Germany, Greece, Italy, Japan, Lithuania, Taiwan, Turkey, the UK, the USA, the Philippines, Pakistan, Republic of Korea, and Singapore), each of < 100 patients with NSCLC, were included in the interest of providing the most comprehensive review possible. Variations in study design and diagnostic and mutation-testing procedures between studies should also be considered.

Further work in less-studied regions-in particular, Africa, the Middle East, Central Asia, and Central and South America-is required to widen the scope and validity of this 'global *EGFR* mutMap'. In addition, global mutation frequency data for multiple oncogenes known to be associated with NSCLC could be used to further inform global registries of the prevalence of NSCLC [1], to facilitate a registry of NSCLC incidence by mutation status. Building on the foundations laid here, further efforts to accurately establish the prevalence of *EGFR* mutations in a greater number of NSCLC/ADC patient populations will help to ensure that the appropriate knowledge, clinical guidelines, and resources are in place to improve treatment outcomes for more patients worldwide.

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Disclosure of conflict of interest

Anita Midha, Simon Dearden and Rose McCormack are employees of AstraZeneca and hold shares in AstraZeneca.

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Supplementary Table 1. Summary of included studies

Published study	Population/Country	NSCLC/ADC	
		Number of patients with NSCLC/ADC	Number of patients with NSCLC/ADC and *EGFR* mutation
An SJ et al. PLoS One 2012; 7 (6): e40109 [39]	China	347	140
Arrieta O et al. J Thorac Oncol 2011; 6 (11): 1955-1959 [30]	Argentina	244	47
	Peru	203	136
Bacchi CE et al. Clinics (Sao Paulo) 2012; 67 (5): 419-424 [171]	Brazil	169	57
Bae NC et al. Cancer Genet Cytogenet 2007; 173 (2): 107-113 [87]	Republic of Korea	55	20
Bai H et al. J Clin Oncol 2009; 27 (16): 2653-2659 [37]	China	171	66
Boch C et al. BMJ Open 2013; 3 (4) [118]	Germany	254	22
Boldrini L et al. Oncol Rep 2009; 22 (4): 683-691 [127]	Italy	411	52
Bozzetti C et al. Diagn Cytopathol 2013; 41 (7): 595-598 [128]	Italy	15	5
Brannan JM et al. Clin Cancer Res 2009; 15 (13): 4423-4430 [153]	USA	158	18
Cai YR et al. Oncol Rep 2011; 26 (4): 877-885 [47]	China	80	25
Capuzzo F et al. J Clin Oncol 2009; 27 (10): 1667-1674 [129]	Italy	144	14
Carneiro JG et al. Genet Res (Camb) 2014; 96: e002 [172]	Brazil	45	4
Castro AS et al. Rev Port Pneumol 2013; 19 (1): 7-12 [142]	Portugal	216	29
Cetin Z et al. Med Oncol 2010; 27 (3): 853-860 [148]	Turkey	9	2
Chang YL et al. Clin Cancer Res 2007; 13 (1): 52-58 [108]	Taiwan	51	39
Chang YL et al. Ann Surg Oncol 2011; 18 (2): 543-550 [109]	Taiwan	34	18
Chitale D et al. Oncogene 2009; 28 (31): 2773-2783 [154]	USA	199	43
Chougule A et al. PLoS One 2013; 8 (10): e76164 [168]	India	780	202
Cooper WA et al. J Clin Pathol 2013; 66 (9): 744-748 [174]	Australia	204	30
D'Angelo SP et al. J Thorac Oncol 2012; 7 (12): 1815-1822 [155]	USA	1118	222
Ding L et al. Nature 2008; 455 (7216): 1069-1075 [7]	USA	188	30
Doval DC et al. J Carinog 2013; 12: 12 [169]	India	166	43
Errihani H et al. J Thorac Oncol 2013; 8 (9): 1212-1214 [177]	Morocco	137	29
Fong Y et al. Respirology 2010; 15 (4): 700-705 [111]	Taiwan	77	42
Gahr S et al. Br J Cancer 2013; 109 (7): 1821-1828 [119]	Germany	944	93
Gandara DR et al. J Thorac Oncol 2010; 5 (12): 1933-1938 [156]	USA	712	144
Gaughan EM et al. Lung Cancer 2013; 79 (3): 193-197 [178]	USA	199[a]	87[a]
Girard N et al. Eur Respir J 2012; 39 (2): 366-372 [157]	France	2392	604
Gow CH et al. Ann Oncol 2009; 20 (4): 696-702 [106]	Taiwan	42	15
Han B et al. Oncol Lett 2011; 2 (6): 1233-1237 [46]	China	24	8

Han CB et al. Cancer Letters 2012; 314 (1): 63-72 [40]	China	15	4
He C et al. Int J Cancer 2009; 125 (10): 2393-2399 [38]	China	101	60
He Y et al. Lung Cancer 2013; 81 (2): 162-166 [44]	China	441	198
Helland Å et al. J Thorac Oncol 2011; 6 (5): 947-950 [138]	Norway	141	16
Hlinkova K et al. Diagn Mol Pathol 2013; 22 (2): 70-75 [145]	Slovakia	285	56
Honma HN et al. Target Oncol 2014; 9: 389-394 [173]	Brazil	25	6
Hoque MO et al. J Thorac Oncol 2010; 5 (12): 1887-1893 [158]	USA	49	3
Horiike A et al. Chest 2007; 131 (6): 1628-1634 [53]	Japan	58	23
Hosokawa S et al. Lung Cancer 2009; 66 (1): 107-113 [54]	Japan	68	36
Hsieh MH et al. Lung Cancer 2006; 53 (3): 311-322 [107]	Taiwan	52	30
Inamura K et al. J Thorac Oncol 2008; 3 (1): 13-17 [55]	Japan	74	41
Isaksson S et al. Virchows Arch 2013; 463 (6): 755-764 [147]	Sweden	148	16
Iwakiri S et al. Cancer 2009; 115 (11): 2580-2593 [56]	Japan	53	26
Kalikaki A et al. Lung Cancer 2010; 69 (1): 110-115 [126]	Greece	117	26
Kalikaki A et al. Br J Cancer 2008; 99 (6): 923-929 [125]	Greece	20	4
Kamila WK et al. Clin Exp Metastatis 2013; 30 (8): 1063-1071 [139]	Poland	61	7
Kang HJ et al. Respir Med 2014; 108 (2): 388-394 [88]	Republic of Korea	440	90
Kang SM et al. Cancer 2007; 109 (3): 581-587 [89]	Republic of Korea	25	11
Kim HJ et al. Lung Cancer 2012; 75 (3): 321-325 [90]	Republic of Korea	152	78
Kim HR et al. Lung Cancer 2014; 83 (2): 252-258 [91]	Republic of Korea	99	55
Kim YT et al. J Thorac Oncol 2013; 8 (2): 171-178 [92]	Republic of Korea	636	346
Kobayashi M et al. Anticancer Res 2011; 31 (12): 4619-4623 [57]	Japan	381	185
Koga T et al. Int J Cancer 2011; 128 (5): 1009-1017 [58]	Japan	165	48
Kondo M et al. Lung Cancer 2005; 50 (3): 385-391 [59]	Japan	53	13
Kosaka T et al. Cancer Res 2004; 64 (24): 8919-8923 [60]	Japan	224	110
Kosaka T et al. J Thorac Oncol 2009; 4 (1): 22-29 [61]	Japan	397	196
Krawczyk P et al. Pathol Oncol Res 2014; 20 (1): 107-112 [140]	Poland	431	55
Lai Y et al. Int J Mol Sci 2013; 14 (12): 24549-24559 [41]	China	293	155
Lee JO et al. J Thorac Oncol 2011; 6 (9): 1474-1480 [93]	Republic of Korea	78	37
Lee SY et al. J Thorac Oncol 2010; 5 (11): 1734-1740 [94]	Republic of Korea	117	36
Lee YJ et al. J Cancer Res Clin Oncol 2009; 135 (12): 1647-1654 [95]	Republic of Korea	117	49
Lee YJ et al. J Cancer Res Clin Oncol 2010; 136 (12): 1937-1944 [96]	Republic of Korea	233	100
Li C et al. J Thorac Oncol 2011; 6 (6): 1016-1021 [49]	China	89	59
Li Y et al. PLoS One 2013; 8 (1): e52093 [45]	China	95	42
Liam CK et al. Asian Pac J Cancer Prev 2014; 15 (1): 321-326 [85]	Malaysia	132	52

Lim EH et al. J Thorac Oncol 2009; 4 (1): 12-21 [104]	Singapore	42	18
Lin CC et al. J Thorac Oncol 2010; 5 (9): 1424-1429 [110]	Taiwan	97	50
Liu Y et al. Int J Clin Exp Pathol 2013; 6 (9): 1880-1889 [42]	China	193	118
Ludovini V et al. J Thorac Oncol 2011; 6 (4): 707-715 [130]	Italy	126	38
Mäki-Nevala S et al. J Thorac Oncol 2014; 9 (6): 886-891 [115]	Finland	398	58
Marchetti A et al. J Clin Oncol 2011; 29 (26): 3574-3579 [132]	Italy	739	86
Marchetti A et al. J Clin Oncol 2005; 23 (4): 857-865 [131]	Italy	375	39
Mariano C et al. Lung Cancer 2014; 83 (1): 73-77 [151]	Canada	381	52
Matsumoto S et al. Oncogene 2007; 26 (40): 5911-5918 [62]	Japan	155	54
McMillen E et al. Exp Lung Res 2010; 36 (9): 531-537 [48]	USA	128	48
Mehmood T et al. Lung Cancer 2013; 80 (Suppl 1): S2 [170]	Pakistan	11	3
Mitsudomi T et al. J Clin Oncol 2005; 23 (11): 2513-2520 [63]	Japan	50	32
Mochinaga K et al. Clin Lung Cancer 2014; 15 (2): 136-144 [64]	Japan	64	34
Moiseyenko VM et al. Onkologie 2010; 33 (5): 231-238 [143]	Russia	192	38
Mounawar M et al. Cancer Res 2007; 67 (12): 5667-5672 [144]	Russia	48	15
Mu XL et al. Clin Cancer Res 2005; 11 (12): 4289-4294 [35]	China	51	26
Munfus-McCray D et al. Hum Pathol 2011; 42 (10): 1447-1453 [159]	USA	60	13
Na II et al. Lung Cancer 2010; 67 (1): 76-80 [97]	Republic of Korea	53	18
Na II et al. ISRN Oncol 2011; 2011: 756265 [98]	Republic of Korea	81	32
Nagashima O et al. J Thorac Dis 2013; 5 (1): 27-30 [65]	Japan	11	4
Nakajima T et al. Chest 2011; 140 (5): 1319-1324 [66]	Japan	127	39
Nakamura R et al. J Thorac Oncol 2014; 9 (9): 1340-1344 [67]	Japan	69	33
Ninomiya H et al. Lung Cancer 2009; 63 (2): 235-240 [68]	Japan	107	63
Oh JE et al. APMIS 2011; 119 (7): 403-411 [99]	Republic of Korea	70	31
Okayama H et al. Cancer Res 2012; 72 (1): 100-111 [69]	Japan	226	127
Onozato R et al. J Thorac Oncol 2009; 4 (1): 5-11 [70]	Japan	211	103
Paik PK et al. J Clin Oncol 2011; 29 (15): 2046-2051 [160]	USA	687	165
Paik PK et al. Cancer 2012; 118 (23): 5840-5847 [161]	USA	675	164
Pallier K et al. Mol Carcinog 2009; 48 (7): 581-585 [116]	France	145	25
Park S et al. J Thorac Oncol 2009; 4 (7): 809-815 [100]	Republic of Korea	61	18
Pesek M et al. Anticancer Res 2009; 29 (7): 2767-2773 [114]	Czech Republic	101	21
Qin BM et al. Cell Res 2005; 15 (3): 212-217 [34]	China	17	7
Ragusa M et al. Am J Clin Oncol 2014; 37 (4): 343-349 [133]	Italy	102	20
Rahman S et al. Int J Clin Oncol 2014; 19 (1): 45-49 [167]	Japan	61	14
Reinersman JM et al. J Thorac Oncol 2011; 6 (1): 28-31 [166]	USA (African Americans)	121	23

Reinmuth N et al. Lung Cancer 2008; 62 (2): 193-201 [120]	Germany	120	20
Rosell R et al. N Engl J Med 2009; 361 (10): 958-967 [146]	Spain	1634	283
Sakuma Y et al. Am J Clin Pathol 2007; 128 (1): 100-108 [71]	Japan	118	74
Santis G et al. PLoS One 2011; 6 (9): e25191 [150]	UK	89	11
Sartori G et al. Am J Clin Pathol 2009; 131 (4): 478-489 [134]	Italy	286	49
Sasaki H et al. Clin Cancer Res 2005; 11 (8): 2924-2929 [179]	Japan	49	12
Sasaki H et al. J Cancer Res Clin Oncol 2008; 134 (5): 569-577 [74]	Japan	22	14
Sasaki H et al. Lung Cancer 2007; 58 (3): 324-328 [73]	Japan	205	43
Sasaki H et al. Lung Cancer 2006; 54 (1): 103-108 [72]	Japan	362	112
Schittenhelm MM et al. Mol Cancer Ther 2009; 8 (3): 481-489 [121]	Germany	18	1
Schmid K et al. Clin Cancer Res 2009; 15 (14): 4554-4560 [113]	Austria	96	7
Schmid-Bindert G et al. PLoS One 2013; 8 (10): e77948 [122]	Germany	49	20
Seo AN et al. Lung Cancer 2014; 83 (3): 316-323 [101]	Republic of Korea	240	111
Sequist LV et al. Oncologist 2007; 12 (1): 90-98 [180]	USA	176	63
Shi Y et al. J Thorac Oncol 2014; 9 (2): 154-162 [27]	Hong Kong	161	76
	India	72	16
	China	741	372
	Philippines	65	34
	Taiwan	174	108
	Thailand	117	63
	Vietnam	120	77
Shi Yeen TN et al. J Biomed Sci 2013; 20: 22 [86]	Malaysia	467	220
Shibata T et al. Cancer Sci 2007; 98 (7): 985-991 [163]	Japan	86	36
Shigematsu H et al. J Natl Cancer Inst 2005; 97 (5): 339-346 [75]	Japan	154	67
	Taiwan	55	31
	USA	44	11
	Australia	36	5
Smits AJ et al. Cell Oncol (Dordr) 2012; 35 (3): 189-196 [13]	The Netherlands	620	66
Sonobe M et al. Br J Cancer 2005; 93 (3): 355-363 [76]	Japan	108	60
Soung YH et al. Virchows Arch 2005; 446 (5): 483-488 [102]	Republic of Korea	69	26
Sriram KB et al. Eur Respir J 2011; 38 (4): 903-310 [175]	Australia	294	21
Sugio K et al. Lung Cancer 2009; 64 (3): 314-318 [77]	Japan	322	136
Sun M et al. Clin Cancer Res 2009; 15 (15): 4829-4837 [164]	USA	30	1
Sun PL et al. J Thorac Oncol 2012; 7 (2): 323-330 [103]	Republic of Korea	358	190
Sun Y et al. J Clin Oncol 2010; 28 (30): 4616-4620 [181]	China	52[a]	41[a]

Suzuki M et al. Cancer 2006; 106 (10): 2200-2207 [78]	Japan	79		36
Szumera-Ciećkiewicz A et al. Int J Clin Exp Pathol 2013; 6 (12): 2800-2812 [141]	Poland	186		26
Takahashi T et al. Ann Surg Oncol 2010; 17 (3): 889-897 [79]	Japan	211		105
Tam IY et al. Clin Cancer Res 2006; 12 (5): 1647-1653 [51]	Hong Kong	215		115
Togashi Y et al. Med Oncol 2012; 29 (5): 3169-3175 [80]	Japan	178		95
Toh CK et al. J Thorac Oncol 2010; 5 (1): 17-22 [105]	Singapore	100		39
Tomizawa Y et al. Clin Cancer Res 2005; 11 (19 Pt 1): 6816-6822 [81]	Japan	72		29
Toyooka S et al. Cancer Res 2006; 66 (3): 1371-1375 [82]	Japan	164		74
Tsao AS et al. J Thorac Oncol 2006; 1 (3): 231-239 [165]	USA	89		14
Tsao MS et al. J Thorac Oncol 2011; 6 (1): 139-147 [152]	Canada	231		32
Uhara M et al. Clin Chim Acta 2009; 401 (1-2): 68-72 [83]	Japan	44		19
Ulivi P et al. Int J Oncol 2012; 41 (1): 147-152 [135]	Italy	25		3
Unal OU et al. Asian Pac J Cancer Prev 2013; 14 (6): 3705-3709 [149]	Turkey	32		13
Vagulienė N et al. Medicina (Kaunas) 2012; 48 (4): 175-181 [136]	Lithuania	65		8
Vallee A et al. Int J Oncol 2013; 43 (4): 1045-1051 [117]	France	1144		168
Varella-Garcia M et al. J Thorac Oncol 2009; 4 (3): 318-325 [84]	USA	38		26
Vincenten J et al. J Thorac Oncol 2012; 7 (10): 1522-1527 [137]	The Netherlands	490		96
Wang Z et al. Onkologie 2008; 31 (4): 174-178 [36]	China	20		13
Webb S et al. Asia Pac J Clin Oncol 2009; 5 (1): 66-71 [176]	Australia	36		13
Wiesweg M et al. Eur J Cancer 2013; 49 (15): 3076-3082 [123]	Germany	148		10
Wong DW et al. Cancer 2009; 115 (8): 1723-1733 [52]	Hong Kong	209		121
Wu CC et al. Cancer 2008; 113 (11): 3199-3208 [112]	Taiwan	157		90
Xu JM et al. J Cancer Res Clin Oncol 2009; 135 (6): 771-782 [50]	China	78		28
Zhang H et al. J Mol Diagn 2013; 15 (6): 819-826 [43]	China	65		34
Zimmer S et al. J Cancer Res Clin Oncol 2009; 135 (5): 723-730 [124]	Germany	40		9
Total[b]		33162	9749	

[a]Data only available for patients with NSCLC/ADC who are never/light smokers. [b]Not including data only available for patients with NSCLC/ADC who are never/light smokers. *ADC* adenocarcinoma, *EGFR* epidermal growth factor receptor, *N/A* not available, *NSCLC* non-small-cell lung cancer.