Review Article

# Prevalence of the epidermal growth factor receptor mutations in lung adenocarcinoma patients from the Middle East region

**Arafat Hussein Tfayli, Ghina Bassam Fakhri, Majd Sassine Al Assaad**

*Department of Internal Medicine, Division of Hematology and Oncology, American University of Beirut, Beirut, Lebanon*

**Address for correspondence:**
Dr. Arafat Hussein Tfayli, American University of Beirut Medical Center, Naef K. Basile Cancer Institute, 11-0236, Riad El Solh, 1107 2020, Beirut, Lebanon.
E-mail: at35@aub.edu.lb

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**Abstract:**

Lung cancer remains a major cause of cancer mortality with a 5-year survival in advanced stages around 4%. Platinum-based chemotherapy was routinely used as the standard of care in patients with advanced nonsmall cell lung cancer, but it is being progressively replaced by targeted molecular therapy. One of the molecular aberrations harbored by lung adenocarcinoma is the epidermal growth factor receptor (EGFR). A large ethnic variation has been reported in the prevalence of EGFR mutations in patients with lung adenocarcinoma. Data regarding its prevalence from the Middle East area remains limited. This paper aims at reviewing the data available for the prevalence of this mutation in the Middle Eastern patient population and comparing it with other reported series.

**Keywords:**

Epidermal growth factor receptor, lung adenocarcinoma, middle east, prevalence

Lung cancer continues to be the leading cause of cancer death in both men and women, claiming 1.59 million lives worldwide in 2012.[1-3] The estimated number of new lung cancer cases in 2018 is 234,030 in the US alone and it is projected that lung cancer remains the second most common cancer in males, after prostate cancer, and females, after breast cancer.[4] Cancer Registries from various countries in the Middle East area confirm the same findings, with lung cancer being one of the most common cancers in that region.[5-7] It ranks after prostate, colon and bladder for males, and after breast and cervical cancer for females. In males, the highest age-standardized incidence of lung cancer per 100,000 was reported in Palestine (40.4) followed by Tunisia (37.1), Bahrain (34.2), and Lebanon (31.8).[5-7] One reason for this high incidence of lung cancer is the high prevalence of tobacco smoking.[8,9]

In contrast to the steady increase in survival observed for most cancer types, advances have been slow for lung cancer that is typically diagnosed at an advanced stage. The 5-year survival rate is 55% for cases detected when the disease is still localized, 27% for regional disease, and 4% for late-stage disease.[4,10] Unfortunately, 70% of patients with nonsmall cell lung cancer (NSCLC) present at a later stage and are not eligible for surgery. There is strong evidence showing that the standard chemotherapy and supportive care can prolong overall survival, and improve quality of life, but prognosis remains poor, especially in patients with advanced stage NSCLC.[11-14]

The recent discovery of driver mutations in lung adenocarcinomas has made significant

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changes in the diagnostic and therapeutic approach for this disease.[15,16] Multiple studies have consistently shown that using targeted agents that specifically block a driver mutation leads to improved responses and survival as compared to standard chemotherapy.[14,17] The most commonly described driver mutations in lung adenocarcinomas are Kirsten rat sarcoma viral oncogene homolog (KRAS), epidermal growth factor receptor (EGFR), and echinoderm microtubule associated protein-like 4 anaplastic lymphoma kinase (ALK) translocation. While KRAS is the most commonly described mutation; it, unfortunately, remains an elusive target with no drugs showing significant activity in patients whose tumor harbor that mutation. On the other hand, patients whose tumors have other mutations such as EGFR, ALK, mesenchymal-epithelial transition , and ROS-1, have derived significant benefit from agents that target these mutations.[18-20]

## Methodology

This review was conducted in early 2018. The search was conducted in accordance with the checklist of the Association of American Medical Colleges for review articles. The literature review is up to date and articles were critically appraised for validity and relevance. A comprehensive search was conducted in PubMed, Medline, and Google Scholar for the presence of gray literature. Articles were included if they were published in the English language, and reported the prevalence of the EGFR mutation rate in any country in the Arab World. No limitations were made on year of publication. The search strategy consisted of three concepts. The first concept regarding lung cancer was searched using the following terms: lung cancer, lung tumor, lung oncology, lung adenocarcinoma, or nonsmall cell. MeSH terms and keywords used for the concept of the EGFR consisted of: EGFR, epidermal growth factor, EGFR, EGFR mutation, or EGFR frequency. The last concept was regarding the region of interest and the MeSH terms and keywords used were: Middle East, Middle Eastern, Gulf, the Arab world, Arab country, or Levant. Our final search yielded six published articles that fit our eligibility criteria. Critical appraisal of all of the yielded articles was performed and a summary of the results is synthesized and summarized in Table 1.

## Results

### Epidermal growth factor receptor mutations worldwide

Reports on EGFR prevalence are abundant worldwide with reports showing a wide variation of EGFR mutation frequency among different ethnic backgrounds and geographical locations. The variability arises from the different demographic characteristics of the participants, study designs, assays used to test for EGFR, number of sequenced exons, tumor source (primary or metastasis), and eligibility criteria for enrolment.[26-33] A recent systematic review reported the spectrum of EGFR mutation frequencies in Europe, Asia, North America, India subcontinent, and South America. A table representing the pooled data from these regions compared to the Middle East is represented in Figure 1.[34]

EGFR prevalence has been extensively studied in Asia. A recent review paper from China reported that EGFR mutations ranged between 24.5% and 43% in NSCLC and between 40.9% and 78% in adenocarcinomas. The majority of mutations were in exon 19 and 21 (45.7% and 48%, respectively).[16,35] On the other hand, a recent Indian study reported EGFR mutation prevalence ranging from 5.3% to 45.4% among lung adenocarcinomas with the most frequent ones belonging to exons 19 and 21.[2]

In Europe, the European Tarceva versus chemotherapy study was the first prospective phase III trial of erlotinib versus chemotherapy in non-Asian patients with EGFR mutation–positive NSCLC. As part of their screening, 225

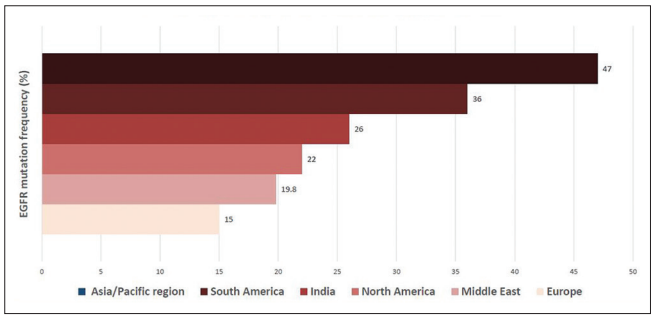


**Figure 1:** Epidermal growth factor receptor mutation frequencies from major regions worldwide

**Table 1: Characteristics of patients tested for epidermal growth factor receptor mutations in the Arab world**

| References | Number of samples tested for EGFR | Median age (years) | Male gender (%) | Current or former smokers (%) | EGFR mutation frequency (%) | Exon 19 deletion (%) | Exon 21 L858R mutation (%) |
|---|---|---|---|---|---|---|---|
| Fakhruddin *et al*.[5] | 106 | 62 | 67.9 | 55.7 | 8.5 | 89 | 11 |
| Al-Kuraya *et al*.[21] | 34 | 59 | 79 | N/A | 2.9 | 0 | 0 |
| Errihani *et al*.[22] | 137 | 59 | 66 | 58 | 21 | 69 | 21 |
| Naderi *et al*.[23] | 201 | 65.2 | 61.2 | 78.1 | 11.9 | 48 | 40 |
| Jazieh *et al*.[24] | 230 | 61 | 70.4 | 41.7 | 28.7 | 54.5 | 39.4 |
| Tfayli *et al*.[25] | 205 | 62.9 | 66.2 | 72. | 15.6 | 78.1 | 21.9 |

N/A=Not applicable, EGFR=Epidermal growth factor receptor

out of 1044 patients tested positive for either exon 19 or 21 suggesting a prevalence of 22%.[36,37] In a 4200 patient cohort from Germany, 432 had a positive mutation in EGFR (10.3%).[33]

In a series from Memorial Sloan-Kettering Cancer Center, Dogan *et al*. reported an EGFR mutation rate of 20%.[26] As for patients who were African–American, a large-cohort study was conducted in 2012 in patients diagnosed with lung adenocarcinoma revealing an EGFR mutation of 19% with the majority (78%) being in exon 19 and the rest in exon 21. In 2014, the lung cancer mutation consortium published its report on using multiplexed assays testing adenocarcinomas of the lung for driver mutations in ten genes. In 1007 patients who participated in this trial, the frequency of EGFR was determined to be 21% with the majority belonging to exon 19.[38]

### Epidermal growth factor receptor prevalence in the Arab world

The first paper to be published concerning EGFR mutation prevalence from the Middle East Area was reported in 2006. 47 NSCLC surgically-treated formalin-fixed paraffin-embedded (FFPE) tissues were analyzed between 1989 and 2003 in King Faisal Hospital in the Kingdom of Saudi Arabia (KSA). Samples were analyzed using a tissue microarray format for immunohistochemistry (IHC), fluorescent *in situ* hybridization (FISH), and DNA sequencing. Genetic analysis of the EGFR gene was performed using polymerase chain reaction (PCR) amplification of exon 18, 19, 20, and 21. IHC was performed using the EGFR antibody (20.005; Zymed/Invitrogen; Germany) to detect EGFR protein overexpression and membranous staining was considered positive. Of 43 tissues that were analyzed for IHC, 30 of them showed positivity for EGFR expression (69.8%). As for EGFR amplification testing using FISH, 6 out of 39 interpretable samples tested positive for EGFR amplification (15.3%). Sequencing was successful in 34 specimens and only one mutation (2.9%) was detected in exon 20 (R803 L). This study has multiple limitations including the small sample size and inclusion of nonadenocarcinoma cases.[21]

In 2013, and in an attempt to report, the frequency of EGFR mutations in Northern Africa, a study was reported from Morocco. Genetic analysis of 137 FFPE tumor tissues was performed using TaqMan PCR. A total of 29 EGFR mutations were detected (21%) with the most frequent EGFR aberration being in exon 19 (69%) followed by exon 21 (21%). The authors noted that the percentage of EGFR mutations was higher in women and never-smokers.[22]

The first endeavor to determine the frequency of EGFR in Lebanon was attempted by Fakhruddin *et al*. and was published in 2014. One hundred and six cases of NSCLC were selected for genetic testing using PCR kits that detect can 29 somatic mutations via the RotorGene-Q platform. EGFR mutations were detected in nine samples (8.5%) where eight of them belonged to a deletion in exon 19 and one case to the L858R locus in exon 21.[5] The second attempt to report EGFR mutation prevalence in Lebanon was completed and published in 2015.[23] Two hundred and one patients with NSCLC were included and had an EGFR mutation rate of 11.9%. The methodology utilized was the amplification refractory mutation system (ARMS) and Scorpions technology real-time PCR. Most of the mutations belonged to exon 19 deletions (48%), followed by exon 21 L858R missense mutation (40%) and exon 18 G719X mutation (4%). The majority of the patients were males (61.2%), and current or former smokers (78.1%); a result that fits the reported mutational profile of EGFR mutations in the West.

A large multisite study was published in 2015 extracting data about the prevalence of EGFR mutations from three different countries: KSA, United Arab Emirates and Qatar.[24] EGFR analysis was performed using PCR and 230 records were analyzed retrospectively for EGFR mutations and other clinical characteristics. Sixty-six patients harbored the EGFR mutation (28.7%) with the majority representing a deletion in exon 19 (54.5%) followed by exon 21 mutations (39.4%) with significant association with female gender, and smoking status ($P < 0.01$).

The first and most recent study of prospective nature was published in 2017 collecting information from nine different sites in Lebanon, Jordan, and Iraq. Patients represented a wide variety of nationalities: Lebanese, Syrian, Palestinian, Jordanian, and Iraqi. Tumor tissues for 205 patients were analyzed using the multiplex PCR ARMS and Scorpion method on the RotorGene-Q platform. The majority of the patients were men (66.2%), former or current smokers (72.4) with a mean age of 62.9 years at diagnosis. A mutation rate of 15.6% was reported with the majority belonging to exon 19 deletions (78.1%) followed by exon 21 L858R missense mutation (21.9%).[25]

## Discussion

EGFR is a transmembrane glycoprotein that is a member of the protein kinase superfamily. The EGFR gene is located on the short arm of chromosome 7 (7p11.2) and encodes a 170 kDa Type I transmembrane growth factor receptor with tyrosine kinase (TK) activity.[36,39-41] EGFR belongs to the human epidermal growth factor receptor/erbB family of receptor TKs where homodimerization and/or heterodimerization in response to ligand binding activates the TK. This

process causes auto-phosphorylation of the cytoplasmic domain of the receptor allowing it to interact with other molecules affecting downstream signaling pathways. This downstream EGFR signaling sequentially leads to increased proliferation, angiogenesis, and decreased apoptosis.[14,21,42-45] The TK activity of EGFR may be dysregulated by several oncogenic mechanisms, such as EGFR gene mutation. Gain-of-function or activating mutations of the EGFR gene occur in some NSCLCs, leading to constitutive TK activity. These findings make EGFR a rational target for therapeutic intervention and support the development of novel anticancer agents that target EGFR.[46-52]

## Assays for epidermal growth factor receptor testing

The standard method of testing of EGFR mutations is the direct sequencing of PCR-amplified DNA. This genomic DNA corresponds to exons 18–21 of the EGFR gene. The sensitivity of PCR testing is affected by the presence of noncancerous tissue in the sample. In addition to that, PCR testing is done using FFPE, and this, alone, can contribute to the artefacts in sequencing.[14,53] To increase the sensitivity of the mutational assay described above, other methods were developed. The ARMS, combined with the Scorpion Amplified Refractory Mutation assay, has been commercially developed to detect mutated DNA from previously-identified known mutations and this usually requires more DNA than PCR would.[54] The most common EGFR mutations are small in-frame deletions in exon 19 and L858R missense mutations in exon 21 and together, these two mutations account for 90% of all EGFR mutations. The remaining 10% is represented by mutations in exon 18 and exon 20 such as G719A, G719S, and G719C in exon 18 and T790M and S7681 in exon 20 among many others.[21,55,56]

The prevalence of EGFR mutations varies according to gender, race, smoking history, and histology. EGFR mutations are reported to be more common in women, Asians, never-smokers, and in adenocarcinoma histology.[2,11,26-29,40] An inverse relationship has been suggested between the intensity or duration of smoking and frequency of EGFR mutation proposing that smoking history has a predictive value for EGFR mutations. There is an on-going controversy as to whether routine EGFR testing should be performed in the subset of patients perceived as having a low probability of mutation such as Caucasian male smokers.[26,30,31]

Collectively, these studies are crucial as they lead to the documentation of molecular driver mutations and establish the molecular complexity of NSCLC. As reported above, the frequencies for EGFR mutations in lung adenocarcinoma patients are markedly different among the Western, Asian, and Arab populations. This has raised the notion that ethnic variations and geographical locations alter the genomic background of lung tumors in addition to other demographic traits. This has prompted researchers in the Arab countries to report the prevalence of their sample populations.[5-8,21,42] The prevalence of EGFR in Asia has reached 45.5%, whereas in Europe, the highest prevalence was reported as 22%. In the Arab countries area, the numbers ranged from 2.9% to 28.7% where the low-frequency report in the first publication can be explained by small sample size and testing methodology.[57-59]

The studies discussed above were conducted in the Arab countries to evaluate the prevalence of EGFR mutations in patients diagnosed with lung cancer and estimate the percentage of them who would benefit from EGFR-targeted therapy.[60] The reported EGFR mutation rates in the Arab countries are in the line of what is reported in Western populations ranging between 12% and 15% in the most recent series. The first study reported from Saudi Arabia has multiple limitations as discussed above. The study reported by Jazieh from the Gulf region was a retrospective collection of data on patients already tested for EGFR mutation. This automatically introduces selection bias because testing was initially being done on patients with a high likelihood of harboring the mutation. This is evident by the high percentage of nonsmokers on that study. The two series reported from Lebanon are more likely to reflect the true prevalence of EGFR mutations as the testing was being done on all comers with lung adenocarcinoma.

## Conclusion

The EGFR mutation frequencies in the Middle East remain slightly higher than the numbers reported from the Western countries. However, the highest mutation rates remain in the Asian population. More studies addressing EGFR mutations and subsequent therapy are needed in countries of the Middle East specifically and the Arab World generally.

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## Conflicts of interest

There are no conflicts of interest.

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