Prevalence and Patterns of EGFR Mutations in Non-Small Cell Lung Cancer in the Middle East and North Africa: A Systematic Review

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Abstract

To summarize current evidence and estimate the prevalence of epidermal growth factor receptor (EGFR) mutation frequency and its association with ethnicity and clinic-pathological features in non-small cell lung cancer (NSCLC) patients in the Middle East (ME) and North Africa (NA), a systematic literature review was undertaken. We conducted a literature search of original articles published in six databases (PubMed, Science Direct, Web of Science, Embase, Scopus, and Google scholar) from the time of inception until April 2021. Search terms included “lung cancer”, “NSCLC”, “EGFR mutation”, “Middle East”, “North Africa”, and specific country names belonging to the considered region. The included studies had to meet the following criteria: the study must relate to the role of the EGFR gene in NSCLC, analyze mutations in exon 18, 19, 20, and 21 or select exons of the EGFR gene, and provide sufficient information on the clinic-pathological characteristics of the included NSCLC patients. A total of 24 eligible studies were included ([66.6%] in the ME and [34.4%] in NA). Overall, 6544 patients with NSCLC were analyzed for EGFR mutations ([55.1%] in the ME and [44.8%] in NA). The overall prevalence of EGFR mutations was 17.9%. In the ME, the reported frequency was 17.3%, whereas in NA, the prevalence of EGFR mutations was 18.5%. The most frequently encountered mutations were the exon 19 deletions (45.2%) and exon 21 substitutions (30.9%). Exon 20 alterations were detected in 11.2%, of which, the T790M resistance mutation was the most prevalent (45.5%). Exon 18 mutations were reported in 3.8%. In the ME, 50.5% of NSCLC patients were positive for exon 19 deletions versus 48.3% in NA. Exon 21 mutations were slightly more commonly detected in the ME (36.3%) than in NA (31.3%). There was 1.2% of patients that had concurrent EGFR mutations. Overall, EGFR mutations prevalence was higher in females, non-smokers, and patients with adenocarcinoma. Our systematic literature review concurs that EGFR mutation prevalence among MENA populations is slightly higher than that seen in NSCLC patients of Caucasian ethnicity but is lower than that identified in Asian NSCLC patients. The distribution of these mutations varies significantly throughout the MENA region.

Introduction

Lung cancer occurred in approximately 2.2 million patients, representing 22.7% of the global cancer burden. In 2020, 1.8 million patients died of lung cancer [1]. It is the leading cause of cancer morbidity and mortality in men, whereas in women, it is the third most common cancer, behind breast and colorectal cancers, and the second leading cause of female cancer death. Incidence and mortality rates are roughly 2 times higher in men than in women, and the male-to-female ratio varies widely across regions, ranging from 1.2 in Northern America to 5.6 in Northern Africa [1]. The incidence and mortality estimates for lung cancer are 3 to 4 times higher in countries with a high Human Development Index (HDI) than in countries with a low HDI; this pattern may well change as the tobacco epidemic evolves given that 80% of smokers aged ≥15 years resided in low-income and middle-income countries in 2016 [2]. Worldwide, the lung cancer mortality rate is foreseen to increase up to 3 million by 2035. The figures are set to double for both genders (men: from 1.1 million in 2012 to 2.1 million by 2035; and women: from 0.5 million in 2012 to 0.9 million by 2035) and the existing gender gap is expected to persist. Most prominent increases are expected in Africa and the Eastern Mediterranean region [3].

The Middle East (ME) and North Africa (NA) countries have witnessed a steady increase in the incidence rates of lung cancer [4]. In 2018, an estimated new 79887 lung cancer cases were registered in the MENA region versus 470000 new diagnoses in Europe. The age-standardized incidence rate of lung cancer in the MENA region is less than international rates, with figures varying from lowest in Yemen (4.2 per 100,000) to highest in Lebanon (23 per 100,000) [5]. Lung cancer incidence rates increases are more eminent among older age groups in the MENA area [6]. Despite recent breakthroughs in lung cancer management, the 5-year relative survival rate in the region doesn't surpass 8%. This is largely due to late diagnoses. In the MENA countries, the highest mortality rates were reported in Morocco and Tunisia, whereas the lowest were in Yemen and Egypt [5].

Lung carcinomas are categorized by the size and appearance of the malignant cells and are divided into two broad categories of small cell lung cancers (SCLC) and non-small cell lung cancers (NSCLC). SCLC comprises about 10%-15% of all lung cancers. NSCLC is the most common type of lung cancer and accounts for 80-90% of all lung tumors. SCLC, commonly centrally located in the major airway, tends to grow and spread faster than NSCLC. It is estimated that 70% of SCLC patients present with locally advanced or distant metastatic disease at the time of diagnosis [7]. NSCLC is a highly heterogeneous disease and is mainly divided into three major histological subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, it harbors various genetic alterations within each subtype. The identification of mutations in certain histological subtypes has led to molecular sub-classification of NSCLC and also opened therapeutic opportunities for personalized medicine based on targeted drugs [8, 9]. Several mutations in NSCLC are considered actionable with available or promising targeted therapies. Some of the most common mutations for NSCLC occur in epidermal growth factor receptor (EGFR) and favor cell survival, proliferation and migration, and metastasis development by increasing the activity of EGFR tyrosine kinase [10]. EGFR tyrosine kinase inhibitors (TKIs) are established effective therapies in patients who have mutations in exons 18, 19, 20, and 21 of EGFR, leading to longer progression-free survival intervals with fewer or at least different side-effects than chemotherapy [11, 12].

Previous studies have established marked variations in EGFR mutation rates depending on different geographic locations and race/ethnicity backgrounds. It occurs at the rate of 10-15% in North Americans and Europeans, 15–20% in African-Americans, 20-30% in various East Asian series (Chinese, Koreans, Japanese), and 20–25% in patients from the Indian subcontinent [13–17]. In ME and African populations, the EGFR mutation frequency is higher than that shown in white populations but still lower than the frequency reported in Asian populations [18]. In the MENA, the frequency of EGFR mutations is considered among the lowest. To summarize current evidence and estimate the prevalence of EGFR mutations and its association with geographic region/country and clinic-pathological features of EGFR mutation-positive NSCLC patients in the Middle East (ME) and North Africa (NA). A systematic literature review was undertaken in Bahrain, Egypt, Iran, Iraq, Jordan, Kingdom of Saudi Arabia, Kuwait, Lebanon, Oman, Palestine, Qatar, Syria, Turkey, United Arab Emirates, Yemen, Algeria, Egypt, Morocco, and Tunisia.

Methods

We conducted a systematic review of literature published on EGFR mutation prevalence and its association with geographic region/country and clinic-pathological features in NSCLC patients in MENA region. We carried out a literature search of original articles published in six databases (PubMed, Science Direct, Web of science, Embase, Scopus, and Google scholar) from the time of inception until April 2021. Included articles have been published in English in
indexed and peer-reviewed journals. Search terms included lung cancer, or lung tumor, or lung adenocarcinoma, or NSCLC, or EGFR, or EGFR mutation, or EGFR oncogene mutations, or EGFR oncogenic driver mutation, or EGFR activating mutation, or EGFR prevalence, or EGFR rate, or EGFR incidence or EGFR frequency. An additional literature search was also conducted using Middle East, Middle Eastern, North Africa, North African and specific country names belonging to the considered region and any other variant names for any of the MENA countries (ex: Maghreb, Levant, Gulf, Arab). We manually checked reference lists of the included studies and relevant review articles to identify additional studies. We also searched relevant abstracts reported in the most important multi-disciplinary societies of medical oncology such as the American Society of Clinical Oncology (ASCO) meetings to identify unpublished studies.

Original articles were identified from Jordan [19], Iran [20, 21], Turkey [22–26], Bahrain [27], Iraq [29, 30], Lebanon [31–33], Morocco [35–37], Tunisia [38–40], Egypt [41], and Algeria [42]. A multicenter prospective study from Levant (Lebanone, Syria, Palestine, Jordan, Iraq, and Egypt) [34] and a multisite retrospective study from Gulf region (Saudi Arabia, the United Arab Emirates and Qatar) were also identified and will part of our analysis [28]. The included studies had to meet the following criteria: the study must relate to the role of the EGFR gene in NSCLC, analyze mutations in exon 18, 19, 20, and 21 or select exons of the EGFR gene, and provide sufficient information on the clinico-pathological characteristics of the included NSCLC patients.

A total of 24 studies met the inclusion criteria. In most studies, materials were formalin-fixed paraffin-embedded (FFPE) tissues and included small biopsies such as trans-bronchial biopsy or tru-cut biopsy and also resection materials. DNA extraction was applied on tissue samples using kits that extracted DNA from paraffin blocks. Mutations in exon 18 (codon 719), exon 19 deletions, exon 20 (codons 768 and 790), and exon 21 (codons 858 and 861) were assessed in 79.1% (19/24) of the studies. A wide variety of detection methods were used to identify recognized mutations of the EGFR kinase domain, from exon 18 to 21. Direct sequencing was broadly used, as it was used in the most of the studies [19–21, 23, 24, 26, 33, 34, 36, 37, 40]. RT-PCR-based assays, namely scorpions-amplification refractory mutation system (ARMS/Scorpion) methodology, was also widely used [27, 29, 31–33, 37, 40]. EGFR mutation analysis was carried out with quantitative PCR analysis in the study from Gulf region [41]. The INFINITI system using BioFilmChip-based microarray assay was used in one study from Turkey [22]. Details of the study methods and population characteristics are summarized in Table 1.
| Country/Region | Author [reference] | Year of publication | cases | Age (years) | Male/female n (%) | Smokers/non smokers n (%) | ADK/NADK n (%) | Detection Site (exon) | Test type |
|----------------|-------------------|---------------------|-------|-------------|-----------------|--------------------------|----------------|---------------------|-----------|
| Jordan         | Obeidatet al. [19] | 2016                | 166   | 59 ± 12.6   | 116 (70)/50 (30) | 129 (77)/37 (23)          | 166 (100)/0 (0) | 18, 19, 20, and 21  | PCR/Sequencing |
| Iran           | Mohammad et al. [20] | 2019               | 50    | 58.4 ± 13   | 30 (60)/20 (40)  | 31 (42)/29 (58)           | 50 (100)/0 (0)  | 18, 19, 20, and 21  | PCR/Sequencing |
|                | Basi et al. [21]   | 2018                | 103   | 67          | 51 (49.5)/52 (50.5) | 37 (36)/66 (64)          | 103 (100)/0 (0) | 18, 19, 20, and 21  | PCR/Sequencing |
| Turkey         | Calibasi et al. [22] | 2020               | 409   | 60          | 299 (73.1)/110 (26.9) | 246 (60.1)/163 (35.9)    | 409 (100)/0 (0) | 18, 19, 20, and 21  | INFINITI method |
|                | Bircan et al. [23] | 2014                | 25    | 65.3        | 21 (84)/4 (16)   | 17 (73.9)/6 (26.1)        | 14 (56)/11 (44) | 19 and 21           | Sequencing |
|                | Unal et al. [24]   | 2013                | 48    | 63.2        | 41 (85.4)/7 (14.6) | 43 (89.6)/5 (10.4)       | 32 (66)/16 (34)  | 18, 19, 20, and 21  | Sequencing |
|                | Tezel et al. [25]  | 2017                | 959   | 60          | 700 (73)/259 (27) | (10) 1/25 (2.6)          | 698 (72.8)/261(27.2) | 18, 19, 20, and 21 | RT-PCR |
|                | Ozcelik et al. [26] | 2019               | 703   | 63.3±12.5   | 545 (77.6)/158 (22.3) | 546 (83.5)/154 (16.5)   | 613 (87)/90 (13) | -                   | PCR/Sequencing |
| Bahrain        | Mubarak et al. [27] | 2020               | 65    | 68          | -               | -                        | 61 (93.8)/4 (6.2) | 18, 19, 20, and 21  | Scorpion-ARMS technology |
| Gulf Region    | Jazieh et al. [28] | 2015                | 230   | 61          | 162 (70.4)/68 (29.5) | 96 (41.7)/134 (58.2)     | 191 (83.4)/39 (16.6) | 18, 19, 20, and 21  | PCR |
| Iraq           | Hassani et al. [29] | 2014                | 27    | -           | 14 (51.8)/13 (48.1) | -                        | -               | 18, 19, 20, and 21  | Scorpion-ARMS technology |
|                | Ramadhan et al. [30] | 2021               | 138   | 60.1±12.4   | 79 (57.2)/59 (42.8) | -                        | -               | 18, 19, 20, and 21  | RT-PCR / PCR |
| Lebanon        | Naderia et al. [31] | 2015                | 201   | 65.2±10.4   | 123 (61.2)/78 (38.8) | 157 (78.1)/44 (21.9)     | 182 (90.5)/19 (9.5) | 18, 19, 20, and 21  | Scorpion-ARMS technology |
|                | Kattan et al. [32] | 2015                | 170   | 65.2        | 102 (59.8)/68 (40.2) | 131 (76.8)/39 (23.9)     | 157 (92.1)/13 (7.9) | 18, 19, 20, and 21  | Scorpion-ARMS technology |
|                | Fakhruddin et al. [33] | 2014               | 106   | 62.1±10.4   | 72 (67.9)/34 (32.1) | 59 (55.7)/18 (17)        | 106 (100)/0 (0)  | 18, 19, 20, and 21  | Scorpion-ARMS technology |
| Levant Erea    | Tfayli et al. [34] | 2017                | 210   | 63.4±10.8   | 139 (66.2)/71 (33.8) | 152 (72.4)/49 (27.5)     | 210 (100)/0 (0)  | 18, 19, 20, and 21  | PCR |
| Morocco        | Errihani et al. [35] | 2013               | 137   | 59          | 91 (66)/46 (44)   | 79 (58)/58 (42)          | 137 (100)/0 (0)  | 18, 19, 20, and 21  | Sequencing |
|                | Sow et al. [36]    | 2020                | 334   | 62          | 242 (72.5)/92 (27.5) | 178 (53)/135 (40)       | 314 (94)/20 (6)  | 18, 19, 20, and 21  | PCR/Sequencing |
|                | Kaanane et al. [37] | 2019               | 239   | 61.4 ± 8.9  | 169 (70.7)/70 (29.3) | 139 (58.2)/100 (41.8)   | 218 (91.2)/21 (8.8) | 18, 19, 20, and 21  | ARMS technology and the Idylla system |
| Tunisia        | Dhib et al. [38]   | 2019                | 73    | 73          | 61 (83.5)/12 (16.4) | 45 (76.2)/14 (23.7)      | 73 (100)/0 (0)   | -                   | IHC |

Table 1
Characteristics of the included studies.
| Country/Region | Author [reference] | Year of publication | cases | Age (years) | Male/female n (%) | Smokers/non smokers n (%) | ADK/NADK n (%) | Detection gene Site (exon) | Test type |
|---------------|-------------------|---------------------|-------|-------------|------------------|--------------------------|---------------|---------------------------|-----------|
|              | Mraihi et al. [39] | 2018                | 50    | 59.9        | 48 (96)/2 (4)    | 47 (94)/3 (6)          | 50 (100)/0 (0) | 19 and 21                 | Sequencing and IHC |
|              | Toumi et al. [40]  | 2018                | 26    | 58          | 23 (91.4)/3 (8.6)| 12 (80)/3 (20)        | 26 (100)/0 (0) | 18, 19, 20, and 21        | ARMS technology    |
| Egypt        | Ibrahim et al. [41]| 2019                | 2017  | -           | -                | -                       | -             | 18, 19, 20, and 21        | PCR       |
| Algeria      | Lahmadi et al. [42]| 2021                | 58    | 59          | 53 (91.4)/5 (8.6)| 23 (39.6)/17 (29.3)   | 27 (46.5)/31 (53.5) | Exon 19, Exon 21         | Sequencing |

**Results**

We identified 24 eligible studies: 16 (66.6%) in the ME [19–34] and 8 (34.4%) in NA [35–42]. Overall, *EGFR* mutations were analyzed in 6544 patients with NSCLC [3610 (55.2%) in the ME and 2934 (44.8%) in NA]. The median age is 61.7±3.8 years old, with a range of 22 [25] to 89 [22] years old. Male patients were predominant in all of the considered studies, accounting for 71.3% (3182/4462). Two studies, one from Bahrain [27] and another from Egypt [41] did not include information about male/female proportions. There were more smokers than nonsmokers, as 66.4% (2177/3276) self-reported a history of smoking; they were either former or current smokers. Four of the considered studies did not report data regarding patient smoking history [27, 29, 30, 41]. The histological subtype was defined in only 20 of the included studies [19–28, 31–39, 42]. Specimens were obtained from FFPE blocks in 19 studies [19–25, 30, 31, 33–42]. Five of the considered studies failed to report the type of specimens used [26–29, 32]. Baseline characteristics of enrolled studies are summarized in Table 1.

Overall, *EGFR* exons 18 through 21 mutations were assessed in 19 out of the 24 considered studies in 86.1% (5635/6544) NSCLC patients: Jordan (1 study, 166 patients) [19], Iran (2 studies, 153 patients) [20, 21], Turkey (3 studies, 1416 patients) [22, 24, 25], Bahrain (1 study, 65 patients) [27], the Gulf Region (1 study, 230 patients) [28], Iraq (2 study, 165 patients) [29, 30], Lebanon (3 studies, 477 patients) [31–33], the Levant area (1 study, 210 patients) [34], Morocco (3 studies, 710 patients) [35–37], Tunisia (1 study, 26 patients) [40], and Egypt (1 study, 2017 patients) [41]. Studies from Turkey (1 study, 25 patients) [23], Tunisia (1 study, 50 patients) [39], and Algeria (1 study, 58 patients) [42] identified mutations in exons 19 and 21 in 25, 50 and 58 patients, respectively. One study from Tunisia (73 patients) and another from Turkey (703 patients) did not mention specific exons genotyped [38, 26] (Table 1).

In total, the prevalence of *EGFR* mutations among NSCLC patients in the MENA region was 17.9% (1171/6544). In the ME, the reported frequency was 17.3% (626/3610) and varied throughout the geographic region/country. In the Levant and Gulf regions, *EGFR* mutations were found in 15.6% (32/205) [34] and in 28.7% (66/230) [28], respectively. *EGFR* mutations were least common in Lebanon, accounting for 11.7% (56/477) [31–33]. In Turkey, the *EGFR* mutation rate ranged between 13% and 44% [22–26]. In NA, *EGFR* mutations were found in 18.5% (545/2934) of NSCLC patient. Tunisia highlights a wide range of *EGFR* mutations rates, ranging from 5.5% (4/73) to 44% (22/50) [38–40]. In Morocco, *EGFR* mutation prevalences ranged from 15.9–26.8% [35–37] and one study has shown a frequency of 21.9%, similar to that seen among Caucasian populations [36]. Details of *EGFR* mutation prevalences in the MENA region are summarized in Table 2.
Table 2
Correlation between clinicopathological features of included patients and the EGFR mutational status.

| Country/Region | Author [reference] | Frequency of EGFR mutation n (%) | Male EGFR+/female EGFR+ n (%) | EGFR+ADK/EGFR+NADK n (%) | EGFR+ smokers/EGFR+ nonsmokers n (%) |
|----------------|---------------------|----------------------------------|-----------------------------|--------------------------|--------------------------------------|
| Jordan         | Obeidat et al. [19] | 24 (14.7)                        | 13 (11.2)/11 (22)          | 24 (100)/0 (0)          | 9 (37.5)/15 (62.5)                  |
| Iran           | Mohammad et al. [20]| 14 (28)                          | 8 (26.7)/6 (30)            | 14 (100)/0 (0)         | 3 (9.6)/11 (37.9)                   |
| Basi et al. [21]| 25 (24.3)          | 14 (27.4)/11 (21.1)              |                             |                          | 8 (12.1)/17 (46)                    |
| Turkey         | Calibasi et al. [22]| 68 (16.6)                        | 42 (14)/26 (33.6)          | 68 (100)/0 (0)         | 32 (13)/36 (22)                     |
| Bircan et al. [23]| 25 (24.3)          | 14 (27.4)/11 (21.1)              |                             |                          | 8 (12.1)/17 (46)                    |
| Unal et al. [24]| 18 (37.5)          | 13 (31.7)/5 (31.3)               |                             |                          | 13 (30.2)/5 (100)                   |
| Tezel et al. [25]| 160 (16.7)         | 64 (9.1)/96 (37.1)               |                             |                          | 142 (20.3)/18 (6.8)                 |
| Ozcelik et al. [26]| 92 (13)           | -                               |                             |                          | 2 (20)/10 (40)                      |
| Bahrain        | Mubarak et al. [27] | 14 (21.5)                        |                             |                          | 14 (22.9)/0 (0)                     |
| Gulf Region    | Jazieh et al. [28] | 66 (28.7)                        | 79.1 (129)/93.5(63)        | 62 (32.4)/4 (10.2)      |                                      |
| Iraq           | Hassani et al. [29] | 8 (29.6)                         | 4 (28.5)/4 (30.7)          | -                        | -                                    |
| Ramadhan et al. [30]| 38 (27.5)       | 22 (27.8)/16 (27.1)              |                             | -                        |                                      |
| Lebanon        | Naderia et al. [31] | 25 (12.4)                        | 8 (6.5)/16 (20.5)          | 25 (13.7)/0 (0)         | 8 (5)/16 (36.3)                     |
| Kattan et al. [32] | 22 (12.7)         | 8 (7.8)/14 (20.5)                |                             |                          | 8 (6.1)/14 (35.8)                   |
| Fakhruddin et al. [33]| 9 (8.8)        | 2 (2.7)/7 (20.5)                 |                             |                          | 1 (1.6)/5 (27.7)                    |
| Levant Erea    | Tfayli et al. [34] | 32 (15.6)                        | 12 (9.6)/20 (40.8)         | 32 (15.2)/0 (0)         | 14 (10.4)/16 (50)                   |
| Morocco        | Errihani et al. [35] | 29 (26.8)                        | 7 (7.6)/22 (47.8)          | 29 (21.1)/0 (0)         | 5 (6.3)/24 (41.3)                   |
| Sow et al. [36] | 73 (21.9)          | 35 (14.5)/38 (43.1)              |                             | -                        | 23 (13)/47 (35)                     |
| Kaanane et al. [37] | 38 (15.9)         | 21 (12.4)/17 (22.4)              |                             |                          | 16 (11.5)/22 (22)                   |
| Tunisia        | Dhieb et al. [38]  | 4 (5.5)                          | 3 (4.9)/1 (8.3)            | 4 (5.4)/0 (0)           | 3 (6.6)/1 (7.1)                     |
| Mraihi et al. [39] | 22 (44)           | -                               |                             | -                        | -                                    |
| Touni et al. [40] | 3 (11.5)          | 3 (13)/0 (0)                     |                             |                          | 3 (25)/0 (0)                        |
| Egypt          | Ibrahim et al. [41] | 353 (17.5)                       | -                           | -                        | -                                    |
| Algeria        | Lahmadi et al. [42] | 23 (39.6)                        | 22 (41.5)/1 (20)           | 9 (39.1)/6 (35.3)       | 14 (51.8)/9 (29)                    |

Overall, the most frequently encountered EGFR mutations were the exon 19 deletions (45.2%, 523/1157) and exon 21 substitutions (30.9%, 358/1157) of all detected mutations. Exon 20 alterations were detected in (11.2%, 112/998) including the T790 M mutation (45.5%, 51/112), which is the primary cause of acquired resistance to first-generation TKI. Exon 18 mutations were reported in 3.8% (38/998) of the EGFR mutated patients (Table 3). In the ME, we report that 50.5% (270/534) of NSCLC patients were positive for exon 19 deletions versus 48.3% (253/523) in NA. Exon 19 deletion were most commonly detected in the Levant region (78.1%, 25/32) and in Morocco (67.8%, 95/140), in ME and NA, respectively. Exon 21 L858R mutation was slightly less commonly detected in ME (64.4%, 125/194) compared with NA (68.2%, 112/164). Algeria from NA and Jordan from ME had a noticeably higher exon 21 mutation detection rate at (91.3%, 21/23) and (50%, 12/24), respectively. Exon 20 and exon 18 mutations were the least commonly identified EGFR alterations in ME and NA. Exon 20 mutations were most common in Egypt (16.7%, 59/2017) and Turkey (13.4%, 33/246) in NA and the ME, respectively. Exon 18 mutations were most prevalent in Jordan (37.5%, 9/24) and Morocco (6.4%, 9/140) from ME and NA, respectively.
Patients genotyping for these alterations should be a standard of care right along standard clinical examination, pathology and imaging studies. Furthermore, it has been established that EGFR mutations in tumors of NSCLC patients has led to personalized molecular therapies and to a paradigm shift for patients with lung cancer candidates for targeted therapy. In overall cases from studies that reported patients’ histological features (Table 3), in adenocarcinoma were far more likely to carry EGFR mutations (adenocarcinoma versus non-adenocarcinoma: 19% (516/2703) versus 9.7% (42/431)). The prevalence of EGFR mutations was higher in non-smokers [non-smokers versus current smokers: 31.1% (252/808) versus 11.1% (169/1479)]. Histology was reported in all of the considered studies. NSCLC patients with adenocarcinoma were far more likely to carry EGFR mutations [adenocarcinoma versus non-adenocarcinoma: 19% (516/2703) versus 9.7% (39/402)] in overall cases from studies that reported patients’ histological features (Table 2).

**Discussion**

The identification of EGFR mutations in tumors of NSCLC patients has led to personalized molecular therapies and to a paradigm shift for patients with lung cancer candidates for targeted therapy. Furthermore, it has been established that EGFR mutations are key diagnostic biomarkers in NSCLC, therefore NSCLC patients genotyping for these alterations should be a standard of care right along standard clinical examination, pathology and imaging studies [43].
Worldwide, 32.4% of NSCLCs involve \( \text{EGFR} \) mutations \[46\]. Previous studies have established marked variations in \( \text{EGFR} \) rates depending on different geographic regions and race/ethnicity backgrounds. The frequency of mutations was greater for \( \text{EGFR} \) mutation-positive NSCLC patients of East Asian ethnicity than those of other ethnicities (30% versus 8%) \[47\]. A slightly lower incidence of \( \text{EGFR} \) mutations (12%) has been identified among the Oceanic ethnicities and other insular Mediterranean patients with NSCLC \[48, 49\]. A prevalence of 21.2% of \( \text{EGFR} \) mutations has been observed in the ME and African NSCLC patients \[18\]. Different frequencies of \( \text{EGFR} \) mutations have been found in Russia (18%), South Africa (23%), Australia (23.8%), and Latin America (26%) \[50–53\]. In our systematic review, an overall prevalence of 17.8% was identified in patients with \( \text{EGFR} \) mutation-positive NSCLC across the MENA region. The reported prevalence was slightly higher than those observed among Western populations but still lower than frequencies reported in Latino and Asian populations. In the Levant countries, a region flanked by the ME and Europe, and the Gulf region (also known as Arabian Gulf), the reported \( \text{EGFR} \) mutation frequency was 15.6% \[34\] and 28.7% \[28\], respectively. The lowest mutation frequencies were seen in Lebanon (8.8 to 12.7%) \[31–33\]. Among the Turkish population, an \( \text{EGFR} \) mutation frequency of 42.6% in NSCLC patients was identified in western Turkey \[25\], when Tezel et al., showed that the mutations rate in Turkish patients with \( \text{EGFR} \) mutation-positive NSCLC was 16.7% \[25\]. Regional distribution of genetic mutations of lung cancer in Turkey, as reported in the \text{REDIGMA} study, including 25 centers, showed that mutation tests were found to be positive in 18.9% of these patients. The mutations were 69.9% \( \text{EGFR} \), 26.3% \( \text{ALK} \), 1.6% \( \text{ROS} \) and 2.2% \( \text{PDL} \) \[26\]. Our systematic review also highlights a wide range in \( \text{EGFR} \) mutation frequencies in NA populations. The overall \( \text{EGFR} \) mutation rate of NSCLC patients varied from 15.9% \[37\] to 26.8% \[35\] in Morocco. Additionally, one Moroccan study showed similar \( \text{EGFR} \) incidence rates (21%) as in patients of Caucasian descent \[36\]. An overall rate of 39.6% was found in \( \text{EGFR} \) mutation-positive NSCLC patients in Algeria \[42\]. In Tunisia, while first reports account for an \( \text{EGFR} \) mutation frequency as low as 5.5% \[38\], other reports show discrepant data of 11.5% and 44% \[40, 39\].

The mechanism behind the differences of \( \text{EGFR} \) mutation rates across geographic regions and the race/ethnicity is still unclear. A persistent finding in the literature is the substantial variation in \( \text{EGFR} \) mutation prevalence across different geographic areas and among various race/ethnicity backgrounds \[54\]. Although such mutations are over-represented in more than 40% of \( \text{EGFR} \) mutation-positive NSCLC in Japan and China, they are detected in roughly 15% of \( \text{EGFR} \) mutation-positive NSCLC patients in France and Italy \[48\]. It has been demonstrated that ethnic genetic variation may explain these differences \[55, 56\]. In the ME, the frequency of \( \text{EGFR} \) mutations was reported to range between 16.6% and 44% in the Turkish population \[22–26\]. This disproportion is a result of the genetic heterogeneity and the ethnic diversity that characterize Turkey, a country endowed with a distinguished geographic location that is between Europe and Asia and near the ME. In NA, the \( \text{EGFR} \) mutation frequency in Tunisians range from 5.5% and 44% \[38–40\]. This disparity in frequencies is mainly attributable to the ethnicities that have succeeded in Tunisia, contributing to this country’s ethnic diversity and therefore genetic heterogeneity \[57\].

Some studies showed that difference in \( \text{EGFR} \) mutations frequencies might be caused by exposing to indoor and/or outdoor air pollution \[58\]. The unique \( \text{EGFR} \) mutation spectrum in southwestern China might be related to the exposure of air pollution from local smoky coal and can reflect a specific environmental exposure \[59\]. In Europe, a positive association between various indicators of indoor air pollution and lung cancer risk has also been reported \[60\]. Indoor air pollution from burning in poorly ventilated houses, burning of wood and other solid fuels, as well as fumes from high-temperature cooking using unrefined vegetable oils such as rapeseed oil \[61\]. Cooking oil fumes from vegetable oils are mutagenic \[62, 63\]. The International Agency for Research on Cancer classifies outdoor air pollution as an established lung carcinogen in humans \[64\]. In 2017, the global proportion of lung cancer deaths attributable to outdoor ambient PM2.5 air pollution was 14%, ranging from 4.7% in the United States to 20.5% in China \[65\]. PM2.5 is generally described as fine particles and is emitted by vehicles, coal-burning in power plants, industrial activity, waste burning, and other human activities.

Several studies have reported a higher incidence of \( \text{EGFR} \) mutations among women in comparison to men, with figures up to 69.7%. In effect, up to 42% of females versus only 14% of males with NSCLC are expected to harbor an \( \text{EGFR} \) TK domain mutation \[46, 47, 66\]. In our review, \( \text{EGFR} \) mutation prevalence was higher in females (females versus males: 33.4% versus 17%). This is similar to data from Europe, Spain and other Asian studies which concluded that \( \text{EGFR} \) mutations were more common in women \[67–69\]. A systematic review covering 151 worldwide studies published in 2014 observed that the \( \text{EGFR} \) mutation-positive proportions were 60% and 37% in women and in men, respectively \[48\]. Previous studies showed that women can be more exposed to domestic radon which poses a risk for lung cancer at exposure levels approaching those for underground miners \[70\]. Others studied reported that domestic radon is associated with a low excess risk for lung cancer \[71, 72\]. Generally, women tend to be non-smokers or light smokers compared to men, but their domestic lifestyle may expose them to certain indoor mutagens. If the occurrence of \( \text{EGFR} \) mutations is associated with potential indoor mutagens, women would have a higher mutation rate than men \[73\]. Furthermore, female endocrine factors such as progesterone receptor and aromatase expression could also play a role in the prevalence of the \( \text{EGFR} \) mutations \[74\]. Further studies are needed to investigate the role of hormones in \( \text{EGFR} \) mutation-positive NSCLC.

In our review article, the prevalence of \( \text{EGFR} \) mutations in non-smokers was more than two folds higher in non-smokers than current smokers (31.1% versus 11.1%). In European or American studies, \( \text{EGFR} \) mutations rates in non-smokers ranged from 10–30% \[75\]. \( \text{EGFR} \) mutations are the most common driver gene found in never-smoker adenocarcinoma from East Asia, constituting 60–78% of this subgroup \[76–78\]. While some studies found that non-smokers were associated with a significantly higher \( \text{EGFR} \) mutations prevalence \[79\]. Others have reported an association between \( \text{EGFR} \) mutations and the amount and duration of cigarette smoking, with a higher incidence of mutations than that seen in never smokers \[80\]. Furthermore, clinical studies have suggested that the pathogenesis, clinical manifestation, and prognosis of non-smokers and smokers are different in lung cancer tumors \[81–83\]. Genetic differences have been also found in the tumors of non-smokers versus smokers \[84, 85\]. The proportion of non-smokers with NSCLC is increasing. Multiple environmental factors are implicated in lung carcinogenesis including exposure to secondhand tobacco smoke, pre-existing lung diseases, and family history of cancer. Exposure to industrial substances such as toxin (ex: arsenic, nickel, chromium, tar, soot), some organic chemicals (ex: radon, asbestos), radiation exposure, air pollution, tuberculosis and environmental tobacco smoke in non-smokers also increases the risk of developing lung cancer. More thorough investigations are needed to pinpoint causal mutagens and determine the amplitude of their potential mutagenic capability.
Deletions in exon 19 and the single amino acid substitution L858R in exon 21 account for approximately 85%-90% of all EGFR mutations in NSCLC, they are the most common and can predict response to EGFR TKIs and confer sensitivity to EGFR TKIs [86]. Exon 18 and 20 insertion mutations are less common and represent the remaining 10% of EGFR mutants in NSCLC. The exon 20 T790M point mutation, and most EGFR exon 20 mutations, are predictive of treatment resistance to first- and second-generation EGFR TKI therapies [44, 87]. In our article review, the average frequency of the exon 19 and substitutions in exon 21 were 45.2% and 30.9%, respectively, among all EGFR mutations. Together, these two mutations account for up to 76.1% of identified EGFR mutations. Our findings also identified potential EGFR TKI-resistant mutations in 11.2% (112/998) among which, the T790M substitution was the most prevalent resistance mutation to first-generation TKI (45.5%, 51/112). The low frequency of exon 19 del and the point mutation L858R at exon 21 (73.4%) among the MENA population is likely the result of the heterogeneity in screening and targeted methods, potentially engendering inaccuracies in the incidence rates of otherwise common EGFR mutations. Direct sequencing was the most commonly used methodology in MENA studies (45.9%, 11/24). However, Direct sequencing has some critical limitations among which the low mutation detection sensitivity; below a certain threshold of mutant DNA, mutations could not be detected. The sensitivity of this technique is under par in representative clinical tumor samples and can yield accurate results only at higher concentrations of mutant DNA [88]. Sousaa et al. showed that approximately 3% of NSCLC patients have rare mutations not identified by real-time PCR approaches [89]. The molecular characterization of peripheral blood may provide a strategy for the non-invasive serial monitoring of tumor genotypes during treatment, particularly for the EGFR T790M mutation [90]. The frequency of T790M mutation depends on the types of assays for this mutation [91]. Oxnard et al. found that 31% of NSCLC patients who are negative for T790M on central tumor genotyping have detectable T790M in plasma and recommend that tissue biopsy T790M genotyping would be substituted by liquid biopsy [92]. Other plasma assays have similarly identified unexpected false-positives for T790M in the absence of false-positives for other mutations [93]. T790M mutational analysis in liquid biopsies is currently incorporated in recent guidelines for the management of acquired TKI resistance [94]. Recent studies have confirmed that EGFR mutations from plasma can predict the clinical response to targeted therapy [95, 96]. In the MENA region, the T790M mutation, using liquid biopsy, has been conducted only in NSCLC patients from Lebanon [97]. In addition, Next Generation Sequencing (NGS) has the ability to detect the whole exome or genome and is not restricted to specific target sequences. NGS can simultaneously analyze multiple variations, including uncommon alterations. Uncommon EGFR mutations make up a highly heterogeneous subgroup of NSCLCs that account for approximately 10%-18% of EGFR-mutated patients, and NGS testing can broaden the spectrum of alterations within the uncommon group in NSCLC patients [98]. However, Non-invasive plasma-based detection of EGFR mutations using digital PCR is still the most suitable method in clinical EGFR testing, thanks to its higher sensitivity, easier-to-understand results, low turn-around time and low cost to predicting the efficiency of EGFR-TKI [96].

This report revealed that the molecular epidemiology of EGFR mutations is heavily influenced by ethnicity and geography; EGFR mutations were found to be more frequent in patients in the MENA region than in patients of caucasian ancestry, in contrast, the rates reported among Asian populations were quite higher. Although results from this study were consistent with findings in previous reports, they should be considered cautiously due to some limitations. Firstly, a considerable portion of the considered studies have low statistical power as 8 of them included less than 100 patients. This could misrepresent the true prevalence of EGFR mutations in the region. Also, data about the stage of the tumors lacked from the majority of the included studies. Therefore, the correlation of tumor-stage and EGFR mutational status remains undefined in the region. Furthermore, the majority of the analyzed cases of the studies had adenocarcinomas, consequently, the reported influence of this particular histological subtype on EGFR mutational status could be inaccurate. Despite these limitations, a major strength of this review is the inclusion of available studies from a wide range of countries in the region. These estimates can serve as a reference for future research or policy making. Since EGFR mutation rates vary depend depending on, inter alia, ethnicity, NSCLC patients genotyping should be a standard of care in the MENA region in order to have more accurate and realistic data on EGFR mutation frequencies.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

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Authors’ Contributions: YB, AL, and HEIR have conceived the study, exploited data, coordinated and drafted the paper. TB, BEIM, HEIA, and HC participated in the designed. HS, HE, IAR and, TM generated data and involved in data analyses. YS, BB, KE, IL-A, MI, RT, AA, and MO have read and agreed to the published version of the manuscript. All authors have read and agreed to the published version of the manuscript.

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