Population-based incidence rates and increased risk of EGFR mutated non-small cell lung cancer in Māori and Pacifica in New Zealand

Phyu Sin Aye1 *, Mark James McKeage2,3, Sandar Tin Tin1, Prashannata Khwaounjoo2, J Mark Elwood1

1 Epidemiology and Biostatistics, University of Auckland, Auckland, New Zealand, 2 Pharmacology and Clinical Pharmacology, University of Auckland, Auckland, New Zealand, 3 Auckland Cancer Society Research Centre, University of Auckland, Auckland, New Zealand

* p.aye@auckland.ac.nz

Abstract

Background

Non-squamous non-small cell lung cancer (NSCLC) patients with Epidermal Growth Factor Receptor (EGFR) mutation benefit from targeted treatments. Previous studies reported EGFR mutation-positive proportions among tested non-squamous NSCLC patients. However, incidence rates and population risk of EGFR mutation-positive and EGFR mutation-negative non-squamous NSCLC have not been assessed. This study therefore aimed to estimate the population-based incidence rates of EGFR mutation-positive and EGFR mutation-negative non-squamous NSCLC in different population groups defined by sex, ethnic group and smoking status.

Methods

This study included data from all non-squamous NSCLC patients diagnosed in northern New Zealand between 1/02/2010 and 31/07/2017 (N = 3815), obtained from a population-based cancer registry. Age-specific incidence rates, WHO age-standardised rates (ASRs) and rates adjusted for incomplete testing were calculated for EGFR mutation-positive and EGFR mutation-negative non-squamous NSCLC in different population groups defined by sex, ethnic group and smoking status.

Results

Among 3815 patients, 45% were tested for EGFR mutations; 22.5% of those tested were EGFR mutation-positive. The ASR of EGFR mutation-positive NSCLC was 5.05 (95%CI 4.71–5.39) per 100,000 person-years. ASRs for EGFR mutation-positive NSCLC were higher for females than males: standardised incidence ratio (SIR) 1.50 (1.31–1.73); higher for Pacifica, Asians and Māori compared with New Zealand Europeans: SIRs 3.47 (2.48–4.85), 3.35 (2.62–4.28), and 2.02 (1.43–2.87), respectively; and, only slightly increased in
ever-smokers compared with never-smokers: SIR 1.25 (1.02–1.53). In contrast, the ASR of EGFR mutation-negative NSCLC was 17.39 (16.75–18.02) per 100,000 person-years, showing a strong association with smoking; was higher for men; highest for Māori, followed by Pacifica and then New Zealand Europeans, and lowest for Asians. When corrected for incomplete testing, SIRs by sex, ethnicity and smoking, for both diseases, remained similar to those based on tested patients.

**Conclusion**

The population risk of EGFR mutation-positive NSCLC was significantly higher for Māori and Pacifica compared with New Zealand Europeans.

**Introduction**

Lung cancer was the most common cancer for both sexes globally, accounting for 11.6% of total cancer incidence in 2018 [1]. In New Zealand, it contributed 8.4% of total cancer incidence in 2017, showing an age-standardised rate of 27.8 cases per 100,000 population [2].

Lung cancer, according to pathology, can be classified into two main groups: non-small cell lung cancer (NSCLC) and small cell lung cancer, accounting for 85% and 15%, respectively [3]. Squamous NSCLCs contribute about 25–30% of all lung cancers; the remaining non-squamous NSCLCs comprise adenocarcinoma, large-cell carcinoma, and NSCLC not otherwise specified (NOS). Non-squamous NSCLCs may harbour targetable mutations which define different subtypes of lung cancer with different aetiologies, molecular pathology, personalised treatment pathways and disease prognosis [4].

A significant advance in personalised treatment for NSCLC patients was the identification of lung cancers with Epidermal Growth Factor Receptor (EGFR) gene mutations [5], which benefit from targeted treatments with EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib, erlotinib and osimertinib [6,7], with significantly prolonged progression-free survival compared to standard chemotherapy [8]. With the approval of the use of EGFR-TKIs in EGFR mutation-positive lung cancer patients, EGFR mutation testing is generally recommended to non-squamous NSCLC patients [9–13].

Most previous studies of EGFR mutation-positive lung cancer have reported the proportion of patients with EGFR mutations among the tested patients. Such EGFR mutation-positive proportions vary widely from 10% to 51% in non-squamous NSCLC patients depending on sex, ethnicity and smoking status [14–16]. A systematic review covering 151 worldwide studies published up to 2014 observed that the EGFR mutation-positive proportion was reported as highest in the Asia-Pacific region (China, Hong Kong, Japan, Korea and Taiwan) and lowest in Oceania (Australia)– 47% versus 12% [16]. Specifically, the EGFR mutation-positive proportions were 60% in women and 37% in men, and 64% in never-smokers and 33% in ever-smokers as in the Asia-Pacific subgroup [16].

Despite the various reports on EGFR mutation-positive proportions, it is difficult to estimate the actual disease burden as most studies are not population-based, so little is known about the incidence rates of EGFR mutation-positive and negative non-squamous NSCLC in the general population and in subgroups. This population-based study therefore aimed to estimate the population-based incidence rates of EGFR mutation-positive and EGFR mutation-negative non-squamous NSCLC in different population groups defined by age, sex, ethnic...
Materials and methods

Study population

This study used the data of all patients who presented with non-squamous NSCLC in northern New Zealand, which comprises Northland, Waitemata, Auckland and Counties Manukau, contributing approximately 40% of New Zealand population, between 1 February 2010 and 31 July 2017 (N = 3815). We previously reported on the EGFR mutation testing [17,18] and developed a predictive model to estimate the EGFR mutation status [19] using this study cohort. In this study, we expanded the analysis to include population data to estimate the population-based EGFR mutation-positive and EGFR mutation-negative non-squamous NSCLC incidence.

Eligible patients were identified from the New Zealand Cancer Registry (NZCR), which is a well-established legally-mandated population-based cancer registry that registers all primary cancers diagnosed in New Zealand, excluding squamous and basal cell skin cancers [20]. Information on the following patient background characteristics was extracted from the NZCR: National Health Index (NHI) number, district health board (DHB) of residence, date of birth, date of diagnosis, gender, ethnicity and smoking status. These data were linked, using the NHIs, to individual patient medical records to obtain more information on smoking status, and to TestSafe to obtain information on EGFR mutation status. TestSafe is a clinical information sharing service in northern New Zealand that compiles the laboratory and radiology results and reports from DHB and community facilities [21].

EGFR mutations were detected by the Roche Cobas® real-time PCR [22] or Agena MassARRAY OncoFOCUS™ [23] tests, which were validated previously [24]. We categorised all the diagnosed EGFR mutations as EGFR(+) in the analysis regardless of their sensitivity to EGFR-TKIs [25]; these included G719X and E709A in exon 18, exon 19 deletions, R776C, S768I, T790M and insertions in exon 20, L858R and L861Q in exon 21, detected alone or in combination (S3 Table). A majority of EGFR mutations (exon 19 deletion and exon 21 L858R; 80.5%) are sensitive to EGFR-TKIs (S3 Table). With rapidly advancing research, newer generations of EGFR-TKIs are emerging that can target those EGFR mutations currently known to be resistant. Therefore, in our current study, we included all EGFR mutations regardless of the sensitivity to EGFR-TKIs.

The ethical approval for this research was obtained from the New Zealand Government Ministry of Health Northern B Health and Disability Ethics Committee (reference: 13/NTB/165/AM02). This research used routinely collected data and did not involve direct contact with patients. The human participants in this retrospective study were not required to give informed consent because informed consent was considered impractical and undesirable by both the researchers and by the ethics committee and governance groups who approved the study. Individual patient-level data were provided from various sources to the researchers without anonymization. These data were then compiled into a study database that included several direct and indirect identifiers. The ethical and legal requirements of the Ministry of Health for maintaining confidentiality and privacy of the study participants were met by limiting access to the study database to the healthcare professionals and research staff who were directly involved in the project and sharing only aggregate and de-identified data.
Data analysis

The analyses were based on the total of 3815 non-squamous NSCLC patients, limited to 3776 in analyses by ethnicity, and to 1855 in analyses by smoking status due to missing data. The smoking status was grouped into never-smokers and ever-smokers; the latter comprises current smokers and former smokers. The ethnic groups were categorised as New Zealand European, Māori, Pacific and Asian according to the New Zealand national collections [26].

Within each sex, ethnicity, smoking status group and 10-year age group, the proportion of EGFR mutation-positive non-squamous NSCLC among tested patients was multiplied by the annual numbers of non-squamous NSCLC to estimate the annual numbers of EGFR mutation-positive cases. These numbers of EGFR mutation-positive cases were then divided by the appropriate northern New Zealand population using the 2013 New Zealand census data (S2 Table) to estimate population-based incidence rates, reported annual numbers per 100,000 population (i.e. per 100,000 person-years).

The incidence rates were presented as crude rates, age-specific rates and age-standardised rates (ASRs) using the WHO world standard population [27] (S1 Table) based on the tested patient proportions. The incidence rates were also corrected for incomplete testing using the formula published in our previous research article [18]. The ASRs between groups were compared by means of Standardised Incidence Ratios (SIRs). The definitions of the estimates and formulas are depicted below. The results were reported in groups specified by gender, ethnicity and smoking status. The data analyses were conducted using Stata 16 and Microsoft Excel.

**Tested proportions (%)**: are the numbers of those tested for EGFR mutation among all non-squamous NSCLC cases, shown in per cent.

**EGFR mutation-positive proportions (%)**: are the number of EGFR mutation-positive patients divided by the total number of tested patients, shown in per cent.

**Crude and age-specific EGFR mutation-positive incidence rates**: are the annual number of EGFR mutation-positive non-squamous NSCLC per 100,000 population, where crude rates are overall rates and the rates in each age group are age-specific rates. The resident population was obtained from the 2013 New Zealand census data [28].

**Age-standardised EGFR mutation-positive incidence rates (ASRs)**: are the EGFR mutation-positive non-squamous NSCLC incidence rates that are age-standardised using the WHO world standard population [27] (S1 Table). It was calculated as the sum of the product of age-specific EGFR mutation-positive incidence and WHO standard population proportions in the respective age groups, divided by the total WHO standard population.

**Standardised incidence ratios (SIRs)**: are the ratios of two age-standardised incidence rates (ASRs). The 95% confidence intervals (CIs) of ASRs and SIRs were calculated using the methods published by Boyle & Parkin (1991) [29].

**EGFR mutation-negative incidence rates**: were obtained by applying the same concepts of incidence rate calculations for the EGFR mutation-positive disease to the EGFR mutation-negative disease. However, we only presented age-standardised incidence rates (ASRs) for EGFR mutation-negative disease, without crude rates, in this study.

**Uncorrected incidence rates (crude or ASRs)**: are those calculated based on the actual tested proportions.

**Corrected incidence rates (crude or ASRs)**: refer to those estimated based on 100% testing (i.e. if all non-squamous NSCLC patients were tested for EGFR mutation) using the following formula published in our previous study [18].

$$m_i = e^{\ln(m_0) - 0.994 \times (1 - \tau)},$$

where
m₁ = estimated proportion of \( EGFR \) mutation-positive cases if all patients were tested, 
m = observed proportion of \( EGFR \) mutation-positive cases in tested patients, and 
t = proportion of patients tested.

**Results**

This study included 3815 non-squamous NSCLC patients in total (Table 1). The patients were predominantly 60–79 years old (2237/3815, 58.6%), females (1950/3815, 51.1%), of New Zealand European ethnic group (2335/3776, 61.8%), and ever-smokers (1380/1855, 74.4%). About 45% (n = 1709) of the total 3815 patients had \( EGFR \) mutation testing. Specifically, \( EGFR \) mutations was more often tested for younger patients– 15–39 years (82.1%) and 40–59 years (57%); females (49.1%); and Asians (61.3%). Smoking data were mostly available for tested patients; thus, a majority of patients in both smoking groups were tested patients (ever-smokers 90.8% and never-smokers 89.7%).

**\( EGFR \) mutation-positive proportions**

Among those tested, 22.5% (384 patients) were \( EGFR \) mutation-positive, being higher in females (27.3%) and never-smokers (49.8%) compared to their counterparts (Table 1). Among ethnic groups, Asians had the highest proportion (51.8%), followed by Pacifica (29%) and New Zealand Europeans (16.5%), with Māori having the lowest proportion (10.9%). The \( EGFR \) mutation-positive proportions varied with age, ranging from 18.4% in 60–69 years to 37% in 70–79 years.

| Age   | Non-squamous NSCLC | Tested     | \( EGFR(+) \) among tested |
|-------|-------------------|------------|-----------------------------|
|       | N     | N (%)   | N (%)                       |
| Overall| 3815 | 1709 (44.8) | 384 (22.5) |
| 15–29  | 6     | 5 (83.3)  | 1 (20.0)        |
| 30–39  | 22    | 18 (81.8) | 4 (22.2)        |
| 40–49  | 152   | 92 (60.5) | 34 (37.0)       |
| 50–59  | 513   | 287 (55.9)| 66 (23.0)       |
| 60–69  | 1068  | 538 (50.4)| 99 (18.4)       |
| 70–79  | 1169  | 575 (49.2)| 135 (23.5)      |
| 80+    | 885   | 194 (21.9)| 45 (23.2)       |

| Gender | Non-squamous NSCLC | Tested | \( EGFR(+) \) |
|--------|-------------------|--------|---------------|
| Male   | 1865              | 752 (40.3) | 123 (16.4)   |
| Female | 1950              | 957 (49.1) | 261 (27.3)   |

| Ethnicity | Non-squamous NSCLC | Tested     | \( EGFR(+) \) |
|-----------|-------------------|------------|---------------|
| NZ European | 2335             | 1006 (43.1) | 166 (16.5) |
| Māori     | 643               | 248 (38.6)  | 27 (10.9)    |
| Pacific   | 392               | 183 (46.7)  | 53 (29.0)    |
| Asian     | 406               | 249 (61.3)  | 129 (51.8)   |

| Smoking status | Non-squamous NSCLC | Tested | \( EGFR(+) \) |
|----------------|-------------------|--------|---------------|
| Never-smoker   | 475               | 426 (89.7) | 212 (49.8) |
| Ever-smoker    | 1380              | 1253 (90.8)| 166 (13.2) |

Total 3815 non-squamous NSCLC; limited to 3776 in analyses by ethnicity; and limited to 1855 in analyses by smoking status due to missing data. Ever-smokers comprise current smokers and former smokers.

https://doi.org/10.1371/journal.pone.0251357.t001
40–49 years (Table 1). However, it was unclear from these $EGFR$ mutation-positive proportion values how the trends relate to the incidence rates of $EGFR$ mutation-positive or negative disease. For example, Māori may have had a lower proportion of $EGFR$ mutation-positive cancers because of a higher incidence of $EGFR$ mutation-negative disease, a lower incidence of $EGFR$ mutation-positive disease or both.

**Total and age-specific incidence rates by $EGFR$ mutation status**

Incidence rates were then calculated separately for $EGFR$ mutation-positive and $EGFR$ negative disease based on the tested proportions.

The crude all-ages incidence rate of $EGFR$ mutation-positive disease was 9.14 (95% Confidence Interval (95%CI) 8.9–9.4) per 100,000 person-years. The age-specific rates increased with age, ranging from 0.05 (95%CI 0.02–0.08) in the youngest 15–29 years group to 58.56 (95%CI 55.64–61.49) per 100,000 person-years in the oldest 80+ years group (Fig 1).

The crude all-ages incidence rate of $EGFR$ mutation-negative disease was 31.6 (95%CI 31.2–32.0) per 100,000 person-years. The age-specific rates showed a similar increase with age as mutation-positive disease, ranging from 0.19 (95%CI 0.13–0.25) in the youngest 15–29 years group to 193.9 (95%CI 188.6–199.23) per 100,000 person-years in the oldest 80+ years group (Fig 1).

**Age-standardised incidence rates by $EGFR$ mutation status**

To compare rates of disease between different groups, age-standardised incidence rates were calculated. The WHO standard population has larger numbers in younger age groups and fewer in older age groups compared to the population of a developed country like New Zealand (S1 & S2 Tables). Thus, for lung cancer where the incidence rates are much higher in older age groups, the WHO age-standardised incidence rates are considerably lower than actual incidence rates. The age distribution also varies by population subgroups. For example, Māori and Pacifica has younger age distribution compared to New Zealand Europeans. Therefore, differences between crude rates and ASR were more pronounced for New Zealand Europeans.

Based on tested proportions, the age-standardised incidence rate (ASR) of total non-squamous NSCLC was 22.4 per 100,000 person-years. The ASR for $EGFR$ mutation-positive NSCLC was 5.05 (95%CI 4.71–5.39) per 100,000 person-years (Table 2). The ASR for $EGFR$
mutation-positive NSCLC was higher for females than males: standardised incidence ratio (SIR) 1.50 (95%CI 1.31–1.73). Incidence rates were higher for Pacifica, Asians and Māori compared with New Zealand Europeans: SIR for Pacifica 3.47 (95%CI 2.48–4.85), Asians 3.35 (95%CI 2.62–4.28), Māori 2.02 (95%CI 1.43–2.87). The ASR of EGFR mutation-positive NSCLC was only slightly increased in ever-smokers compared with never-smokers: SIR 1.25 (95%CI 1.02–1.53) (Table 2, Fig 2).

EGFR mutation-negative NSCLC was more common, showing an ASR of 17.4 (95%CI 16.75–18.02) per 100,000 person-years, based on the tested proportions (Table 2). In contrast to the EGFR mutation-positive disease, the ASR of EGFR mutation-negative NSCLC was lower in females than males: SIR 0.8 (95%CI 0.75–0.87); it was lower in Asians compared with New Zealand Europeans: SIR 0.68 (95%CI 0.6–0.78), but much higher in Māori: SIR 3.53 (95%CI 3.04–4.11) and higher in Pacifica: SIR 1.88 (95%CI 1.6–2.2). These ASR trends of EGFR mutation-negative lung cancer corresponded to the proportions of ever-smokers in those ethnic subgroups, except for Pacifica versus New Zealand Europeans (S2 Table). The ASR was much higher in ever-smokers compared with never-smokers: SIR 7.9 (95%CI 6.88–9.11) (Table 2, Fig 2).

To assess consistency over time, SIR’s by sex, ethnicity and smoking were assessed separately for the earlier period 2010–13 (n = 1864) and for the later period 2014–17 (n = 1951). The results were not substantially changed and all confidence limits overlapped; the SIRs for the whole time period presented here are similar to those restricted to the later time period.

### Table 2. Incidence rates of non-squamous non-small cell lung cancer by EGFR mutation status, showing the estimates based on the EGFR mutation tested proportions.

|        | EGFR(+) crude incidence (95% CI) | Overall NSCLC ASR (95%CI) | EGFR(+) proportion | EGFR(+) ASR (95%CI) SIR (95%CI) | EGFR(-) ASR (95%CI) SIR (95%CI) |
|--------|----------------------------------|---------------------------|--------------------|----------------------------------|----------------------------------|
| Overall| 9.14 (8.92–9.36)                 | 22.44 (21.72–23.16)       | 22.5               | 5.05 (4.71–5.39)                 | - 17.39 (16.75–18.02)           |
| Gender |                                  |                           |                    |                                  |                                  |
| Male   | 7.00 (6.72–7.28)                 | 23.56 (22.48–24.63)       | 16.4               | 3.95 (3.51–4.39)                 | 1 19.61 (18.63–20.59)           |
| Female | 10.79 (10.46–11.13)              | 21.81 (20.83–22.79)       | 27.3               | 5.93 (5.42–6.45)                 | 1 15.88 (15.04–16.72)           |
| Ethnicity |                                  |                           |                    |                                  |                                  |
| NZ European |                                  | 7.54 (7.28–7.81) | 18.54 (17.77–19.32) | 16.5               | 3.16 (2.84–3.48)                 | 1 15.38 (14.68–16.09)           |
| Māori | 7.13 (6.51–7.75)                 | 60.73 (55.89–65.58)       | 10.9               | 6.40 (4.83–7.97)                 | 2.02 (1.43–2.87) 54.34 (49.75–58.92) 3.53 (3.04–4.11) |
| Pacific | 11.32 (10.54–12.09)             | 39.84 (35.84–43.84)       | 29.0               | 10.95 (8.88–13.03)              | 3.47 (2.48–4.85) 28.88 (25.47–32.30) 1.88 (1.60–2.21) |
| Asian | 11.11 (10.56–11.66)              | 21.04 (18.94–23.15)       | 51.8               | 10.57 (9.10–12.05)              | 3.35 (2.62–4.28) 10.47 (8.96–11.97) 0.68 (0.60–0.78) |
| Smoking status |                                  |                           |                    |                                  |                                  |
| Never-smoker |                                  | 4.23 (4.03–4.43) | 5.30 (4.82–5.78)   | 49.8               | 2.64 (2.30–2.98)                 | 1 2.66 (2.32–3.00) 1          |
| Ever-smoker |                                  | 6.48 (6.14–6.82) | 24.35 (23.06–25.64) | 13.2               | 3.31 (2.82–3.79)                 | 1.25 (1.02–1.53) 21.04 (19.84–22.24) 7.92 (6.88–9.11) |

ASR = Age-standardised incidence rates, cases per 100,000 person-years; SIR = standardised incidence ratio. Age standardised rates are based on WHO world standard population. Analysis is based on total 3815 non-squamous NSCLC; limited to 3776 in analyses by ethnicity; and limited to 1855 in analyses by smoking status due to missing data. Ever-smokers comprise current smokers and former smokers.

https://doi.org/10.1371/journal.pone.0251357.t002
Incomplete testing may bias estimates of disease incidence within a given population [18]. When corrected for incomplete testing, the corrected \( \text{EGFR} \) mutation-positive incidence rates were generally somewhat lower compared to the respective uncorrected rates (Table 3). The age-specific incidence rates of \( \text{EGFR} \) mutation-positive NSCLC increased with age up to 70–79 years: 27.2 (95% CI 25.7–28.7) per 100,000 person-years (S1 Fig).

Table 3. Incidence rates of non-squamous non-small cell lung cancer by \( \text{EGFR} \) mutation status, showing the estimates for 100% testing.

|                | \( \text{EGFR}(+) \) crude incidence (95%CI) | Overall NSCLC ASR (95%CI) | \( \text{EGFR}(+) \) proportion | \( \text{EGFR}(+) \) | \( \text{EGFR}(-) \) |
|----------------|---------------------------------------------|--------------------------|---------------------------------|-----------------|-----------------|
|                | \( \text{ASR} \) (95%CI)                  | \( \text{SIR} \) (95%CI) | \( \text{ASR} \) (95%CI)        | \( \text{SIR} \) (95%CI) | \( \text{ASR} \) (95%CI) |
| Overall        | 5.33 (5.16–5.50)                           | 22.44 (21.72–23.16)      | 13.0                            | 3.00 (2.74–3.27) | -               |
| Gender         |                                             |                          |                                 |                 |                 |
| Male           | 3.86 (3.65–4.07)                           | 23.56 (22.48–24.63)      | 9.0                             | 2.20 (1.87–2.53) | 1               | 21.36 (20.34–22.38) | 1 |
| Female         | 6.59 (6.33–6.85)                           | 21.81 (20.83–22.79)      | 16.4                            | 3.71 (3.30–4.12) | 1.69 (1.41–2.02) | 18.10 (17.21–18.99) | 0.85 (0.79–0.91) |
| Ethnicity      |                                             |                          |                                 |                 |                 |
| NZ European    | 4.22 (4.02–4.42)                           | 18.54 (17.77–19.32)      | 9.4                             | 1.84 (1.59–2.08) | 1               | 16.70 (15.97–17.44) | 1 |
| Maori          | 3.97 (3.51–4.44)                           | 60.73 (55.89–65.58)      | 5.9                             | 3.47 (2.33–4.61) | 1.89 (1.20–2.97) | 57.26 (52.56–61.97) | 3.43 (2.97–3.96) |
| Pacific        | 6.81 (6.21–7.41)                           | 39.84 (35.84–43.84)      | 17.0                            | 6.46 (4.88–8.03) | 3.51 (2.28–5.42) | 33.38 (29.71–37.06) | 2.00 (1.71–2.33) |
| Asian          | 7.65 (7.19–8.11)                           | 21.04 (18.94–23.15)      | 35.3                            | 7.17 (5.97–8.37) | 3.90 (2.85–5.34) | 13.87 (12.14–15.60) | 0.83 (0.73–0.94) |
| Smoking status |                                             |                          |                                 |                 |                 |
| Never-smoker   | 3.82 (3.63–4.00)                           | 5.30 (4.82–5.78)         | 44.9                            | 2.38 (2.06–2.70) | 1               | 2.92 (2.56–3.28) | 1 |
| Ever-smoker    | 5.89 (5.57–6.22)                           | 24.35 (23.06–25.64)      | 12.1                            | 3.00 (2.54–3.46) | 1.26 (1.02–1.55) | 21.35 (20.14–22.56) | 7.31 (6.38–8.38) |

\( \text{ASR} \) = age-standardised incidence rates, cases per 100,000 person-years; \( \text{SIR} \) = standardised incidence ratio. Age standardised rates are based on WHO world standard population. Analysis is based on total 3815 non-squamous NSCLC; limited to 3776 in analyses by ethnicity; and limited to 1855 in analyses by smoking status due to missing data. Ever-smokers comprise current smokers and former smokers.
ratios by sex, ethnicity and smoking, for both EGFR mutation-positive and EGFR mutation-negative diseases, were similar (and in no instance significantly different) to the ratios of uncorrected rates already shown (Table 3).

Discussion

We estimated the population-based incidence rates of EGFR mutation-positive and EGFR mutation-negative non-squamous NSCLC based on all 3815 patients registered over 7.5 years. The age-standardised incidence rate (ASR) of non-squamous NSCLC was 22.4 cases per 100,000 person-years overall, 5.1 and 17.4 per 100,000 person-years for EGFR-positive and -negative disease, respectively, based on the tested proportions. The age-standardised incidence rates of EGFR mutation-positive disease were higher in women (SIR 1.5); highest in Pacific and Asian populations (SIRs 3.5, 3.4), followed by Māori (SIR 2.0), and lowest in New Zealand Europeans, all these associations being statistically significant. The ASR of EGFR mutation-positive disease was only slightly higher in ever-smokers than never-smokers (SIR 1.25). These associations were not influenced by effects in the earlier time period where testing was less frequent.

This study revealed that assessing the risk of EGFR mutation-positive lung cancer just by EGFR mutation-positive proportions in tested patients [14–16], ignoring underlying population incidence, can be misleading. Based only on the EGFR mutation-positive proportions, it appeared that being Māori was of lower risk and being Pacific was of higher risk but not as much as Asians, compared with New Zealand Europeans. On the contrary, the population-based incidence rates showed that Māori had approximately two times increased risk, and Pacifica and Asians had approximately 3.5 times increased risk for EGFR mutation-positive lung cancer compared with New Zealand Europeans.

The age-standardised incidence rates of EGFR mutation-positive NSCLC were close to or higher than those of many common cancers in New Zealand, such as cancers of stomach (5.3 cases per 100,000 population), brain (5.4), thyroid (5.8), cervix (6.1), ovary (6.6), testis (7.5), kidney (7.9), and leukaemia (10.2) based on 2017 diagnoses [2].

This study showed contrasting patterns of incidence rates between EGFR mutation-positive and negative non-squamous NSCLC. It suggests that the two diseases have different risk factors, in addition to having different management pathways. The majority group, with EGFR mutation-negative accounting for 77.5% of the total, was strongly associated with smoking, more common in men than women, and had the highest incidence in Māori, followed by Pacific peoples, the New Zealand European population, and then was lowest in people of Asian ethnicity. Most of these findings of EGFR mutation-negative group contradict those of EGFR mutation-positive group. These results are generally consistent with those of major reviews, which concluded that EGFR mutations and smoking had independent effects on lung cancer, and that EGFR mutations were more common in Asians, females, and never-smokers [16,30–33]. Smoking is a predominant risk factor of lung cancer; yet, lung cancer incidence in never-smokers is also evident [34]. Studies suggested that persistent differences in lung cancer incidence among different ethnic populations were not entirely explained by variations in smoking history [35–37], for which, EGFR mutation-positive lung cancer exemplifies [38]. Some studies claimed that interethnic genetic variations may play a role in EGFR mutation positivity [39,40]. Current understanding of the aetiology of lung cancer, and health policies and practices for its prevention and early detection, are based almost solely on risk factors for smoking-related lung cancer. A better understanding of the risk factors for EGFR mutation-positive lung cancer will be required to identify its causes and to develop public health strategies for its prevention and early detection.
Every population-based study of EGFR mutation testing has shown incomplete testing [41]. Evidence showed that testing tends to be selective due to multiple reasons, including limited testing facilities, high costs and insufficient tissue samples [17,18,41–43]. Patients with a higher chance of EGFR mutation positivity were therefore more likely to be offered testing, resulting in high EGFR mutation-positive proportions in the tested proportion. This was seen in this study. We and others have previously shown that as the proportions of all NSCLC cases tested has increased over time, the reported EGFR mutation-positive proportions have decreased [17,18]. We showed that in this northern New Zealand area, the EGFR mutation-positive proportions decreased from 43.8% to 16.8% in parallel with increased testing rates from 3.7% to 64.6% over the period of 2010–2014 [17,18]. If testing were complete rather than selective, the true proportions of mutations would be lower. We addressed this issue to reflect the true population incidence by estimating the corrected incidence rates, using a nonlinear regression equation, which assumes a decrease in EGFR mutation-positive proportion with an increase in testing, derived from our previous work [18]. This changed the estimated incidence rates substantially, but importantly, made little difference to the associations with sex, ethnicity and smoking that we reported. The largest effect was in the SIR for Asians for EGFR mutation-positive disease, increased by the correction for incomplete testing.

The key advantage of our study was the use of a large population-based dataset covering 7.5 years, obtained from the robust national data sources. This study was also the first to report the incidence of EGFR mutation-specific lung cancer in Māori and Pacifica, the populations of interest in New Zealand, revealing that these populations had increased risk of developing EGFR mutation-positive lung cancer, as seen for lung cancer overall [44–47]. Our study also had limitations. This study used the retrospective data and therefore the analyses were limited to the information that had been collected. Smoking data was missing for a significant proportion of patients, particularly those who were untested for EGFR mutation. It resulted in a smaller room for correction for incomplete testing in estimating the incidence rates by smoking status. More detailed information, for example, pack-years, which is the product of the number of cigarette packs smoked per day and the number of years smoked [48], may be useful for future research as smoking is a major risk factor [49] and is also related to EGFR mutation positivity [14]. In this analysis of population-based incidence rates, the available numbers did not permit the results for each factor to be adjusted for other factors, but in the previous analysis, we have used multivariable methods and demonstrated that the effects of gender, ethnicity, and smoking status are independent, and indeed can be combined to predict the mutation status of the cancer [19]. The estimation of the incidence of EGFR mutation-specific NSCLC can be improved as the testing becomes more complete in the future.

**Conclusions**

The population-based incidence rates provide a more complete assessment of the risk of EGFR mutation-positive lung cancer than do the EGFR mutation-positive proportions. The ASRs of EGFR mutation-positive NSCLC were about 3.5 folds higher for Pacifica and Asians, and two folds higher for Māori compared with New Zealand Europeans.

**Supporting information**

S1 Fig. Age-specific incidence rates (cases per 100,000 person-years) of non-squamous non-small cell lung cancer by EGFR mutation status estimated for 100% testing, shown in age groups. The vertical error bars represent 95% confidence intervals of incidence rates. (DOCX)
S2 Fig. Age standardised incidence rates (estimated for 100% testing) of non-squamous NSCLC in terms of EGFR mutation status categorised by gender, ethnicity and smoking status. Age standardised rates represent cases per 100,000 person-years and are based on WHO world standard population. Analysis based on total 3815 non-squamous NSCLC; limited to 3776 in analyses by ethnicity; and limited to 1855 in analyses by smoking status due to missing data. Ever-smokers comprised current smokers and former smokers. The vertical error bars represent 95% confidence intervals of incidence rates.

(DOCX)

S1 Table. WHO world standard population.

(DOCX)

S2 Table. Numbers of resident population, shown by smoking status, based on 2013 New Zealand census data.

(DOCX)

S3 Table. Different types of EGFR mutation by numbers of patients.

(DOCX)

Author Contributions

Conceptualization: Phyu Sin Aye, Mark James McKeage, J Mark Elwood.

Data curation: Prashannata Khwaounjoo.

Formal analysis: Phyu Sin Aye, Sandar Tin Tin.

Funding acquisition: Mark James McKeage.

Methodology: Phyu Sin Aye, Mark James McKeage, Sandar Tin Tin, J Mark Elwood.

Supervision: Mark James McKeage, Sandar Tin Tin, J Mark Elwood.

Writing – original draft: Phyu Sin Aye.

Writing – review & editing: Phyu Sin Aye, Mark James McKeage, Sandar Tin Tin, J Mark Elwood.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA—A Cancer J Clin 2018. https://doi.org/10.3322/caac.21492.

2. Ministry of Health. New cancer registrations 2017. Wellington: 2019.

3. Reckamp KL, Rosen ST, Reckamp KL. Lung Cancer. In: Reckamp KL, editor. Cancer Treat. Res., vol. 170, Switzerland: Springer, Cham; 2016. https://doi.org/10.1007/978-3-319-40389-2_2.

4. Melosky B. Treatment algorithms for patients with metastatic non-small cell, non squamous lung cancer. Front Oncol 2014; 4:1–5. https://doi.org/10.3389/fonc.2014.00256.

5. Lynch J, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib. N Engl J Med 2004; 350:2129–39. https://doi.org/10.1056/NEJMoa040938 PMID: 15118073

6. Abramson R. Overview of Targeted Therapies for Cancer. My Cancer Genome 2017. https://www.mycancergenome.org/content/molecular-medicine/overview-of-targeted-therapies-for-cancer/ (accessed May 18, 2018).

7. Hirsch FR, Scagliotti G V, Mulshine JL, Kwon R, Curran WJ, Wu YL, et al. Lung cancer: current therapies and new targeted treatments. Lancet 2017; 389:299–311. https://doi.org/10.1016/S0140-6736(16)30958-8 PMID: 27874741
8. Lee CK, Wu YL, Ding PN, Lord SJ, Inoue A, Zhou C, et al. Impact of specific Epidermal Growth Factor Receptor (EGFR) mutations and clinical characteristics on outcomes after treatment with EGFR tyrosine kinase inhibitors versus chemotherapy in EGFR-mutant lung cancer: A meta-analysis. J Clin Oncol 2015; 33:1958–65. https://doi.org/10.1200/JCO.2014.58.1736 PMID: 25897154

9. Hicks K, Wong C. Identifying lung cancer patients who may be eligible for epidermal growth factor receptor (EGFR) mutation testing. N Z Med J 2013; 126:49–56. PMID: 24150265

10. NHC. Epidermal Growth Factor Receptor mutation testing for access to gefitinib in first-line treatment for advanced Non-Small Cell Lung cancer. Wellington: 2013.

11. Keedy VL, Temin S, Somerfield MR, Beasley MB, Johnson DH, McShane LM, et al. American Society of Clinical Oncology provisional clinical opinion: Epidermal growth factor receptor (EGFR) mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy. J Clin Oncol 2011; 29:121–7. https://doi.org/10.1200/JCO.2010.31.8923 PMID: 21482992

12. Lindeman NI, Cagle PT, Beth Beasley M, Arun Chitale D, Dacic S, Giaccone G, et al. Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors: Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Patho. J Thorac Oncol 2013; 8:823–59. https://doi.org/10.1097/JTO.0b013e318290868f PMID: 23552377

13. Kerr KM, Bubendorf L, Edelman MJ, Marchetti A, Mok T, Novello S, et al. Second ESMO consensus conference on lung cancer: Pathology and molecular biomarkers for non-small-cell lung cancer. Ann Oncol 2014; 25:1681–90. https://doi.org/10.1093/annonc/mdu145 PMID: 24718990

14. Shi Y, Au JS-KK, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol 2014; 9:154–62. https://doi.org/10.1097/JTO.0000000000000033 PMID: 24419411

15. Gesthelter YB, Billatos E, Kathuria H. Lung Cancer. Genomic Precis. Med., DOI; 2017, p. 165–80.

16. Midha A, Dearden S, McCormack R. EGFR mutation incidence in non-Small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII). Am J Cancer Res 2015; 5:2892–911. https://doi.org/10.5194/hess-11-1609-2007. PMID: 26609494

17. McKeage M, Elwood JM, McKeage MJ, Elwood M, Tin Tin S, Khwaounjoo P, Li A, et al. EGFR Mutation Testing of non-squamous NSCLC: Impact and Uptake during Implementation of Testing Guidelines in a Population-Based Registry Cohort from Northern New Zealand. Target Oncol 2017; 12:663–75. https://doi.org/10.1007/s11523-017-0515-4 PMID: 28699084

18. Tin Tin S, McKeage MJ, Khwaounjoo P, Thi AM, Elwood JM. Incomplete uptake of EGFR mutation testing and its impact on estimation of mutation prevalence in patients with non-squamous NSCLC: A population-based study in New Zealand. Cancer Epidemiol 2018; 57:24–32. https://doi.org/10.1016/j.canep.2018.09.004 PMID: 30278336

19. Aye PS, Tin Tin S, McKeage MJ, Khwaounjoo P, Cavadino A, Elwood JM. Development and validation of a predictive model for estimating EGFR mutation probabilities in patients with non-squamous non-small cell lung cancer in New Zealand. BMC Cancer 2020; 20:658. https://doi.org/10.1186/s12885-020-07162-z PMID: 32664868

20. Ministry of Health NZ. New Zealand Cancer Registry. Minist Heal New Zeal. 2020. https://www.health.govt.nz/nz-health-statistics/data-references/code-tables/ethnicity-code-tables/ethnicity-code-tables (accessed November 26, 2020).

21. CareConnect. TestSafe 2020. http://www.careconnect.co.nz/testsafe/ (accessed March 28, 2020).

22. Roche Diagnostics. The cobas® EGFR Mutation Test 2019. http://www.cobasefrtest.com/ (accessed March 13, 2020).

23. Agena Bioscience. OncoFOCUSTM Panel v3: Genes and Mutations. 2016.

24. Shepherd P, Sheath KL, Tin ST, Khwaounjoo P, Aye PS, Li A, et al. Lung cancer mutation testing: A clinical retesting study of agreement between a real-time PCR and a mass spectrometry test. Oncotarget 2017; 8:101437–51. https://doi.org/10.18632/oncotarget.21023 PMID: 29254176

25. Pao W, Chmielecki J. Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer. Nat Rev Cancer 2010; 10:760–74. https://doi.org/10.1038/nrc2947 PMID: 20966921

26. Ministry of Health. Ethnicity code tables. Minist Heal New Zeal. 2010. https://www.health.govt.nz/nz-health-statistics/data-references/code-tables/common-code-tables/ethnicity-code-tables (accessed July 9, 2020).

27. Ahmad OB, Boschi-pinto C, Lopez AD. Age standardization of rates: a new WHO standard. GPE Discuss Pap Ser 2001:1–14.
28. Statistics New Zealand. Cigarette smoking behaviour and ethnic group (detailed total responses) by age group and sex, for the census usually resident population count aged 15 years and over, 2006 and 2013 Censuses (DHB areas). NZStat Get Data Demand 2013. http://nzdotstat.stats.govt.nz/wbos/index.aspx?DataSetCode=TABLECODE8292 (accessed April 22, 2020).

29. Boyle P, Parkin D. Statistical methods for registries. Cancer Regist Princ Methods 1991:126–58. PMID: 1894318

30. Zhang YL, Yuan JQ, Wang KF, Fu XH, Han XR, Threapleton D, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: A systematic review and meta-analysis. Oncotarget 2016; 7:78985–93. https://doi.org/10.18632/oncotarget.12587 PMID: 27738317

31. Mitsudomi T. Molecular epidemiology of lung cancer and geographic variations with special reference to EGFR mutations. Transl Lung Cancer Res 2014; 3:205–11. https://doi.org/10.3978/j.issn.2218-6751.2014.08.04 PMID: 25806302

32. Altman DG. Analysis of Survival Times. In: Altman DG, editor. Pract. Stat. Med. Res., Chapman and Hall, London; 1991. https://doi.org/10.1007/978-3-319-28316-6_10.

33. Chapman AM, Sun KY, Ruestow P, Cowan DM, Madl AK. Lung cancer mutation profile of EGFR, ALK, and KRAS: Meta-analysis and comparison of never and ever smokers. Lung Cancer 2016; 102:122–34. https://doi.org/10.1016/j.lungcan.2016.10.010 PMID: 27987580

34. Wakelee HA, Chang ET, Gomez SL, Keegan TH, Feskanich D, Clarke CA, et al. Lung cancer incidence in never smokers. J Clin Oncol 2007; 25:472–8. https://doi.org/10.1200/JCO.2006.07.2983 PMID: 17290054

35. Stram DO, Park SL, Haiman CA, Murphy SE, Patel Y, Hecht SS, et al. Racial/Ethnic Differences in Lung Cancer Incidence in the Multiethnic Cohort Study: An Update. J Natl Cancer Inst 2019; 111:811–9. https://doi.org/10.1093/jnci/djy206 PMID: 3069822

36. Pirie K, Peto R, Green J, Reeves GK, Beral V. Lung cancer in never smokers in the UK Million Women Study. Int J Cancer 2016; 139:347–54. https://doi.org/10.1002/ijc.30084 PMID: 26954263

37. Risch N. Dissecting racial and ethnic differences. N Engl J Med 2006; 354:408–11. https://doi.org/10.1056/NEJM e058265 PMID: 16436773

38. Matsuo K, Ito H, Yatabe Y, Hiraki A, Hirose K, Wakai K, et al. Risk factors differ for non-small-cell lung cancers with and without EGFR mutation: Assessment of smoking and sex by a case-control study in Japanese. Cancer Sci 2007; 98:96–101. https://doi.org/10.1111/j.1349-7006.2006.00347.x PMID: 17054433

39. Soraas L, Stebbing J. Geographic Variation in EGFR Mutation Frequency in Lung Adenocarcinoma May Be Explained by Interethnic Genetic Variation. J Thorac Oncol 2018; 13:454–8. https://doi.org/10.1016/j.jtho.2017.11.128 PMID: 29246834

40. Nomura M, Shigematsu H, Li L, Suzuki M, Takahashi T, Estess P, et al. Polymorphisms, mutations, and amplification of the EGFR gene in non-small cell lung cancers. PLoS Med 2007; 4:715–27. https://doi.org/10.1371/journal.pmed.0040125.

41. Thi AM, Tin Tin S, Mckeage M, Elwood JM, Myat A, Sandqvist M, et al. Patients with Non-small Cell Lung Cancer Analyzed for EGFR: Adherence to Guidelines, Prevalence and Outcome. Anticancer Res 2015; 35:3979–85. PMID: 26124345

42. Ellis PM, Verma S, Sehdev S, Younus J, Leigh NB. Challenges to implementation of an epidermal growth factor receptor testing strategy for non-small-cell lung cancer in a publicly funded health care system. J Thorac Oncol 2013; 8:1136–41. https://doi.org/10.1097/JTO.0b013e1829f6a43 PMID: 23887170

43. National Lung Cancer Working Group. Standards of Service Provision for Lung Cancer Patients in New Zealand. 2011.

44. Ministry of Health. Annual Update of Key Results 2015/16 New Zealand Health Survey. 2016. https://doi.org/978-0-947491-49-9.

45. Shaw C, Blakely T, Sarfati D, Fawcett J, Hill S. Varying evolution of the New Zealand lung cancer epidemic by ethnicity and socioeconomic position (1981–1999). J New Zeal Med Assoc 2005; 118:1981–99.

46. Blakely T, Fawcett J, Hunt D, Wilson N. What is the contribution of smoking and socioeconomic position to ethnic inequalities in mortality in New Zealand? Lancet 2006; 368:44–52. https://doi.org/10.1016/ S0140-6736(06)68813-2 PMID: 16815377
48. National Cancer Institute. NCI Dictionary of Cancer Terms 2020. https://www.cancer.gov/publications/dictionaries/cancer-terms/ (accessed July 7, 2020).

49. Planchard D, Popat S, Kerr K, Novello S, Smit E, Faivre-Finn C, et al. ESMO Clinical Practice Guidelines for mNSCLC. Ann Oncol 2019; 29:iv192–iv237.