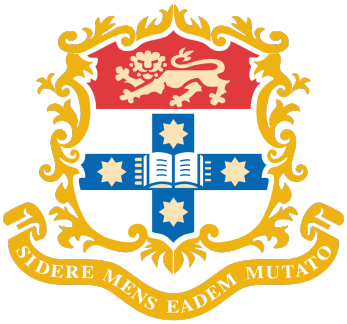
Lung Cancer Driver Mutations in Non-Small Cell Lung Cancer



Charles N. Prabhakar

Faculty of Medicine

The University of Sydney

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Nomenclature

Roman Symbols

$COSMIC$ Catalogue of Somatic Mutations in Cancer

DFS disease free survival

EGF Epidermal Growth Factor

$EGFR$ Epidermal Growth Factor Receptor

LCC large cell carcinoma

$mTOR$ Mammalian target of rapamycin

$NSCLCa$ non-small cell lung cancer

OS overall survival

$SCLCa$ small cell lung cancer

$SqCC$ squamous cell carcinoma

$SqCCa$ Squamous cell carcinoma

TKI Tyrosine Kinase Inhibitors

Chapter 1

Lung Cancer

1.1 See Steven's email 22/10/15

1.2 Epidemiology

Lung cancer is a disease with an ever increasing global burden, contributing to more than 1.5 million deaths world wide in 2010[1] and 2.5 million new diagnoses[2] with an incidence of nearly 500 per 100000[3]. Traditionally, lung cancer has a far higher incidence amongst men than women, however in Australia, from 1982 - 2011 that difference has diminished from over 4 fold to under 2 fold (Fig. 1.1)[4]. This change is due, not only to the falling incidence of lung cancer amongst men, but also to the rising incidence amongst women.

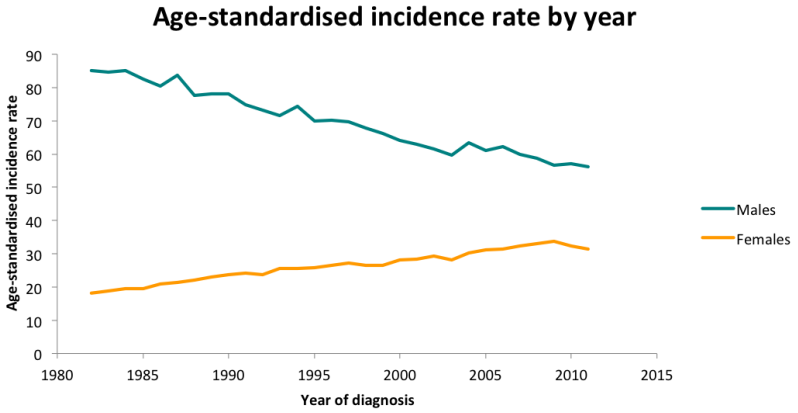

Figure 1.1: Lung Cancer Incidence in Australia, 1982 - 2011

1.3 Aetiology

In 1964, it was first recognised that cigarette smoke was casually related to lung cancer, with a report to the Surgeon General of America concluding "the magnitude of the effect of cigarette smoking [on lung cancer] far outweighs all other factors"[5]. The changing incidence in lung cancer reflects the current Australian societal trend in falling smoking prevalence, amongst both men and women. In 1980 41 % of men and 30 % of women were classified as regular smokers (smoking at least weekly), nearly converging at 22 % and 18 %, respectively, in 2010[6].

1.4 Histopathology

Previously lung cancer was simply divided in to non-small cell lung cancer (NSCLCa) and small cell lung cancer (SCLCa), but as the understanding of lung cancer has developed is now possible, and required, to further differentiate lung cancer in to the various distinct but related subtypes.

Approximately 85 % of lung cancers are NSCLCa[7] which can then be subsequently further divided in to the following three major distinct histological subtypes[8]; adenocarcinoma, squamous cell carcinoma (SqCC) and large cell carcinoma (LCC). From 1980 to 1997 a shift in NSCLCa histopathologies was identified with an increase in the incidence of adenocarcinomas and a fall in the incidence of squamous cell carcinoma[9].

1.5 Mutation

All malignancies are thought to arise from a single or series of genetic mutations which then confer an ability to replicate in an uncontrolled manner. In 2004 it was identified that 10 % of patients with NSCLCa will have a, potentially dramatic, response to tyrosine kinase inhibitors (TKI)[10]. Since then the Catalogue of Somatic Mutations in Cancer (COSMIC)[1] database[11] lists over 26000 different mutations, with 4600 having a frequency of greater than 1 %.

Since then 145 genes have been identified as potential lung cancer driver mutations[12], however only a few currently possess commercially available therapeutic drugs.

1.5.1 EGFR

The Epidermal Growth Factor Receptor (EGFR) is a 170 kdalton member of the ErbB family of cell surface tyrosine kinases[13], and is encoded on chromosome 7. The receptor belongs to the HER/erbB family of tyrosine kinases, which include

[1] http://cancer.sanger.ac.uk/cosmic

HER1 (EGFR/erbB1), HER2 (neu, erbB2), HER3 (erbB3) and HER4 (erbB4)[14].

The EGFR is made of up three portions; an extracellular ligand binding domain, a transmembrane domain and an intracellular tyrosine kinase domain[15,16]. Activation of the protein is achieved by binding of a ligand (such as epidermal growth factor, transforming growth factor-α and neureguelins[16]) to the extracellular domain. Once a ligand is bound to the extracellular domain, the receptor undergoes dimerisation or heterodimerisation with related receptors (especially HER2/neu[17]). Without the aforementioned ligand binding and subsequent dimerisation, there is no intrinsic activity of the tyrosine kinase portion of the receptor[16].

The tyrosine kinase portion of the receptor is normally in a state of autoinhibition, but on dimerisation there is rapid autoposphorylation of the intracellular tyrosine residues. The phosphorylated then functions to allow assembly and activation of intracellular messenger proteins[18,19], especially through the mammalian target of rapamycin (mTOR)[20].

In 1984 Gill *et al* demonstrated that EGFR blockade with a chimeric anti-EGFR antibody, in human epidermoid carcinoma cell lines expressing EGFR, resulted in a reduction in auto-posphorylation[21]. A similar study by Kawamoto *et al* revealed a biphasic cell proliferation response to the same cells exposed to Epidermal Growth Factor (EGF); with cellular proliferation at low levels of EGF and inhibition at higher levels. Taken together, this was felt to demonstrate that in human epidermoid malignancies EGFR expression and activation played a role in cancer proliferation.

Over expression of *EGFR* (?need to add gene here) has been identified in a variety of cancers including: head and neck, ovarian, bladder, oesophageal, gastric, brain, breast, endometrial, colonic and lung[22]. In NSCLCa, *EGFR* overexpression has been identified in 41 % of adenocarcinomas[10] and 89 % of squamous cell carcinomas (SqCCa)[23].

1.5.1.1 T790M

1.5.2 KRAS

1.5.3 ALK / ROS1 Rearrnagment

1.6 Prognosis

1.6.1 Early Stage

Surgery for early NSCLCa provides a potentially currative management strategy. However, even for those patients who receive currative intent surgical resection, followed by optimal adjuvant chemotherapy (when appropriate) will only receive an absolute overall survival (OS) advantage of 5.4 % at 5 years and an improvement in disease free survival of 5.8 %[24]. This equates to a 5 year survival rate for NSCLCa, depending pathological stage, from 25 % to 73 %[25].

1.6.2 Late Stage

However, over 75 % of patients with new NSCLCa diagnoses will present with an advanced stage[26], and will not be eligible for currative intent treatment. Those presenting thusly will have a median survival of only 119 days[27] without chemotherapy. Even those patients who are suitable to receive conventional chemotherapy, an overall survival of only about 8 months is achievable with a response rate of only 19 % achievable[28].

1.7 Diagnosis

Foobar[28].

1.7.1 Radiology

1.7.2 Tissue Obtaining

Difficultly obtaining tissue Earlier diagnosis == smaller nodules Smaller tissue == less to analyse == less DNA to use

1.8 Tissue analysis

1.8.1 current methods

1.8.2 next gen sequencing

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