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# The Effectiveness Of Egfr-Tkis In Treatment Of Non-Small-Cell Lung Cancer: A Meta-Analysis

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**The Effectiveness of EGFR-TKIs in Treatment of Non-Small-Cell Lung Cancer:  
A Meta-Analysis**

**Xiao Li**

Thesis submitted to the faculty of the  
Yale School of Public Health  
in partial fulfillment of the requirements for the degree of

Master of Public Health

In

Biostatistics

**Thesis Advisor:** Professor Maria M. Ciarleglio  
Yale School of Public Health

**Second Reader:** Professor Xinhan Zhao  
Xi'an Jiao Tong University School of Medicine

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***Yale School of Public Health Honor Code***

*I have not given, received, or witnessed inappropriate exchange of information on this assignment, and I certify that this is my own original work.*

*Xiao Li*

## Abstract

Epidermal growth factor receptor- tyrosine kinase inhibitor (EGFR-TKI) is one of the genetic targeted medicines that is used to treat non-small-cell lung cancer. However, because EGFR-TKIs have a specific target, they are not believed to benefit all non-small-cell cancer patients.

We conducted a meta-analysis synthesizing 9 randomized controlled trials (RCTs) to systematically evaluate the effectiveness of EGFR-TKIs among two patient populations: unselected patients with unknown EGFR mutation status and selected patients harboring EGFR mutation

Among unselected patients, the efficacy of EGFR-TKIs is inferior to chemotherapy. The hazard of disease progression in the EGFR-TKI group is 1.46 times that in the chemotherapy group (95% CI (1.29, 1.65)). This result is consistent in the subgroups of male, smoker, and patients with all subtypes of non-small-cell lung cancer. However, there is no significant difference of hazard of disease progression among subgroups of female and non-smoker.

Among EGFR mutant patients, the efficacy of EGFR-TKIs is superior to chemotherapy. Random effects model estimated the hazard of progression in the EGFR-TKI group to be 0.33 times that in the chemotherapy group (95% CI (0.24, 0.46)). Fixed effect model estimates the hazard of progression in the EGFR-TKIs group to be 0.32 times that in the chemotherapy group (95% CI (0.27, 0.38)). This result is consistent in the subgroups of current smoker, non-smoker, male and female. There is no significant difference of hazard of disease progression among subgroup of past smoker (*Pooled HR = 0.83 with a 95% CI (0.36, 1.92)*).

Although EGFR-TKIs have provided an alternate solution for advanced non-small-cell patients, it cannot benefit all patients. Among patients not harboring EGFR mutation, it could be more hazardous than chemotherapy. Among Patients harboring EGFR mutation, it has shown significantly better efficacy than chemotherapy. However, the efficacy of EGFR-TKIs vary considerably among patients who had history of smoking. There is evidence that even among EGFR mutant patients, smoking could hinder the efficacy of EGFR-TKIs. The hazard of disease progression of past smokers is even greater than that of current smokers. More research needs to be done to further explore the pathological relationship between smoking and EGFR-TKI efficacy.

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Finally, I want to thank my mom and dad for the love they have provided through my entire life.

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## **1. Introduction**

### **1.1. Overview of Lung Cancer: Public Health Significance**

Lung cancer is one of the major public health threats and leading causes of death all over the world. In 2012, lung cancer was the most common cancer worldwide, with 1.82 million new cases of lung cancer comprising 13% of all new cancer diagnoses. (1) The mortality-to-incidence rate ratio, which serves as an indirect measure of cancer survival, of lung cancer is 0.87. (2) The high incidence coupled with the high fatality of this disease has made lung cancer the most common cause of cancer death in the world, responsible for approximately 20% of all cancer deaths. (1) Due to constrained medical resources and limited treatment options, lung cancer poses an even more severe public health problem to developing countries, such as China. The incidence rate of lung cancer in China has been rising rapidly in recent years. For example, in Beijing, the incidence rate has increased 38.8% from 39.30 cases per 100,000 population to 54.55 cases per 100,000 population from 1998 to 2007. (3) It is anticipated that by 2025, there will be more than 1 million individuals diagnosed with lung cancer in China. This will make China the country with most lung cancer cases in the world. (4)

Many risk factors are proven to be associated with lung cancer, such as air pollution and cigarette smoking. (4) Air pollution has undoubtedly intensified the public health burden of lung cancer in China as byproducts of China's relentless socioeconomic development in the past decades. With the rapid industrialization process, the air quality continues to deteriorate in China. Many cities in China are often shrouded with a blanket of toxic smog with high concentration of fine particulate matter (PM 2.5), which is considered to be one of the most detrimental particles to health. According to the U.S. Embassy's air quality monitor in Beijing, the PM 2.5 concentration on 12/21/2015 reached a very unhealthy level of 156 micrograms per cubic meter that could cause

severe respiratory effects and lung diseases, with the World Health Organization's maximum recommendation limit of 25 micrograms per cubic meter. (5)

Furthermore, China remains the largest consumer of cigarettes in the world with 350 million smokers and 740 million passive smokers. (6) Each year, China process about 2.66 million tons of tobacco leaves, which approximately equals one-third of world's total tobacco leaf production. (6) If the Chinese government does not effectively control air pollution and regulate cigarette sales, there is no doubt that incidence rate of lung cancer will further increase in the future.

## **1.2. Treatment Strategies and Latest Progress**

There are two types of lung cancer based on the morphological differences of the lung tumor, namely small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). Non-small-cell lung cancer approximately accounts for 80-85% of all lung cancers. (7) At the time of diagnosis with non-small-cell lung cancer, more than 30% of patients are at the late stage of the disease. (7) Due to the limited methods of treatment, the 5-year survival rate of non-small-cell lung cancer patients are often less than 15%. (7) As a consequence, the treatment strategy of non-small-cell lung cancer has become one of the most active clinical research areas.

Differentiated by starting lung cells, non-small-cell lung cancer is further divided into three main subcategories, adenocarcinoma, squamous cell (epidermoid) carcinoma and large cell (undifferentiated) carcinoma. Other types of non-small-cell lung cancer, including adenosquamous carcinoma and sarcomatoid carcinoma are very rare. (7) However, the treatment and prognosis of all types of non-small-cell lung cancers are often very similar.

Depending on the stage of the lung cancer and patient characteristics, multiple treatment options are available for non-small-cell lung cancer patients, including surgery, chemotherapy, radiotherapy, immunotherapy, radiofrequency ablation and targeted therapy. Among all of the

options, surgery is the first choice for those patients in early stage of non-small-cell lung cancer because it has the highest possibility of cure. However, for those patients diagnosed at advanced stage who cannot benefit from surgery, the efficacy of traditional radiotherapy and chemotherapy are often unsatisfactory due to a lack of specificity and severe adverse effects.

In recent years, molecular targeted therapy toward the tumor signaling transduction pathways has gradually become the focus of non-small-cell lung cancer treatment research. After a long period of plateau, scientists have made breakthroughs in the research and application of molecular targeted therapy.

With the development of molecular biology, scientists have a much more clear understanding of tumor signaling transduction pathways, and have identified more and more lung cancer molecular targets, including EGFR mutation, BRAF mutation, KRAS mutation, ALK mutation, and ROS1 fusion. Targeted medicines based on these gene mutations has inaugurated a new era for non-small-cell lung cancer treatment and offered hope for patients with advanced stage non-small-cell lung cancer. Compared with traditional chemotherapy and radiotherapy, targeted therapy could greatly reduce the recurrence rate and prevent metastasis of the tumor without eliciting severe adverse effects for some patients.

There are mainly three types of targeted medicine based on different transduction pathways in non-small-cell lung cancer treatment, namely, epidermal growth factor receptor – tyrosine kinase inhibitors, angiogenesis inhibitors and multi targeted antiangiogenic tyrosine kinase inhibitors. Among all signaling transduction pathways, epidermal growth factor receptor is the one with the most well-developed research and proven evidence of efficacy. Epidermal growth factor receptor - tyrosine kinase inhibitors, such as erlotinib, gefitinib, and afatinib have become the standard first line treatment for advanced stage non-small-cell lung cancer patients.

Because EGFR-TKIs have a specific target, they are not believed to benefit all non-small-cell lung cancer patients. Some research has shown that Asian, non-smoker and females have a relatively higher response rate of EGFR-TKIs. Other research has shown that the response rate among patients with EGFR mutation could reach 50% to 80%. The response rate among patients without EGFR mutation is only 10%-15%. (8, 9)

### **1.3. Motivation Behind this Thesis**

Although there are multiple researches trying to explore the efficacy of EGFR-TKIs in treatment of none-small-cell lung cancer. They are, to certain degree, subject to bias and might not be representative. There has not been a high quality meta-analysis that systematically synthesized those single studies to establish a pooled estimate both in population and representative subgroups. Through this study, we try to provide clinicians with reliable evidence in treatment of non-small-cell lung cancer by systematically reviewing a variety of high-quality, representative randomized clinical trials.

## **2. Methods**

In this study, we conducted a meta-analysis synthesizing 9 randomized controlled clinical trials to systematically compare the effectiveness of EFGR-TKIs (Gefitinib, Erlotinib, Afatinib) and chemotherapy in treatment of non-small cell lung cancer among two patient populations: unselected patients with unknown EGFR mutation status and selected patients harboring EGFR mutation. The study therefore has two primary objectives:

1) Explore the efficacy of EGFR-TKIs compared with chemotherapy among unselected patients;

2) Explore the efficacy of EGFR-TKIs compared with chemotherapy among EGFR mutant patients.

## **2.1. Study Identification and Selection**

### **2.1.1. Criteria for Inclusion and Selection**

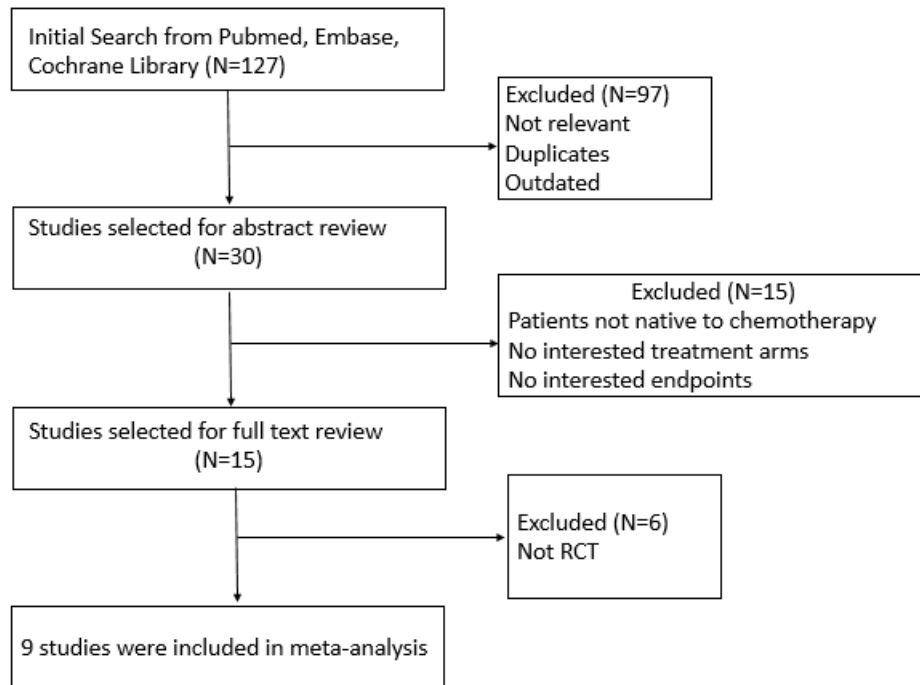
Randomized controlled trials that included treatment arms receiving EGFR-TKIs and treatment arms receiving chemotherapy were considered for inclusion in this systematic review. Non-randomized studies were not eligible for inclusion. Prior to enrolling in the trials patients must be naïve to chemotherapy but could have had resection before. All studies must have included patients that were followed for at least 12 months and reported progression free survival. The primary endpoint of interest is progression free survival because it is a clinically-relevant shorter-term endpoint that is less likely to be affected by subsequent therapies.

### **2.1.2. Literature Search Strategy**

We searched Pubmed, Cochrane Library and EMBASE with the following key words: EGFR, EGFR-TKIs, epidermal growth factor receptor, gefitinib, erlotinib, afatinib, NSCLC, non-small-cell lung cancer, adenocarcinoma, large cell lung cancer, squamous cell carcinoma, adenosquamous carcinoma, sarcomatoid carcinoma. We firstly keep records of papers based on whether the title is relevant. We then browsed the abstract of each paper to decide whether it is qualified for further review. Non-relevant studies were then excluded. The following information were also recorded: title, author, year of publication, journal name, patient characteristics, interventions and outcome variables. We initially identified a total of 127 papers. First screening excluded 97 of those. Reason for exclusion includes non-relevant topics, outdated research, duplication and observational/retrospective study. After reading the abstract of the remaining 30

papers, we then excluded 15 more studies. Among excluded studies, 9 enrolled patients who were not naïve to chemotherapy and 6 studies did not contain our interested treatment arms or endpoints. We then carefully read the full text of the remaining 15 studies. Among those, 6 were excluded because they are not randomized controlled trials. Finally, a total of 9 randomized clinical trials were retained. Figure 1 shows a flow chart of the literature selection process.

Figure 1 Study Selection Flow Diagram



## 2.2. Assessment of Risk of Bias Criteria

Risk of bias was assessed for each study using Effective Practice and Organization of Care (EPOC) criteria. Table 1 describes the nine domains that were evaluated for each study to determine bias. These domains evaluate potential biases including selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each study was rated as having low risk, high risk or unclear risk of bias for each domain. Low risk of bias indicates that the bias is unlikely to affect results. High Risk of bias indicates that bias could have affected results. Unclear risk of bias

indicates that the assessment of bias could not be adequately made or that some doubts exist about the results. The risk of bias summary and risk of bias graph were generated by RevMan 5.3.

Table 1 EPOC Risk of Bias Assessment Criteria

<b>Risk of Bias Domain</b>	<b>Low Risk of Bias</b>	<b>High Risk of Bias</b>
Was the allocation sequence adequately generated?	A random component in the sequence generation process is described	A nonrandom method is used
Was the allocation adequately concealed?	The unit of allocation was by institution, team or professional and allocation was performed on all units at the start of the study	The unit of allocation was by patient or episode of care and there was some form of centralized randomization scheme, an on-site computer system or sealed opaque envelopes were used
Were baseline outcome measurements similar?	Performance or patient outcomes were measured prior to the intervention, and no important differences were present across study groups	Important differences were present and not adjusted for in analysis
Were baseline characteristics similar?	Baseline characteristics of the study and control providers are reported and similar	There is no report of characteristics in text or tables or if there are differences between control and intervention providers
Were incomplete outcome data adequately addressed?	Missing outcome measures were unlikely to bias the results	Missing outcome data was likely to bias the results
Was knowledge of the allocated interventions adequately prevented during the study?	Authors state explicitly that the primary outcome variables were assessed blindly, or the outcomes are objective	Outcomes were not assessed blindly
Was the study adequately protected against contamination?	Allocation was by community, institution or practice and it is unlikely that the control group received the intervention	It is likely that the control group received the intervention
Was the study free from selective outcome reporting?	There is no evidence that outcomes were selectively reported	Some important outcomes are subsequently omitted from the results
Was the study free from other risks of bias?	No evidence of other risk of biases	

### **2.3. Data Extraction**

The following variables from each RCT were recorded: specific EGFR-TKI medicine, dose, chemotherapy plan, number of patients in both experimental group and controlled group, time of the study, region and patient characteristics including gender, age, and stage of the cancer. Information contained in survival curves and hazard ratios were recorded.

### **2.4. Measuring the Treatment Effect**

Hazard ratio and its 95% CI of progression free survival was recorded. We converted these into log scale. The standard error of log hazard ratio was computed using the following formula:

$$Se(\log HR) = \frac{\log HR - \log(\text{lower bond of 95\% CI})}{1.96}$$

### **2.5. Statistical Analysis**

#### **2.5.1. Computing**

Statistical analyses were conducted using the “meta” package in the R statistical software program.

#### **2.5.2. Assessment of Heterogeneity**

Cochran’s Q test was used to evaluate the heterogeneity between each single study. The  $I^2$  statistic and the chi-square test were used to determine if significant heterogeneity was present. An  $I^2$  larger than 75% and a p-value < 0.05 indicated high heterogeneity and a random effects model should be used. Otherwise, fixed effect model would be sufficient. In addition, we reported the estimates from both random effects model and fixed effect model. The pooled estimates were presented by forest plots.



### **2.5.3. Assessment of Publication Bias**

Linear regression test of funnel plot asymmetry (Egger's test) was used to examine publication bias.

### **2.5.4. Subgroup Analyses**

For the unselected patients, we performed subgroup analyses based on smoking status, gender and cancer type. For the EGFR mutant patients, we performed subgroup analyses based on smoking status and gender.

## **3. Results**

### **3.1. Description of the Studies Included**

We included a total of 9 randomized clinical trials published between 2008 and 2014, all in English. (10-18). All trials have two treatment arms, EGFR-TKIs and chemotherapy. Four trials were conducted in Asia (2 in China, 2 in Japan). Four trials were conducted in Europe (2 in Italy, 1 in Spain, 1 in France). One trial was conducted in the U.S. As a result, the samples are representative geographically. Although we wanted to understand the efficacy of EGFR-TKIs among African patients, we failed to find any randomized trial in Africa. We did not observe significant difference between median ages of patients in each study (58-71). We observed some imbalances between sample sizes, ranging from 103 to 973. Five studies enrolled only patients harboring EGFR mutation (Maemodo 2010, Zhou 2011, Wu 2014, Rosell 2012 and Miisudomi 2010). The remaining four trials enrolled unselected patients. In terms of treatment plan, four of the RCTs used Erlotinib as first line EGFR-TKIs treatment, four trials used Gefitinib as first line EGFR-TKIs treatment and one trial used Afatinib as first line EGFR-TKIs treatment. Chemotherapy treatment included Cisplatin, Gemcitabine, Paclitaxel, and Vinorelbine. All

patients enrolled in these studies were either in stage IIIB or IV. Most of the patients had adenocarcinoma or squamous cell carcinoma. A small portion of them had large cell cancer and adenosquamous carcinoma. All of the studies reported progression free survival statistics and the hazard ratios. Overall, these studies included patients with a variety of demographical and clinical characteristics and are therefore considered to be representative. Table 2 shows the detailed information by treatment arm of each study included in this review.

Table 2 Characteristics of Included Studies

Study	Group	Treatment Plan	Gender (M/F)	Median Age	Stage	Classification
Gridelli 2012	EGFR	Erlotinib 150 mg/d	252/128	63	46 IIIB 334 IV	170 SCC+ LCC 210 AC + Other
	Chemo	Cisplatin 80 mg/m <sup>2</sup> Gemcitabine 1200 mg/m <sup>2</sup>	252/128	62	37 IIIB 343 IV	170 SCC+ LCC 210 AC + Other
Maemodo 2010	EGFR	Gefitinib 250 mg/d	42/72	63.9	15 IIIB 88 IV	103 AC 1 LCC 2 ACC 3 SCC 5 Other
	Chemo	Paclitaxel 200 mg/ m <sup>2</sup> Carboplatin AUC 6	41/73	62.6	21IIIB 84 IV	110 AC 0 LCC 1 ACC 2 SCC 1 Other
Zhou 2011	EGFR	Erlotinib 150 mg/d	34/48	57	11 IIIB 71 IV	72 AC 10 Other
	Chemo	Gemcitabine 1000 mg/ m <sup>2</sup> Carboplatin AUC 5	29/43	59	5 IIIB 67 IV	62 AC 10 Other
Wu 2014	EGFR	Afatinib 40 mg/d	87/155	58	16 IIIB 226 IV	N/A
	Chemo	Gemcitabine 1000 mg/ m <sup>2</sup> Cisplatin 75 mg/ m <sup>2</sup>	39/83	58	6 IIIB 116 IV	N/A
Crino 2008	EGFR	Gefitinib 250mg/d	75/22	74	IIIB or IV (detailed number not reported)	47 SCC 34 AC 14 LCC 2 Other
	Chemo	Vinorelbine Tartrate 30mg/ m <sup>2</sup>	73/26	74		44 SCC 45 AC 7 LCC 3 Other
	EGFR	Erlotinib 150 mg/d	23/29	N/A	7 IIB 45 IV	26 AC 26 Other

Lilenbaum 2008	Chemo	Carboplatin Auc 5 Taxol 200 mg/ m <sup>2</sup>	28/23	N/A	7 IIB 44 IV	32 AC 19 Other
Morère 2010	EGFR	Gefitinib 250mg/d	38/5	70	7 IIB 36 IV	13 SCC 22 AC 8 Other
	Chemo I	Gemcitabine 1250 mg/ m <sup>2</sup>	34/8	71	10 IIB 32 IV	13 SCC 21 AC 8 Other
	Chemo II	Taxotere 75 mg/ m <sup>2</sup>	33/9	71	6 IIB 36 IV	9 SCC 19 AC 14 Other
Rosell 2012	EGFR	Erlotinib 150 mg/d	28/58	65	6 IIB 78 IV	82 AC 3 LCC 1 SCC
	Chemo	1. Cisplatin 75 mg/ m <sup>2</sup> + Docetaxel 75 mg/ m <sup>2</sup> or Gemcitabine 1250 mg/ m <sup>2</sup> 2. Carboplatin AUC 6 Docetaxel 75 mg/ m <sup>2</sup> 3. Carboplatin AUC 5 Gemcitabine 1000 mg/ m <sup>2</sup>	19/68	65	5 IIB 82 IV	80 AC 1 LCC 6 Other
Mitsudomi 2010	EGFR	Gefitinib 250 mg/d	27/59	64	10 IIB 41 IV	224 AC 58 LCC 239 SCC 65 OTER
	Chemo	Docetaxel 60 mg/ m <sup>2</sup> Cisplatin 780 mg/ m <sup>2</sup>	26/60	64	9 IIB 41 IV	221 AC 52 LCC 243 SCC 70 OTER

AC: adenocarcinoma; SCC: squamous cell carcinoma; LCC: large cell carcinoma; ACC: adenosquamous carcinoma; PFS: progression free survival

### 3.2. Assessing Risk of Bias

We carefully reviewed each entry in the Effective Practice and Organization of Care (EPOC) criteria to evaluate the potential sources of bias. Overall, the quality of these studies was found to be good. All of these studies have properly randomized patients to treatment arms and reported the procedure. Furthermore, there were no severe problems in allocation concealment, incomplete data and selective reporting. Most of the studies properly balanced the baseline characteristics of patients. However, most of the studies we included either did not report the

blinding information or were not blinded among clinicians and patients. That might be a potential source of bias. Figure 2 and figure 3 visualized the risk of bias information.

Figure 2 Risk of Bias Graph

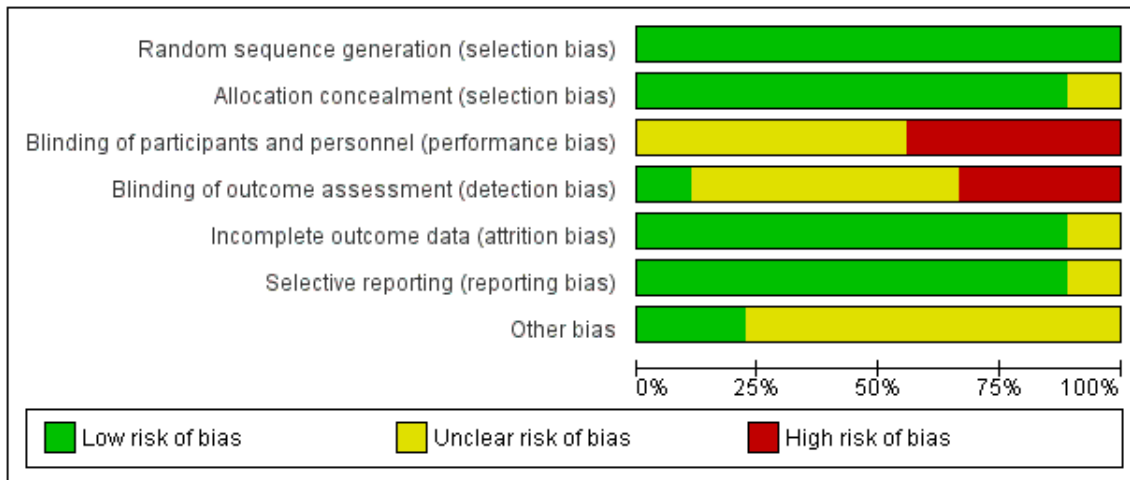


Figure 3 Risk of Bias Summary

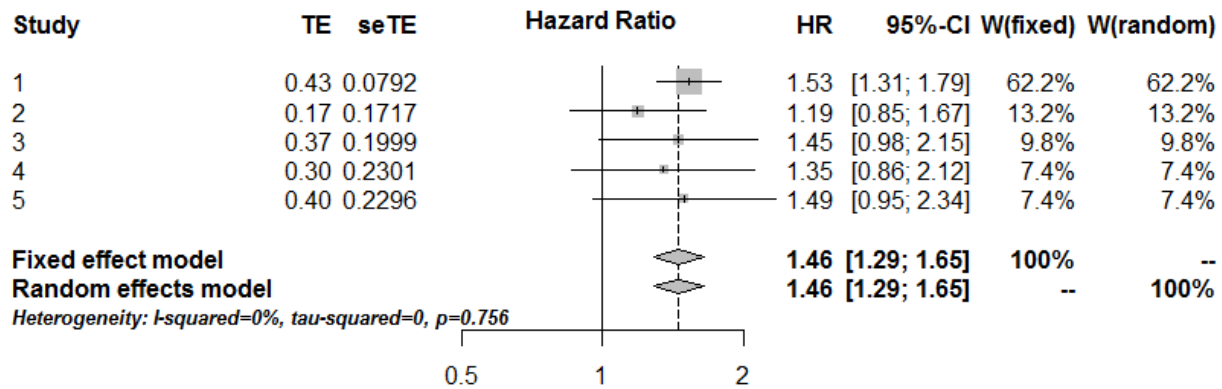
Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Crino 2008	+	+	?	?	?	?	?
Gridelli 2012	+	+	-	+	+	+	?
Lienbaum 2008	+	?	?	?	+	+	?
Maemodo 2010	+	+	?	?	+	+	+
Mitsudomi 2010	+	+	?	?	+	+	+
Morere 2010	+	+	?	?	+	+	?
Rosell 2012	+	+	-	-	+	+	?
Wu 2014	+	+	-	-	+	+	?
Zhou 2011	+	+	-	-	+	+	?

### 3.3. Primary Outcomes

#### 3.3.1. The Efficacy of EGFR-TKIs among Unselected Patients

In this section, we included a total of 4 randomized clinical trials. From table 1, the studies described in Gridelli 2012, Crino 2008, Lilenbaum 2008, Morère 2010 were included in this analysis. Morère 2010 had two controlled chemotherapy treatment groups (Gemcitabine 1250 mg/m<sup>2</sup> and taxotere 75 mg/ m<sup>2</sup>) so we divided it into two separate studies for the purpose of analysis. Rosell 2012 had three chemotherapy treatment plans for the chemotherapy group. However they analyzed those three groups as an integrated chemotherapy group and only reported one hazard ratio. All studies reported progression free survival statistics and we pooled the hazard ratios of these studies. The forest plot shown in Figure 4 reports the detailed results.

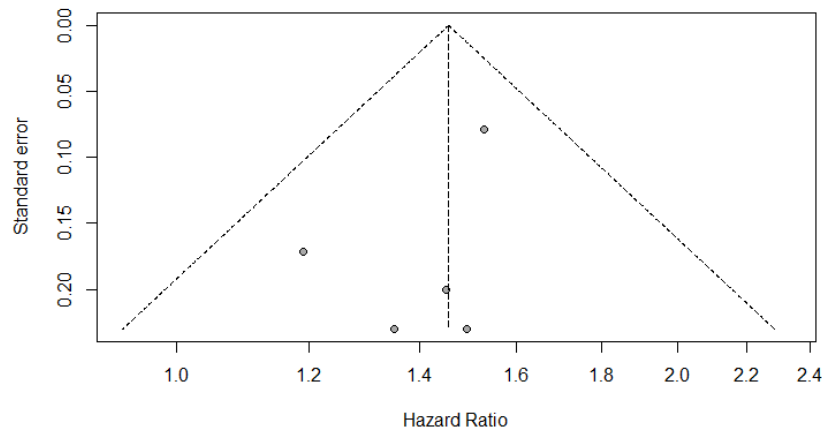
Figure 4 Forest Plot of Hazard Ratios among Unselected Patients



The amount of heterogeneity in the true hazard ratio is estimated to be  $\tau^2 = 0$ . The  $I^2 = 0\%$ , suggesting minimal heterogeneity. In addition, Cochran's Q test of heterogeneity suggests that no statistically significant heterogeneity is present with p-value = 0.756. Therefore a fixed effect model would be sufficient. We reported the estimates from both random effects model and fixed effect model. Both models give same results and suggest that among unselected patients, the progression free survival in EGFR-TKIs group is worse than that in chemotherapy group.

Specifically, the hazard of progression in the EGFR-TKI group is 1.46 times that in the chemotherapy group (pooled HR =1.46 with a 95% CI (1.29, 1.65)). Based on linear regression test of funnel plot asymmetry shown in Figure 5 (Egger's test), we fail to find evidence of asymmetry ( $t = -1.2448$ ,  $df = 3$ ,  $p\text{-value} = 0.3016$ ) suggesting publication bias is not a concern.

Figure 5 Funnel Plot of Asymmetry I



Two studies (Gridelli 2012 and Lilenbaum 2008) also reported hazard ratios based on stratified analysis of smoking status, gender, and cancer type. We then also conducted subgroup analyses based on these stratifications. The result is consistent among subgroups of male, smokers, and patients with adenocarcinoma and other types of cancer. However, among females and non-smokers, we did not observe significant difference of hazard of disease progression between EGFR-TKIs group and chemotherapy group.

The hazard of disease progression among male patients who received EGFR-TKIs is significantly greater than that of male patients who received chemotherapy. Fixed effect model estimates the hazard of progression in the EGFR-TKI group to be 1.99 times that in the chemotherapy group (pooled HR = 1.99 with a 95% CI (1.48, 2.66)). Random effects model estimates the hazard of progression in the EGFR-TKI group to be 2.10 times that in the

chemotherapy group (pooled HR = 2.10 with a 95% CI (1.35, 3.26)). (Figure 6). We did not observe significant difference of hazard of disease progression among female patients who received EGFR-TKIs or chemotherapy. Both fixed effect model and random effects model estimates the hazard of progression in the EGFR-TKI group to be 1.15 times that in the chemotherapy group (pooled HR = 1.15 with a 95% CI (0.91, 1.46)). (Figure 7).

Figure 6 Forest Plot of Hazard Ratios among Unselected Male Patients

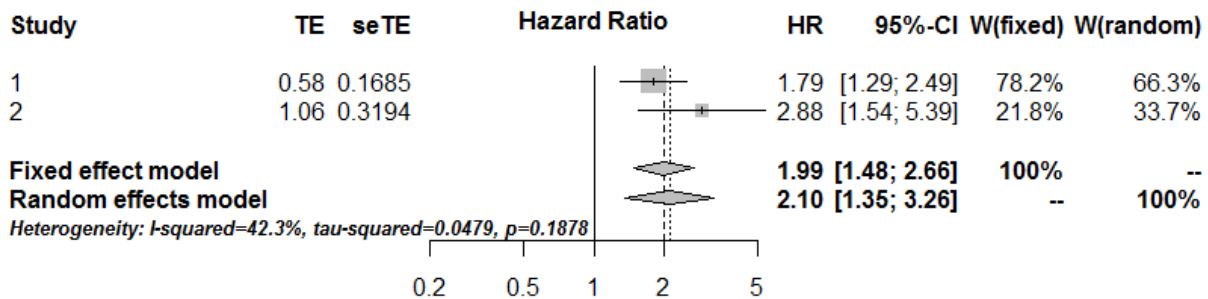
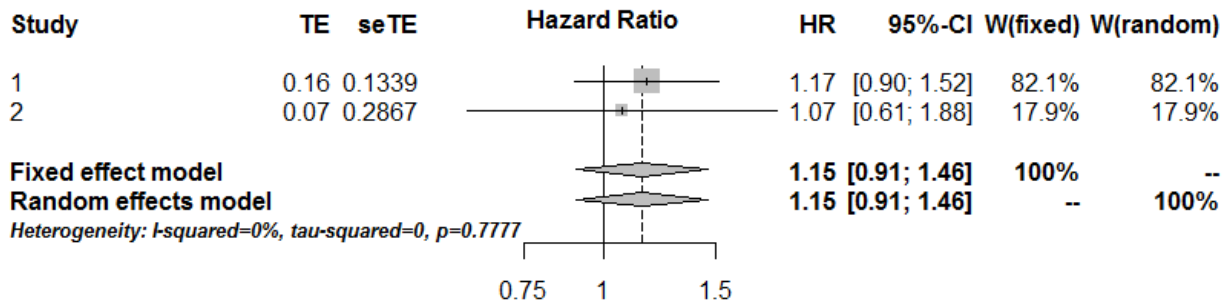
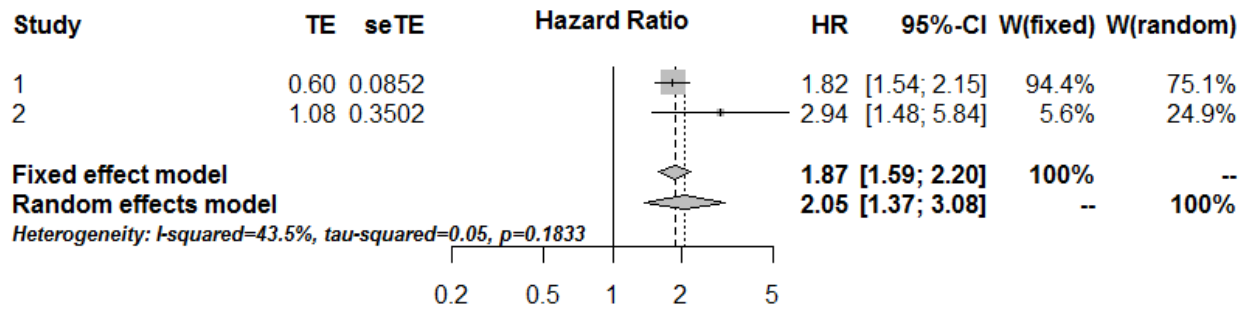


Figure 7 Forest Plot of Hazard Ratios among Unselected Female Patients



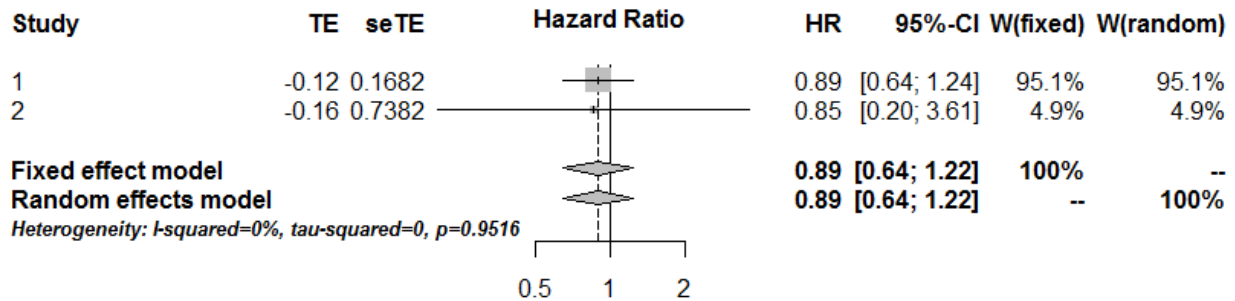
The hazard of disease progression among smokers who received EGFR-TKIs is significantly greater than that of smokers who received chemotherapy. Fixed effect model estimates the hazard of progression in the EGFR-TKI group to be 1.87 times that in the chemotherapy group (pooled HR = 1.87 with a 95% CI (1.59, 2.20)). Random effects model estimates the hazard of progression in the EGFR-TKI group to be 2.10 times that in the chemotherapy group (pooled HR = 2.05 with a 95% CI (1.37, 3.08)). (Figure 8).

Figure 8 Forest Plot of Hazard Ratios among Unselected Smoker



We did not observe significant difference of hazard of disease progression among non-smoking patients who received EGFR-TKIs or chemotherapy. Both random effects and fixed effect model estimates the hazard of progression in the EGFR-TKI group to be 0.89 times that in the chemotherapy group (pooled HR = 0.89 with a 95% CI (0.64, 1.22)). (Figure 9).

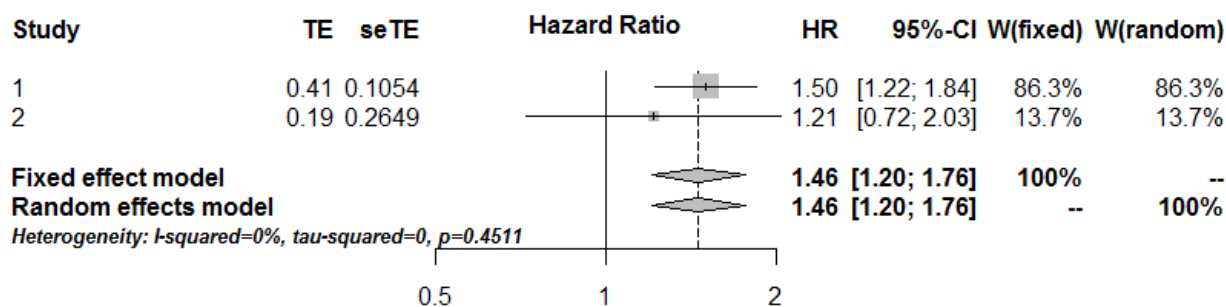
Figure 9 Forest Plot of Hazard Ratios among Unselected Non-smoker



The hazard of disease progression among adenocarcinoma patients who received EGFR-TKIs is significantly greater than that of adenocarcinoma patients who received chemotherapy. Both fixed effect model and random effects model estimates the hazard of progression in the EGFR-TKI group to be 1.46 times that in the chemotherapy group (pooled HR = 1.46 with a 95% CI (1.20, 1.76)). (Figure 10).

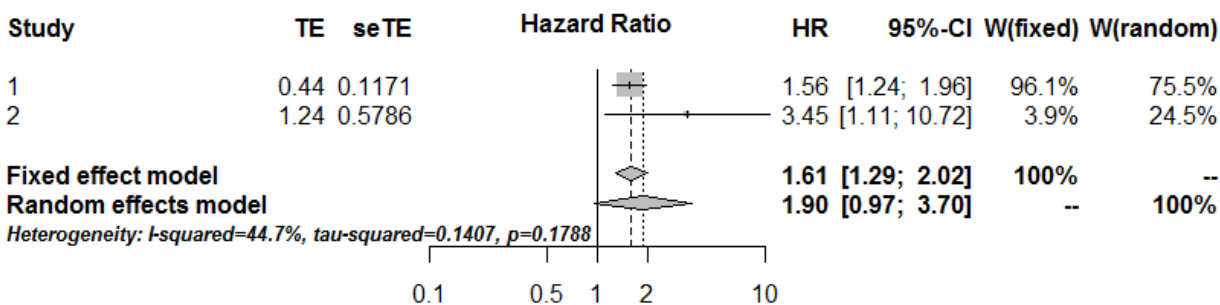


Figure 10 Forest Plot of Hazard Ratios among Unselected Patients with adenocarcinoma



Among patients with other types of NSCLC, the fixed effect model suggest a greater hazard of disease progression of patients in the EGFR-TKIs group. However, random effects model suggests that there is no significant difference of hazard of disease progression of patients in EGFR-TKIs group and chemotherapy group. In this case, the amount of heterogeneity in the true hazard ratio is estimated to be  $\tau^2 = 1407$ . The  $I^2 = 44.7\%$ , suggesting minimal heterogeneity. In addition, Cochran's Q test of heterogeneity suggests that no statistically significant heterogeneity is present with p-value = 0.1788. As a result, fixed effect model would be sufficient. Fixed effect model estimates the hazard of progression in the EGFR-TKI group to be 1.61 times that in the chemotherapy group (pooled HR = 1.61 with a 95% CI (1.29, 2.02)). Random effects model estimates the hazard of progression in the EGFR-TKI group to be 1.90 times that in the chemotherapy group (pooled HR = 1.90 with a 95% CI (0.97, 3.70)). (Figure 11).

Figure 11 Forest Plot of Hazard Ratios among Unselected Patients with Other Types of NSCLC



### 3.3.2. The Efficacy of EGFR-TKIs among Patients Harboring EGFR Mutation

Six trials reported the progression free survival statistics among patients harboring EGFR mutation (Gridelli 2012, Maemodo 2010, Zhou 2011, Wu 2014, Rosell 2012, Mitsudomi 2010). We pooled the hazard ratios. The forest plot below (Figure 12) shows the detailed results. The amount of heterogeneity in the true hazard ratio is estimated to be  $\tau^2 = 0.1043$ . The  $I^2 = 71.8\%$ , suggesting maximal heterogeneity. In addition, Cochran's Q test of heterogeneity suggests that statistically significant heterogeneity is present with p-value = 0.0033. Therefore a random effects model should be used. We reported the estimates from both random effects model and fixed effect model. Both models give similar results and suggest that among EGFR mutant patients, the progression free survival in EGFR-TKIs group is superior to that in chemotherapy group. Random effects model estimates the hazard of progression in the EGFR-TKI group to be 0.33 times that in the chemotherapy group (pooled HR = 0.33 with a 95% CI (0.24, 0.46)). Fixed effect model estimates the hazard of progression in the EGFR-TKI group to be 0.32 times that in the chemotherapy group (pooled HR = 0.32 with a 95% CI (0.27, 0.38)). (Figure 12) Based on linear regression test of funnel plot asymmetry (Egger's test), we fail to find evidence of asymmetry ( $t = 0.3712$ ,  $df = 4$ ,  $p\text{-value} = 0.7293$ ), suggesting publication bias is not a concern. (Figure 13).

Figure 12 Forest Plot of Hazard Ratios among Selected EGFR Mutant Patients

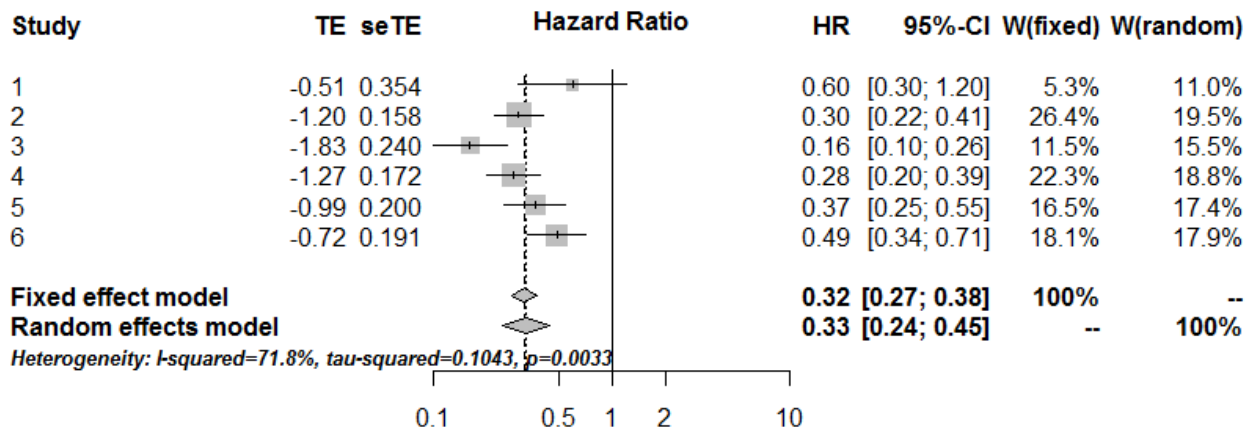
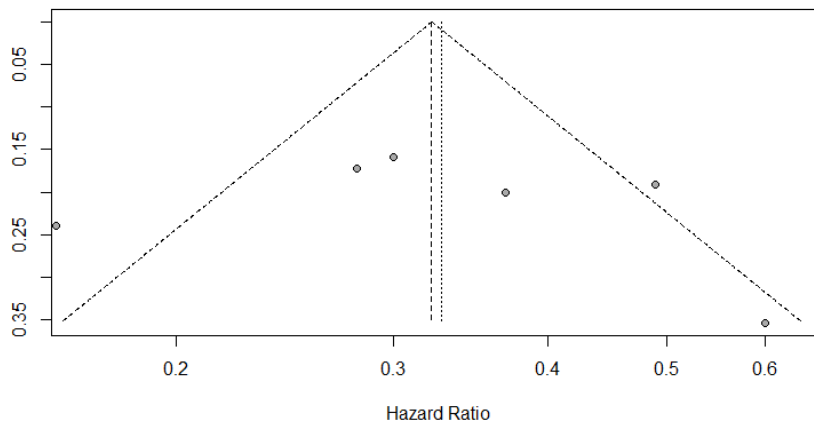


Figure 13 Funnel Plot of Asymmetry II

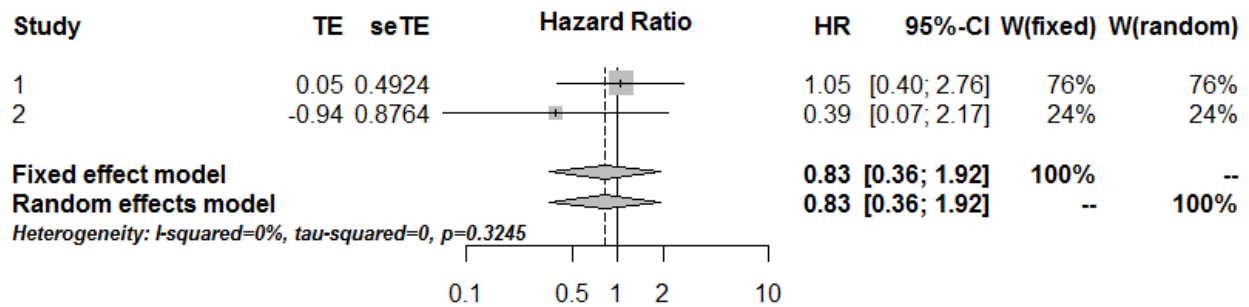


Four studies also performed stratified analyses based on smoking status and gender (Mitsudomi 2010, Rosell 2012, Wu 2014 and Zhou 2011). In terms of smoking status, Rosell 2012 and Wu 2014 divided patients into three subgroups: current smoker, non-smoker and past smoker. Mitsudomi 2010 and Zhou 2011 combined the past smoker and current smoker as one subgroup. As a consequence, we pooled the hazard ratios of current smokers from all four studies. But we only used Rosell 2012 and Wu 2014 for past smoker and current smoker analyses. The results are consistent across male, female and patients who never smoked. Among current smokers, although the hazard of disease progression is lower in EGFR-TKIs group, it is less significant than that in non-smokers. An interesting fact is that, among past smokers, the hazard ratio of disease progression between EGFR-TKIs group and chemotherapy is not significantly different from 1. With a very large variance of hazard ratio, the efficacy of EGFR-TKIs among patients who smoked in the past varies significantly. Many patients who had a history of smoking but quit later did not benefit from EGFR-TKIs even though they were EGFR mutant. Both fixed effect model and random effects model give same estimates of  $HR = 0.83$  with 95% CI (0.36, 1.92). We were surprised that among EGFR mutant patients, the hazard of disease progression of past smokers is even greater than that of current smokers ( $HR=0.48$ , 95% CI = (0.25, 0.92)). However, we only

included two studies so that this result may subject to bias. More research in this area needs to be done to further address this question.

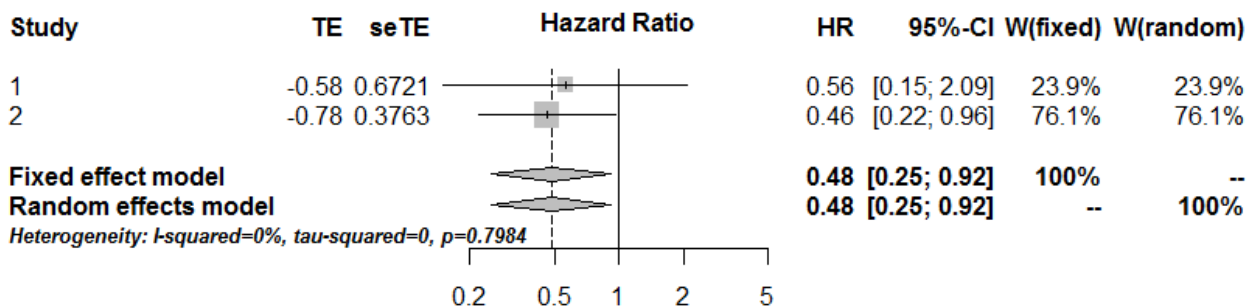
We did not observe significant difference of hazard of disease progression among past smokers who received EGFR-TKIs or chemotherapy. Both fixed effect model and random effects model estimates the hazard of progression in the EGFR-TKI group to be 0.83 times that in the chemotherapy group (pooled HR = 0.83 with a 95% CI (0.36, 1.92)). (Figure 14).

Figure 14 Forest Plot of Hazard Ratios among Selected EGFR Mutant Patients Who are Past Smoker



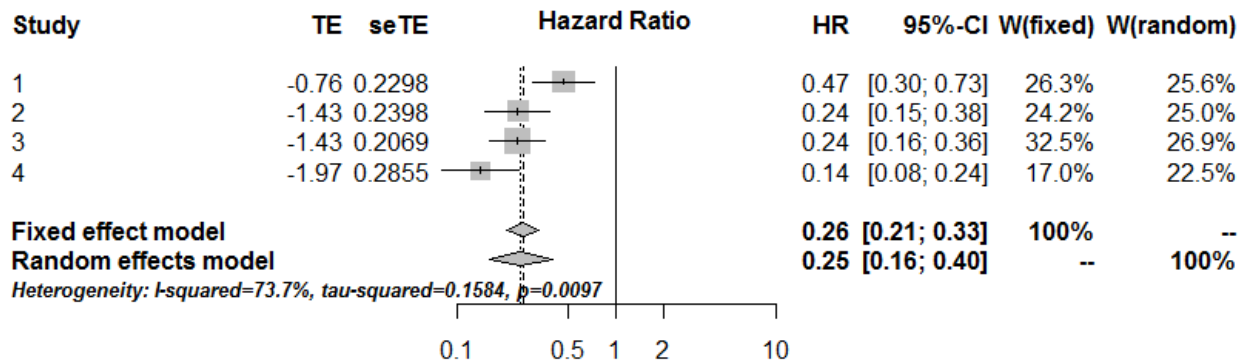
The hazard of disease progression among current smokers who received EGFR-TKIs is significantly lower than that of current smokers who received chemotherapy. Both fixed effect model and random effects model estimates the hazard of progression in the EGFR-TKI group to be 0.48 times that in the chemotherapy group (pooled HR = 0.48 with a 95% CI (0.25, 0.92)). (Figure 15).

Figure 15 Forest Plot of Hazard Ratios among Selected EGFR Mutant Patients Who are Current Smoker



The hazard of disease progression among non-smokers who received EGFR-TKIs is significantly lower than that of non-smokers who received chemotherapy. Random effects model estimates the hazard of progression in the EGFR-TKI group to be 0.25 times that in the chemotherapy group (pooled HR = 0.25 with a 95% CI (0.16, 0.40)). Fixed effect model estimates the hazard of progression in the EGFR-TKI group to be 0.26 times that in the chemotherapy group (pooled HR = 0.26 with a 95% CI (0.21, 0.3)). (Figure 16).

Figure 16 Forest Plot of Hazard Ratios among Selected EGFR Mutant Patients Who are Non-smoker



The hazard of disease progression among male who received EGFR-TKIs is significantly lower than that of male who received chemotherapy. Random effects model estimates the hazard of progression in the EGFR-TKI group to be 0.38 times that in the chemotherapy group (pooled HR = 0.38 with a 95% CI (0.26, 0.56)). Fixed effect model estimates the hazard of progression in the EGFR-TKI group to be 0.38 times that in the chemotherapy group (pooled HR = 0.38 with a 95% CI (0.28, 0.53)). (Figure 17).

The hazard of disease progression among female who received EGFR-TKIs is significantly lower than that of female who received chemotherapy. Random effects model estimates the hazard of progression in the EGFR-TKI group to be 0.28 times that in the chemotherapy group (pooled HR = 0.28 with a 95% CI (0.217, 0.47)). Fixed effect model estimates the hazard of progression

in the EGFR-TKI group to be 0.30 times that in the chemotherapy group (pooled HR = 0.30 with a 95% CI (0.23, 0.39)). (Figure 18).

Figure 17 Forest Plot of Hazard Ratios among Selected EGFR Mutant Male Patients

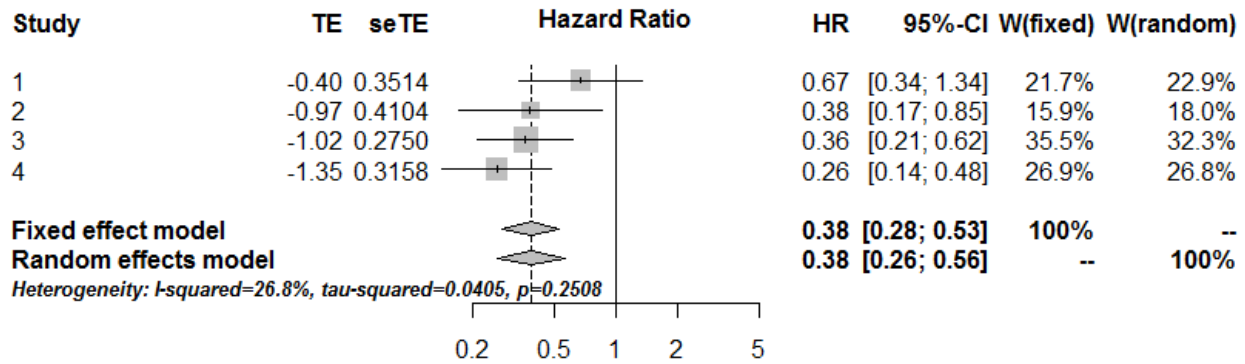
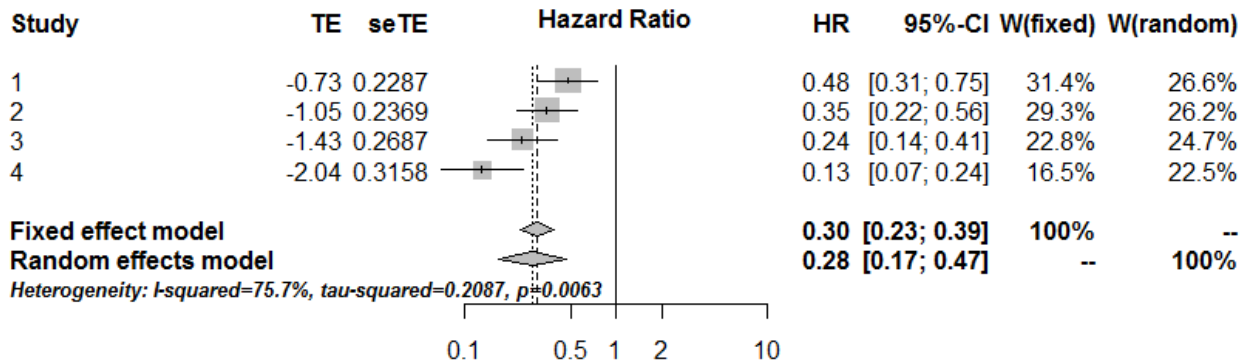


Figure 18 Forest Plot of Hazard Ratios among Selected EGFR Mutant Female Patients



#### 4. Conclusion and Discussion

In this meta-analysis, we systematically evaluated the efficacy of EGFR-TKIs compared with chemotherapy. We included 9 relatively high quality randomized controlled trials which enrolled patients with different clinical characteristics. Statistical analysis shows that among unselected patients (unknown EGFR mutation status), the efficacy of EGFR-TKIs is inferior to chemotherapy. In the EGFR-TKI group, the hazard of disease progression is significantly higher than that in chemotherapy group. However, among females and non-smokers with unknown EGFR mutation status, we did not observe significant difference of hazard of disease progression between

the EGFR-TKI group and the chemotherapy group. Among patients harboring EGFR mutation, EGFR-TKIs showed superb efficacy. The hazard of disease progression in the EGFR-TKIs group is significantly lower than that in chemotherapy group. However, patient's smoking status can greatly affect the efficacy. Among current smokers, although the hazard of disease progression is lower in EGFR-TKIs group, it is less significant than that in non-smokers. Among past smokers, the hazard ratio of disease progression between the EGFR-TKIs group and the chemotherapy group is not significantly different from 1. The efficacy of EGFR-TKIs among patients who smoked in the past varies significantly. Many patients who had a history of smoking but quit later did not benefit from EGFR-TKIs even though they were EGFR mutant.

Although EGFR-TKIs have provided an alternate solution for advanced non-small-cell patients, it cannot benefit all patients. For some patients, it might be less effective and more hazardous than the traditional chemotherapy. EGFR mutated patients are most sensitive to EGFR-TKIs and have the best prognosis. A few studies have paid attention to patient's smoking status. However, most of those studies classified patients to either smoker or non-smoker. In this meta-analysis, we found evidence that the efficacy of EGFR-TKIs among past smokers could be worse than that among current smoker. However, there is no formal definition of past smoker. In Wu 2014, they define past smoker as those who smoked less than 15 pack per year and stopped more than 1 year ago before enrolling to the trial. Rosell 2012 did not clarify the definition of past smoker. However, this unexpected finding shed some light to future research on this topic. More research needs to be done to further explore the pathological relationship between smoking status and efficacy of EGFR-TKIs. Formal standard needs to be established to distinguish between former smoker and current smoker. For example, how many cigarettes per day does a person smoke makes him a smoker? Who should be clarified as former smoker? For how long has a person

need to quit smoking to be considered for former smoker? Moreover, what category should passive smoker fall in? How does the efficacy of EGFR-TKIs among passive smokers compared to chemotherapy?

## **5. The Future of Cancer Treatment**

The current cancer treatment is largely based on evidence-based medicine. Clinicians make medical decisions based on macro-level characteristics such as gender, age, smoking status and cancer type. However, even some of those are significantly associated with prognosis, they cannot perfectly predict prognosis because they cannot differentiate the fundamental characteristics of each patient. Two patients can have exactly same clinical characteristics but does that guarantee their prognosis will also be same? What really differentiate each person is their unique genetic makeup. If scientists could uncover the molecular biomarkers that drive individual variability in clinical responses, then clinicians can then build genetic “regression model” to ensure the best prognosis possible and even prevent cancer from happening. In the future, we look forward to seeing the medical science come down from macro level to micro level and every patient can receive a “personalized medicine” that is specifically designed to him/her.



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## Appendix R-Code

Library(meta)

*### The efficacy of EGFR-TKIs among unselected patients*

```
> unselected = data.frame(
+ yi=c(0.4252677354,0.1739533071,0.3715635564,0.3011050928,0.4004775666),
+ vi=c(0.0792043868,0.1716695085,0.1998807468,0.230065419,0.2296272522))
> res=metagen(yi,vi,sm="HR",data=unselected)
> forest(res)
> funnel(res)
> metabias(res,method="linreg",k.min=5,plotit=TRUE)
```

*### Unselected Male*

```
> unselectedmale = data.frame(
+ yi=c(0.5822156199,1.057790294),
+ vi=c(0.1684611474,0.3193917743))
> res=metagen(yi,vi,sm="HR",data=unselectedmale)
> forest(res)
```

*### Unselected Female*

```
> unselectedfemale = data.frame(
+ yi=c(0.1570037488,0.0676586485),
+ vi=c(0.1338593186,0.2867117195))
> res=metagen(yi,vi,sm="HR",data=unselectedfemale)
> forest(res)
```

*### Unselected Smoker*

```
> unselectedsmoker=data.frame(
+ yi=c(0.5988365011,1.078409581),
+ vi=c(0.0852316758,0.3501874967) )
> res=metagen(yi,vi,sm="HR",data=unselectedsmoker)
> forest(res)
```

*### Unselected Non-Smoker*

```
> unselectednonsmoker=data.frame(
+ yi=c(-0.1165338163,-0.1625189295),
+ vi=c(0.1682414726,0.7382239709) )
> res=metagen(yi,vi,sm="HR",data=unselectednonsmoker)
> forest(res)
```

### *### Unselected adenocarcinoma*

```
> unselectedadenocarcinoma =data.frame(  
+ yi=c(0.4054651081,0.1906203596),  
+ vi=c(0.1054154333,0.2648594013))  
> res=metagen(yi,vi,sm="HR",data=unselectedadenocarcinoma)  
> forest(res)
```

### *### Unselected other*

```
> unselectedother=data.frame(  
+ yi=c(0.4446858213,1.238374231),  
+ vi=c(0.1171298172,0.5785786815))  
> res=metagen(yi,vi,sm="HR",data=unselectedother)  
> forest(res)
```

### *### The efficacy of EGFR-TKIs among patients harboring EGFR mutation*

```
> EGFR = data.frame(  
+ yi=c(-0.5108256238,-1.203972804,-1.832581464,-1.272965676,-0.9942522733,-0.7153927895),  
+ vi=c(0.3536465207,0.1582423104, 0.23979777, 0.1716695085,0.2000214734,0.19145476))  
> res=metagen(yi,vi,sm="HR",data=EGFR)  
> forest(res)  
> funnel(res)  
> metabias(res,method="linreg",k.min=5,plotit=TRUE)
```

### *### EGFR+ Past Smoker*

```
> EGFRpastsmoker=data.frame(  
+ yi=c(0.0487901642,-0.9416085399),  
+ vi=c(0.4923882123,0.8763528046))  
> res=metagen(yi,vi,sm="HR",data=EGFRpastsmoker)  
> forest(res)
```

### *### EGFR+ Current Smoker*

```
> EGFRcurrentsmoker=data.frame(  
+ yi=c(-0.5798184953,-0.7765287895),  
+ vi=c(0.6720925968,0.3763259914))  
> res=metagen(yi,vi,sm="HR",data=EGFRcurrentsmoker)  
> forest(res)
```

### *### EGFR+ Non Smoker*

```
> EGFRnonsmoker=data.frame(  
+ yi=c(-0.7635696449,-1.427116356,-1.427116356,-1.966112856),
```

```
+ vi=c(0.2298232119,0.2397977,0.2068699531,0.2855182592))
> res=metagen(yi,vi,sm="HR",data=EGFRnonsmoker)
> forest(res)
### EGFR+ Male
> EGFRmale=data.frame(
+ yi=c(-0.398986142,-0.9675840263,-1.021651248,-1.347073648),
+ vi=c(0.3513705136,0.4103942937,0.2749982147,0.3158363308))
> res=metagen(yi,vi,sm="HR",data=EGFRmale)
>forest(res)
### EGFR+ Female
> EGFRfemale=data.frame(
+ yi=c(-0.7339691751,-1.049822124,-1.427116356,-2.040220829),
+ vi=c(0.2286901909,0.2368906164,0.268699531,0.3158363308))
> res=metagen(yi,vi,sm="HR",data=EGFRfemale)
> forest(res)
>
```