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Research Article

Are New Zealand Maori More Susceptible to Smoking Related Lung Cancer? - A Comparative Case-Case Study

RJ Hopkins[1], C Kendall[1], GD Gamble[1] and Robert P Young[1,2]*

[1]*Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand*

[2]*School of Biological Sciences, University of Auckland, Auckland, New Zealand*

***Corresponding Author**: Robert P Young, Associate Professor and Director, Respiratory Genetics Group, Faculty of Medical and Health Sciences and School of Biological Sciences, University of Auckland, Auckland, New Zealand.

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Abstract

Rationale: Māori have one of the highest incidences of lung cancer in the world, even after adjustment for age and smoking prevalence. Why this indigenous Polynesian population of New Zealand (NZ) appears so susceptible to lung cancer remains unknown.

Objective: We compared demographic characteristics and risk factors between Māori and NZ Caucasians diagnosed with lung cancer.

Methods: Between Jan 2004-Nov 2014, we identified 472 lung cancer cases in Māori. Data was collected retrospectively and included demographic data, histological type, spirometry, clinical stage and survival. This was compared to 415 NZ Caucasian lung cancer patients recruited from the same referral centre.

Measurements and Main Results: Relative to Caucasians, despite comparable smoking exposure, we found Māori lung cancer patients were younger at the time of diagnosis (61 vs 67 years old) and had more aggressive histological subtypes, with fewer Adenocarcinomas ($P < 0.05$). More importantly at lower smoking exposure (< 20 pack years), the expected dose-response relationship observed between smoking dose and airflow limitation in Caucasians was absent in Māori where the prevalence of airflow limitation in the latter was two-fold higher ($P < 0.05$). In a Cox-Proportional analyses we found that ethnicity was independently associated with all-cause mortality (Māori HR = 1.4, P = 0.03), after allowing for advanced clinical stage (Staging HR = 2.6, $P<0.0001$) and histology (Histology HR = 1.4, P = 0.04).

Conclusion: We found that Māori have more aggressive forms of lung cancer and their greater susceptibility may be mediated in part through a greater susceptibility to COPD, specifically an increased prevalence of COPD, and a loss of the expected dose-response relationship, at lower smoking exposure. We propose that an ethnicity-by-smoking interaction exists, whereby Māori ancestry contributes directly to worse outcomes from smoking that require greater recognition in future NZ tobacco control policies.

Keywords: *Lung Cancer; Histology; Polynesian Ancestry; Maori; COPD*

Abbreviations

NZ: New Zealand; COPD: Chronic Obstructive Pulmonary Disease; SES: Socio-Economic Status; US: United States; ICD 10 C34: International Classification of Diseases Coding System; CT: Computed Tomography; GOLD: Global Obstructive Lung Disease; FEV_1/FVC: Forced Expiratory Volume in 1 Second/Forced Vital Capacity; FEV_1: Forced Expiratory Volume in 1 Second; Yrs: Years; Vs: Versus; CYP2A: Cytochrome P450 2A6; NNK: Nicotine-derived Nitrosamine Ketone

Introduction

Lung cancer is the leading cause of cancer deaths among men and women, attributed in the main, to smoking [1]. Epidemiological studies show that with increasing smoking exposure, the risk of lung cancer increases in a linear or curvilinear dose-response relationship [2,3]. Other factors known to contribute to an increased risk of lung cancer include; increasing age, the presence of chronic obstructive pulmonary disease (COPD), exposure to other aero-pollutants (asbestos, other occupational dusts, air pollution and radon), maternal smoking, lower socio-economic status (SES), poor diet and ethnicity [2-6]. In a large cases series, comparing five different ethnic groups in the United States (US), it was found that, relative to Caucasians, age adjusted lung cancer incidence in ever smokers was greatest for those of Polynesian (Native Hawaiian) or African American ancestry, while lowest in those of Hispanic (primarily Mexican) and Asian ancestry [5,6]. These findings could not be explained by differences in diet, smoking exposure and high school education, where educational level

provides a surrogate of SES [7]. A striking finding of the US study was that while the expected dose-response relationship between increasing cigarette exposure dose (up to 30 cigarettes/day) and lung cancer risk was shown for most ethnicities, it was absent in Hawaiians and African-Americans [8]. In a large prospective study of lung cancer, after adjustment for important risk variables, Hawaiian ancestry conferred the greatest risk of lung cancer relative to Caucasians [9]. This suggests that although smoking generates ethnicity-based differences in lung cancer incidence, these "disparities" appear to be due to factors other than cigarette exposure dose.

Māori are the indigenous Polynesian people of New Zealand (NZ) and have about 3 - 4 times higher age-adjusted lung cancer incidence compared to Caucasians [10-13]. Māori, like Hawaiians, originate from the Pacific Islands and share their genetic ancestry with Polynesians [14]. This Polynesian ancestry is genetically quite distinct from South-East Asians through admixture between Aboriginal Taiwanese and Micronesians [13]. Although smoking rates are two fold higher in Māori compared to NZ Caucasians, this does not explain the 3 - 4 fold greater lung cancer incidence [15]. In New Zealand large disparities for lung cancer mortality specifically [10,12,13] and smoking-related mortality overall [16,17], have been reported between Māori and NZ Caucasians. After a detailed examination of this disparity in smoking-related mortality, investigators concluded that only about 50% of the difference could be explained by the higher smoking rates and lower SES found in Māori [16]. This raises the possibility that like Hawaiians, ethnicity-specific factors among Māori confer greater susceptibility to lung cancer [11,18]. We have previously shown that airflow limitation (or COPD) is associated with an increased risk of lung cancer [19] and propose that this might be relevant for the development of lung cancer in Māori, where COPD rates are two-fold higher [10]. The current study compares the clinical characteristics of Māori and NZ Caucasian diagnosed with lung cancer. Preliminary results have been previously reported in abstract form [20].

Methods

This study involved a retrospective review of case records from the same geographical region of the greater Auckland metropolitan area which included a referral base that encompassed the upper half of the North Island of New Zealand (approximately 40% of the population, 1.5 million).

Lung cancer cases were identified using local district health board databases where lung cancer was reported as the 1st, 2nd or 3rd diagnosis according to the International Classification of Diseases coding system(ICD 10 C34). "Māori ancestry" was assigned according to self-reported ethnic identification in hospital records. Four hundred and seventy-two Māori patients diagnosed with lung cancer between January 1st, 2004 and December 31st 2014 were retrospectively identified. Four hundred and fifteen NZ Caucasian patients diagnosed with lung cancer were prospectively identified as part of a separate epidemiological study [19], between January 1st 2004 and December 31st 2008. Data collected on basic demographic characteristics included; age at diagnosis, gender, ethnicity, smoking history, histological subtype, stage at diagnosis, months of survival from diagnosis, spirometry and date of diagnostic computed tomography CT or diagnostic histology. Never smokers with lung cancer were included in this study.

Date of diagnosis of lung cancer was defined by date of the most definitive investigation, with a descending preference given for histology result or radiological imaging. Staging was defined according to lung cancer staging I-IV in accordance with current guidelines [21]. Histological subtype was identified from pathology reports and classified as small cell, adenocarcinoma, squamous cell, non-small cell (for cancers with no more precise classification), or other which encompassed the remainder of cancers but excluded carcinoid tumours, secondary tumours or benign tumours of the lung. The presence of chronic obstructive pulmonary disease (COPD) was defined according to sighted spirometry reports or lung function results, performed prior to or during the early work up of suspected lung cancer, using Global Obstructive Lung Disease (GOLD) criteria [19]. Smoking histories were exclusively based on recorded pack years of smoking exposure. If not otherwise specified, the average number of cigarettes smoked per day for Māori was calculated using the reported pack years smoked, age at diagnosis (current smokers) or age quit smoking (ex-smokers) and the previously published mean age of smoking uptake in Māori(16 years) [22].

In two sensitivity analyses, we conducted an age-gender matched comparison (N = 331 Māori cases) and we restricted Māori lung cancer cases to those with Māori surnames (N = 249 Māori cases), to potentially enrich them for Māori ancestry. The demographic characteristics were also compared after stratification according to gender, smoking status and presence of COPD, where the latter has been associated with more aggressive lung cancer histology [23]. A stratification approach was preferred over more complex multivariate analysis as most of the variables of interest were discrete and because linear relationships could not be assumed. However, for those diagnosed between 2004 - 2007, we compared survival and factors underlying survival in a Cox-proportional model to examine the relative importance of ethnicity and airflow limitation in the development of lung cancer.

Statistical Analysis

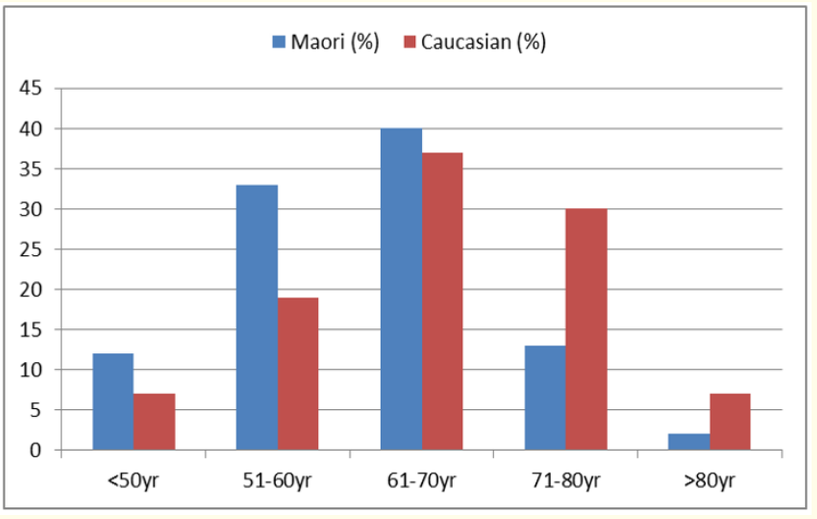
Demographic variables were compared by unpaired t-test for normally distributed continuous variables and chi-squared test for discrete variables with Mid-P Exact test on a two-tailed analysis (www.openepi.com access 18/12/2016). Survival was compared using Cox-

Proportional Hazards regression model, the assumption of proportionality was tested by including log time dependent variables in the model SAS statistical package (v 9.4, Cary, NC, USA was used. All tests were two tailed and $P < 0.05$ was considered significant.

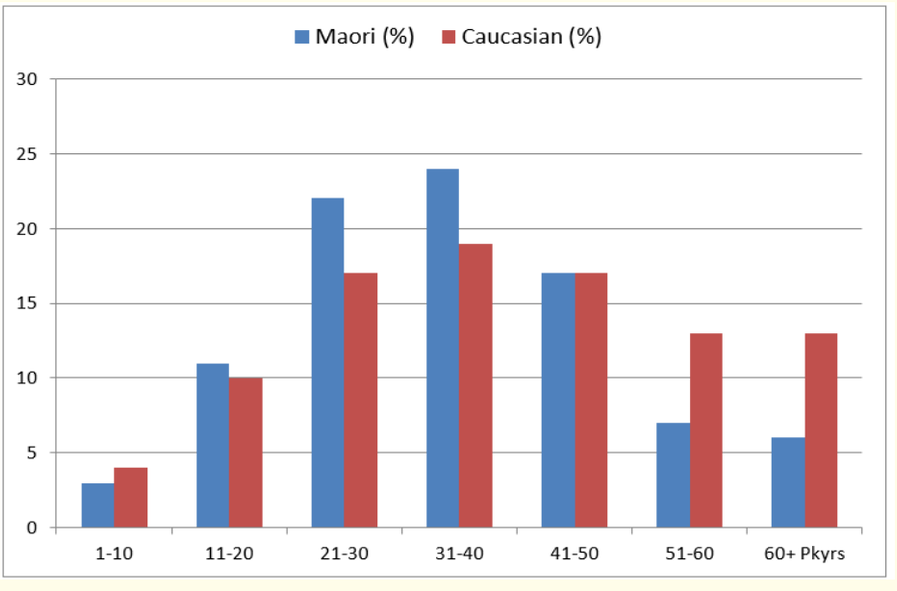
Result

Demographics

Demographic characteristics are presented in table 1. Māori lung cancer cases were younger with a mean age at diagnosis of 61 yrs old, compared to 67 yrs old in NZ Caucasians. In comparison with Caucasians, Māori lung cancer cases were ≈2 fold more likely to be current smokers (67% vs 36%, $P < 0.05$) and less likely to be a never smokers (2% vs 7% respectively, $P < 0.05$), although Māori and Caucasians had similar pack years of smoking (39 vs 41 pack years respectively), irrespective of gender. The estimated average number of cigarettes consumed per day for Māori (17/day) [22], was comparable to that recorded for Caucasian lung cancer cases (16/day). The distribution of age at lung cancer diagnosis for Māori and NZ Caucasian is presented in figure 1a and shows that nearly one half (45%) of cases in Māori were diagnosed at 60 years of age or less, compared to 25% in NZ Caucasian cases ($P < 0.05$). Distribution according to smoking exposure by pack years is shown in figure 1b and suggests Māori with lung cancer were generally lighter smokers than Caucasians.



(a) % according to age at diagnosis of lung cancer.



(b) % according to lifetime pack year smoking exposure.

Figure 1: *Distribution of age at diagnosis of lung cancer (a) and pack year smoking exposure (b), according to ethnicity among the lung cancer cases.*

Demographic Variable	Māori (N = 472)	Caucasian (N = 415)	P value
Mean age at diagnosis (SD) Range	61 yrs (9) 32 - 87 yrs	67 yrs (10) 40 - 92 yrs	< 0.001
Male (%)	205 (43%)	213 (51%)	0.019
Smoking History			
Smoking at diagnosis (%) Current Ex-smoker Never smoker Unknown	 316 (67%) 136 (29%) 8 (2%) 12 (3%)	 151 (36%) 236 (57%) 28 (7%) 0 (0%)	 < 0.001
Mean Pack years Men Women Total	 42 (10) 37 (17) 39 (18)	 45 (25) 36 (17) 41 (22)	 0.16 0.84 0.14
Estimated Cigs/day	17*	16	-
Lung function			
% available	325 (69%)	258 (62%)	0.043
Mean FEV1 (SD)	1.71 (0.63)	1.81 (0.71)	0.067
Mean FEV1% predicted#	64% (19)	71% (24)	< 0.0001
Mean FEV1/FVC	0.64 (0.12)	0.64 (0.14)	0.83
COPD status			
No COPD	118 (36%)	91 (36%)	-
GOLD 1 GOLD 2 GOLD 3 GOLD 4	27 (8%) 122 (38%) 51 (16%) 8 (2%)	32 (12%) 90 (35%) 32 (12%) 12 (5%)	 0.21
Total COPD	208 (64%)	166 (64%)	-
Histology			
Adenocarcinoma Squamous Cell Non-small Cell Small Cell	153 (32%) 124 (26%) 64 (14%) 102 (22%)	176 (42%) 100 (26%) 43 (10%) 73 (18%)	 0.02
Other/Unknown	29 (6%)	23 (6%)	-
Lung Cancer Stage			
NSCLC Stage 1 NSCLC Stage 2 NSCLC Stage 3 NSCLC Stage 4	86 (18%) 46 (10%) 92 (19%) 146 (31%)	93 (22%) 45 (11%) 96 (23%) 105 (25%)	 0.13
Small Cell - Limited Small cell - Extensive	41 (9%) 61 (13%)	23 (6%) 50 (12%)	 0.24
Unknown	-	3 (1%)	-

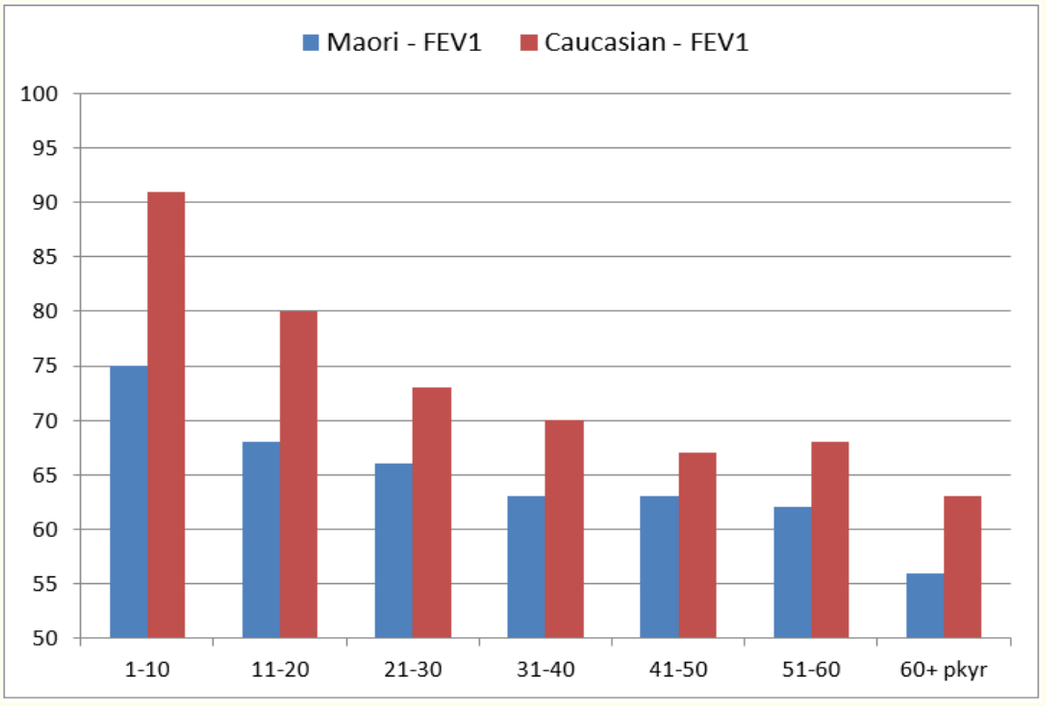
Table 1: *Demographic variables in the Māori and Caucasian lung cancer cases series (Unmatched comparison).*

*#: Predicted values for Caucasians were used for Māori(24). *Ref 22 - based on age of initiation of smoking.*

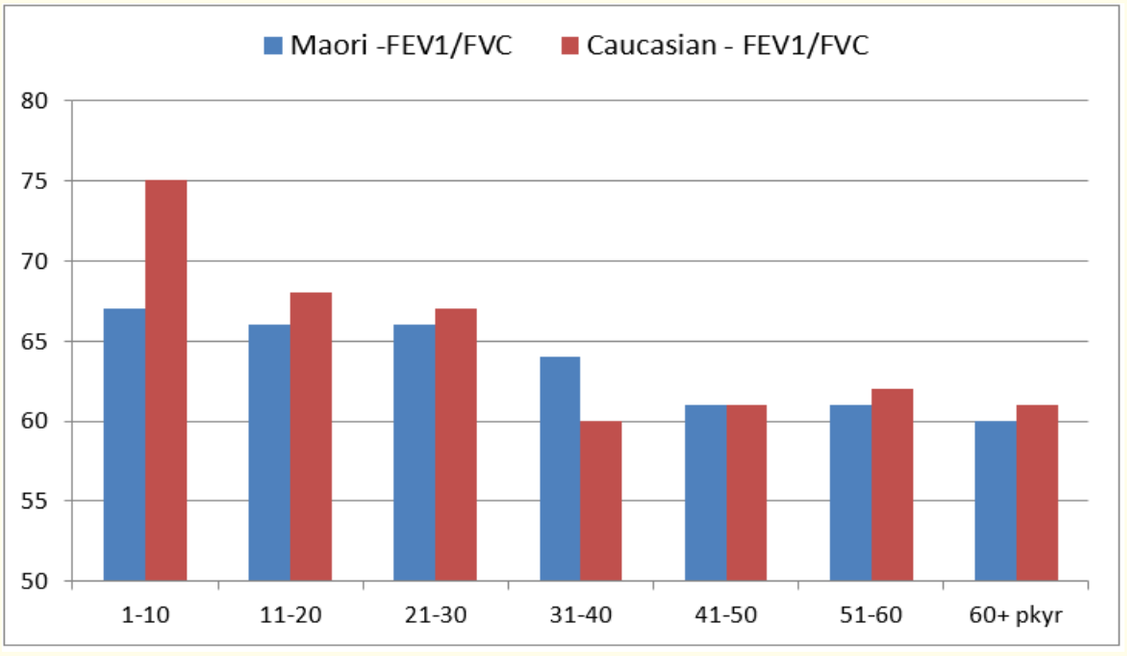
Lung function

Spirometry performed during usual clinical work-up were available for 69% of Māori lung cancer cases and 62% of Caucasian cases (Table 1), reflecting that spirometry is not routinely done during the work-up and management of all lung cancer cases. The mean ratio of forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) was identical at 0.64 but the mean percent predicted FEV_1 was significantly lower in Māori compared to Caucasian (64% vs 71% respectively, $P < 0.05$). Across increasing pack year exposures, the distribution of lung function test results, and COPD prevalence, showed several differences when comparing Caucasian results with Māori, where the same normal reference values were used as previously indicated [24]. For FEV_1% predicted, at every level of accumulated smoking exposure (pack years), we found the FEV_1% predicted was lower in Māori compared to Caucasian lung cancer cases (Figure 2a). This was

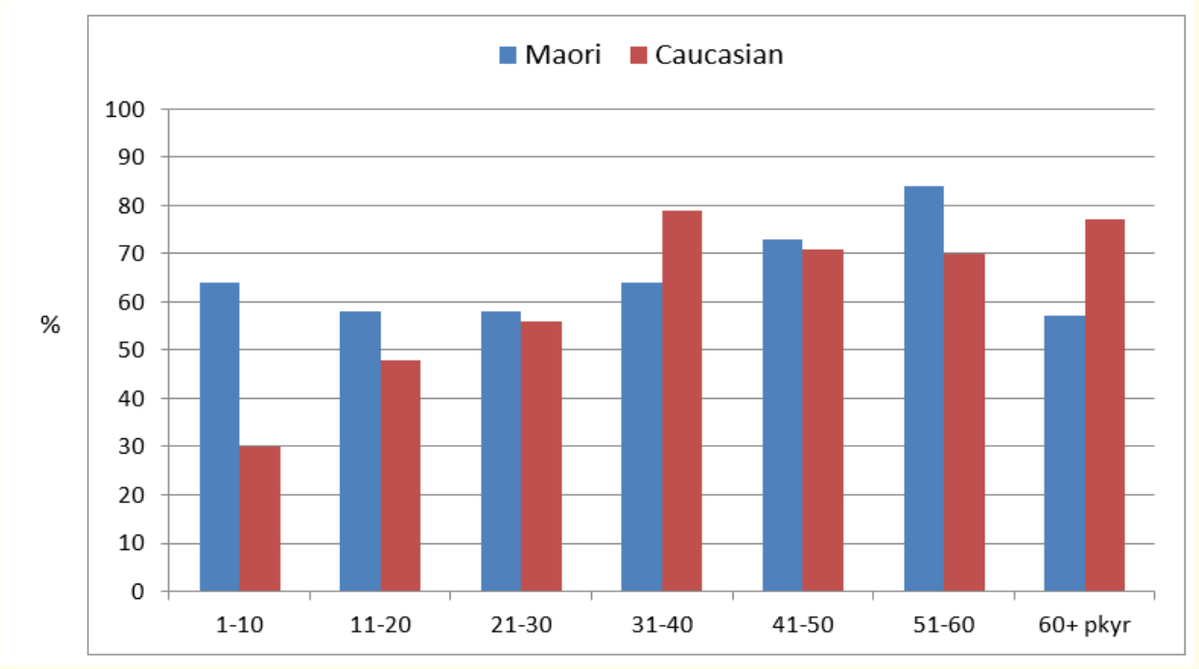
significant at low exposures (1 - 10 and 11 - 20 pack years). For the FEV_1/FVC ratio, Māori had a significantly lower ratio than Caucasians (67% vs 75%) for those who had smoked 1 - 10 pack years (Figure 2b). When COPD prevalence is compared, we note for smokers of 1 - 10 pack years, Māori have two fold greater COPD prevalence than Caucasians (64% vs 30%, $P < 0.05$) and the linear "dose-response" relationship observed in Caucasians is lost in Māori (Figure 2c).



(a) FEV_1%predicted and smoking exposure.



(b) FEV_1/FVC and smoking exposure.



(c) COPD Prevalence (%) and smoking exposure.

Figure 2: *Distribution of lung function (mean FEV_1%predicted and FEV_1/FVC ratio) and prevalence of COPD, according to smoking exposure (pack years) and ethnicity.*

Histology, staging and survival

When the prevalence of each histological group was compared, Māori were found to have less adenocarcinomas than found in Caucasian lung cancer cases (32% vs 42%) and marginally more of the other more aggressive histological subgroups (62% vs 52%, P = 0.02) (Tables 1 and 2, figure 3b and figure 4). This relative under-representation of adenocarcinoma histology in Māori compared to Caucasian was also found in the age-gender matched comparison (P = 0.07) (Table 2) and the Māori-enriched comparison where this under-representation was greatest (P = 0.002) (Table 3). This under-representation of adenocarcinoma in Māori persisted after stratification for gender (female > male, P = 0.00002), smoking status (ex-smoker > current, P = 0.01) and presence of COPD (absence > presence, P = 0.01) (Figure 4 and tables 4-6). When the distribution of lung cancer stages were compared, we found only a marginally lower proportion of early stage (1 - 2) disease in Māori compared to Caucasian (28% vs 33% respectively, P > 0.05, table 1). This difference was significant in those with COPD (37% vs 51% respectively, P < 0.05, table 6). Using Cox-proportional survival curves, when the 1 year, 2 year, 5 year and 10 year survivals were compared, we found that Māori (N = 81) had 1.4 fold lower survival than Caucasians (N = 312) and that stage, age, gender and histology were relevant to mortality but not COPD or smoking status (See discussion and figure 7).

Discussion

In this comparative study, where the demographic characteristics of 472 Māori lung cancer patients were compared with 415 Caucasian lung cancer cases, we found a number of significant differences. Compared to Caucasians, Māori had a younger mean age at diagnosis (61 yrs old vs 67 yrs old), fewer never smokers (2% vs 7%), more aggressive histological subtypes and more advanced airflow limitation. These findings could not be explained by differences in mean pack years of smoking or cigarettes per day and in a sensitivity analysis persisted despite close matching for age, gender and smoking exposure (pack years and cigarettes/day). The differences in COPD prevalence and airflow limitation (FEV1% predicted and FEV1/FVC) were most apparent at lower smoking levels of exposure (< 20 pack years) and attenuated at higher exposure (Figure 2). The differences we report in mean age at diagnosis, smoking status and smoking exposure replicate those of a smaller previously published study which showed that despite comparable smoking exposure, Māori were younger at diagnosis (63 yrs old vs 71 yrs old) and less likely to be never smokers (1% vs 8% in Caucasians) [18]. However in our current study, Māori

Demographic Variable	Māori (N = 331)	Caucasian (N = 330)	P value
Mean age (yo) at diagnosis (SD)	64 yrs (9)	64 yrs (10)	
Range	40 - 87 yrs	40 - 88 yrs	0.99
Gender - Male (%)	149 (45%)	167 (51%)	
Smoking History			
Smoking at diagnosis (%)			
• Current	214 (65%)	130 (39%)	
• Ex-smoker	102 (31%)	179 (54%)	
• Never smoker	6 (2%)	21 (6%)	
• Unknown	9 (3%)	0 (0%)	P < 0.001
Mean pack years			
• Men	42 (20)	44 (23)	0.45
• Women	38 (17)	36 (17)	0.39
• Total	40 (18)	38 (20)	0.76
Lung Function			
% available	238 (72%)	202 (61%)	0.005
Mean FEV_1 (absolute)	1.68 (0.59)	1.86 (0.72)	0.004
Mean FEV_1 % predicted	65% (19)	70% (23)	0.008
Mean FEV_1/FVC	0.64 (0.12)	0.61 (0.14)	0.95
COPD status			
No COPD	83 (25%)	75 (22%)	0.005
• GOLD 1	18 (7.5%)	21 (13%)	
• GOLD 2	94 (28%)	73 (38%)	
• GOLD 3	37 (15.5%)	20 (15%)	
• GOLD 4	5 (2.1%)	12 (5%)	0.08
COPD Total	154 (46%)	126 (38%)	0.036
Histology			
Adenocarcinoma	106 (32%)	142 (43%)	
Squamous Cell	91 (28%)	82 (25%)	
Non-Small Cell	44 (13%)	33 (10%)	
Small Cell	65 (20%)	60 (18%)	0.06
Other/Unknown	25 (8%)	12 (4%)	
Lung Cancer Stage			
NSCLC Stage 1	65 (20%)	61 (18%)	
NSCLC Stage 2	33 (10%)	38 (12)	
NSCLC Stage 3	64 (19%)	81 (25%)	
NSCLC Stage 4	104 (31%)	87 (26%)	0.40
Small Cell Extensive	39 (12%)	42 (13%)	
Small Cell Limited	26 (8%)	18 (5%)	0.24

Table 2: *Demographic variables in the Māori and Caucasian lung cancer cases series (Matched comparison).*

Demographic Variable	Māori (N = 249)	Caucasian (N = 415)	P value
Mean age at diagnosis (SD) Range	61 yrs (9) 32 - 87 yrs	67 yrs (10) 40 - 92 yrs	< 0.001
Male (%)	130 (52%)	213 (51%)	0.019
Smoking History			
Smoking at diagnosis (%) Current Ex-smoker Never smoker Unknown	 171 (69%) 70 (28%) 2 (1%) 6 (2%)	 151 (36%) 236 (57%) 28 (7%) 0 (0%)	< 0.001
Mean Pack years Men Women Total	 43 37 40 (19)	 45 36 41	 0.14
Lung function			
% available	178 (71%)	258 (62%)	-
Mean FEV_1 (SD)	1.79 (0.64)	1.81 (0.71)	0.054
Mean FEV_1% predicted	65%	71%	< 0.001
Mean FEV_1/FVC	0.69 (0.12)	0.64	0.08
COPD status			
No COPD	66 (37%)	92 (36%)	
GOLD 1 GOLD 2 GOLD 3 GOLD 4	14 (12%) 72 (64%) 22 (20%) 4 (4%)	32 (19%) 90 (54%) 32 (19%) 12 (7%)	 0.21
COPD Total	112 (63%)	166 (64%)	
Histology			
Adenocarcinoma Squamous Cell Non-small Cell Small Cell	68 (27%) 70 (28%) 35 (14%) 58 (23%)	176 (42%) 101 (24%) 43 (10%) 73 (18%)	 0.0020
Other/Unknown	18 (7%)	23 (6%)	
Lung Cancer Stage			
NSCLC Stage 1 NSCLC Stage 2 NSCLC Stage 3 NSCLC Stage 4	44 (18%) 24 (10%) 49 (20%) 77 (31%)	93 (22%) 45 (11%) 96 (23%) 105 (25%)	 0.23
Small Cell - Limited Small Cell - Extensive	22 (9%) 33 (13%)	23 (6%) 50 (12%)	 0.32

Table 3: *Demographic variables in the Māori and Caucasian lung cancer cases - Māori-Enriched.*

#: Predicted values for Caucasians were used for Māori [24,25].

Demographic Variable	Māori Men N = 205	Caucasian Men N = 213	Maori Women N = 267	Caucasian Women N = 202
Mean age at diagnosis (SD) Range	61 yrs 40 - 81yrs	68 yrs 41 - 89 yrs	61 yrs 32 - 87 yrs	66 yrs 40 - 92 yrs
Male (%)	100%	100%	0%	0%
Smoking History				
Smoking at diagnosis (%) Current Ex-smoker Never smoker Unknown	 133 (65%) 61 (30%) 2 (1%) 9 (4%)	 77 (36%) 129 (61%) 7 (3%) -	 183 (69%) 75 (28%) 6 (2%) 3 (1%)	 74 (37%) 108 (53%) 20 (10%) -
Mean Pack years Range	41.5 (4 - 100)	44.7 (2 - 191)	36.6 (8 - 120)	36.3 (4 - 88)
Lung function				
% available	138 (67%)	129 (61%)	188 (70%)	128 (63%)
Mean FEV_1 (SD)	2.09 (0.65)	2.03 (0.42)	1.49 (0.38)	1.58 (0.44)
Mean FEV_1% predicted	63%	69%	66%	74%
Mean FEV_1/FVC	0.62	0.63	0.65	0.64
COPD status				
No COPD	43 (31%)	44 (34%)	75 (40%)	47 (37%)
GOLD 1 GOLD 2 GOLD 3 GOLD 4	15 (11%) 52 (38%) 24 (17%) 4 (3%)	15 (12%) 45 (35%) 18 (14%) 7 (5%)	12 (6%) 70 (37%) 27 (14%) 4 (2%)	17 (13%) 45 (35%) 14 (11%) 5 (4%)
Total COPD	95 (69%)	85 (66%)	113 (60%)	81 (63%)
Histology				
Adenocarcinoma# Squamous Cell Non-small Cell Small Cell	55 (27%) 67 (33%) 27 (13%) 46(22%)	75 (35%) 69 (32%) 20 (9%) 38 (18%)	98 (37%) 57 (21%) 37 (14%) 56 (21%)	101 (50%) 31 (15%) 23 (11%) 35 (17%)
Other/Unknown	10 (5%)	11 (5%)	19 (7%)	12 (6%)
Lung Cancer Stage				
NSCLC Stage 1 NSCLC Stage 2 NSCLC Stage 3 NSCLC Stage 4	33 (16%) 15 (7%) 44 (21%) 67 (33%)	44 (21%) 24 (11%) 49 (23%) 56 (26%)	53 (20%) 31 (12%) 48 (18%) 79 (30%)	49 (24%) 21 (10%) 47 (23%) 49 (24%)
Small Cell - Limited* Small Cell - Extensive	14 (7%) 32 (16%)	8 (4%) 30 (14%)	27 (10%) 29 (11%)	15 (7%) 20 (10%)

Table 4: *Demographic variables in the Māori and Caucasian lung cancer cases - stratified by gender.*

*#P = 0.00002, *P = 0.04.*

Demographic Variable	Māori Current N = 316	Caucasian Current N = 151	Maori Ex-smoker N = 136	Caucasian Ex-smoker N = 237
Mean age at diagnosis (SD) Range	60 yrs (8.8) 32 - 87 yrs	64 yrs (9.5) 40 - 84 yrs	64 yrs (8.0) 44 - 83 yrs	69 yrs (9.6) 41 - 92 yrs
Male (%)	133 (42%)	77 (51%)	61 (45%)	129 (54%)
Smoking History				
Smoking at diagnosis (%) Current Ex-smoker	 100% 0%	 100% 0%	 0% 100%	 0% 100%
Mean Pack years Men Women Total	 44.0 37.8 40.4	 52.7 39.2 46.1	 37.7 36.5 37.1	 40.0 34.3 37.4
Lung function				
% available	219 (69%)	78 (52%)	102 (75%)	163 (69%)
Mean FEV_1 (SD)	1.74 (0.63)	1.76 (0.58)	1.62 (0.48)	1.81 (0.69)
Mean FEV_1% predicted	65%	66%	63%	73%
Mean FEV_1/FVC	0.64	0.61	0.64	0.64
COPD status				
No COPD	84	20	33	59
GOLD 1 GOLD 2 GOLD 3 GOLD 4	18(13%) 79 (58%) 32 (24%) 6 (4%)	4 (7%) 38 (66%) 12 (21%) 4 (7%)	8 (12%) 41 (59%) 18 (26%) 2 (3%)	26 (25%) 51 (49%) 19 (18%) 8 (8%)
Total COPD	135	58	69	104
Histology				
Adenocarcinoma* Squamous Cell Non-small Cell Small Cell	101 (32%) 85 (27%) 39 (12%) 75 (24%)	61 (40%) 28 (19%) 17 (11%) 38 (25%)	38 (28%) 37 (27%) 24 (18%) 25 (18%)	94 (40%) 70 (30%) 23 (10%) 35 (15%)
Other/Unknown	16 (5%)	7 (5%)	12 (9%)	15 (6%)
Lung Cancer Stage				
NSCLC Stage 1 NSCLC Stage 2 NSCLC Stage 3 NSCLC Stage 4	53 (17%) 29 (9%) 65 (21%) 94 (30%)	27 (18%) 12 (8%) 33 (22%) 41 (27%)	29 (21%) 13 (10%) 24 (18%) 45 (33%)	58 (25%) 33 (14%) 55 (24%) 54 (23%)
Small Cell - Limited Small Cell - Extensive	30 (9%) 45 (14%)	12 (8%) 26 (17%)	9 (7%) 16 (12%)	11 (5%) 24 (10%)

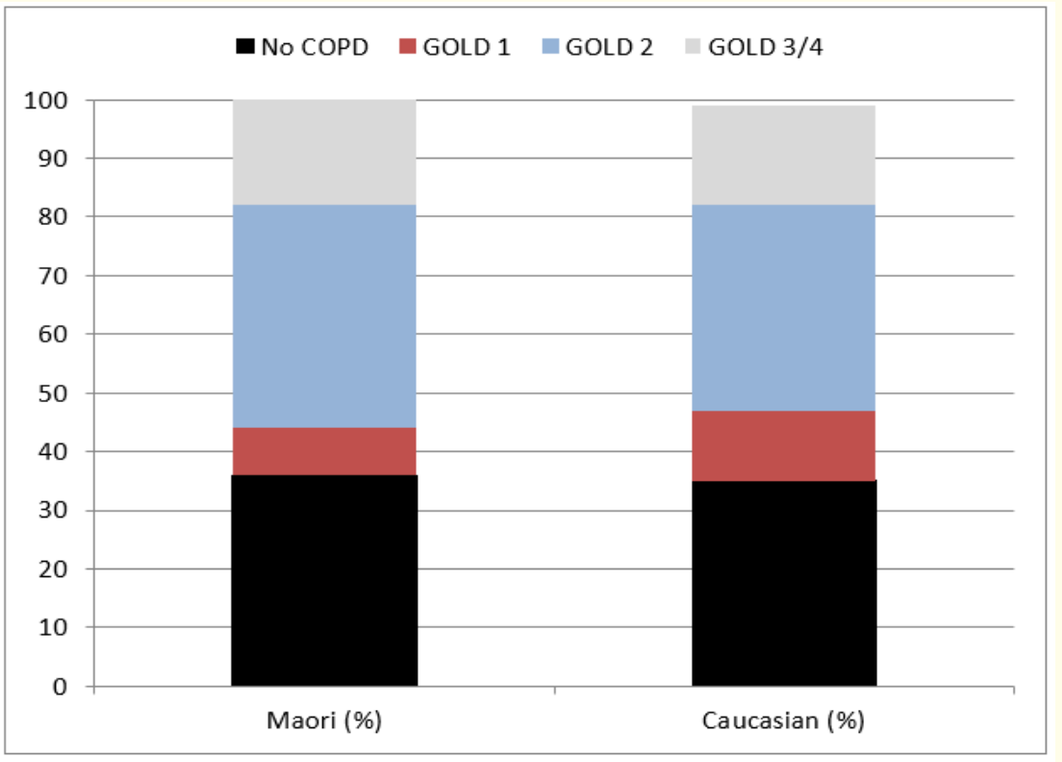
Table 5: *Demographic variables in the Māori and Caucasian lung cancer cases - stratified by smoking status.*

**P = 0.01.*

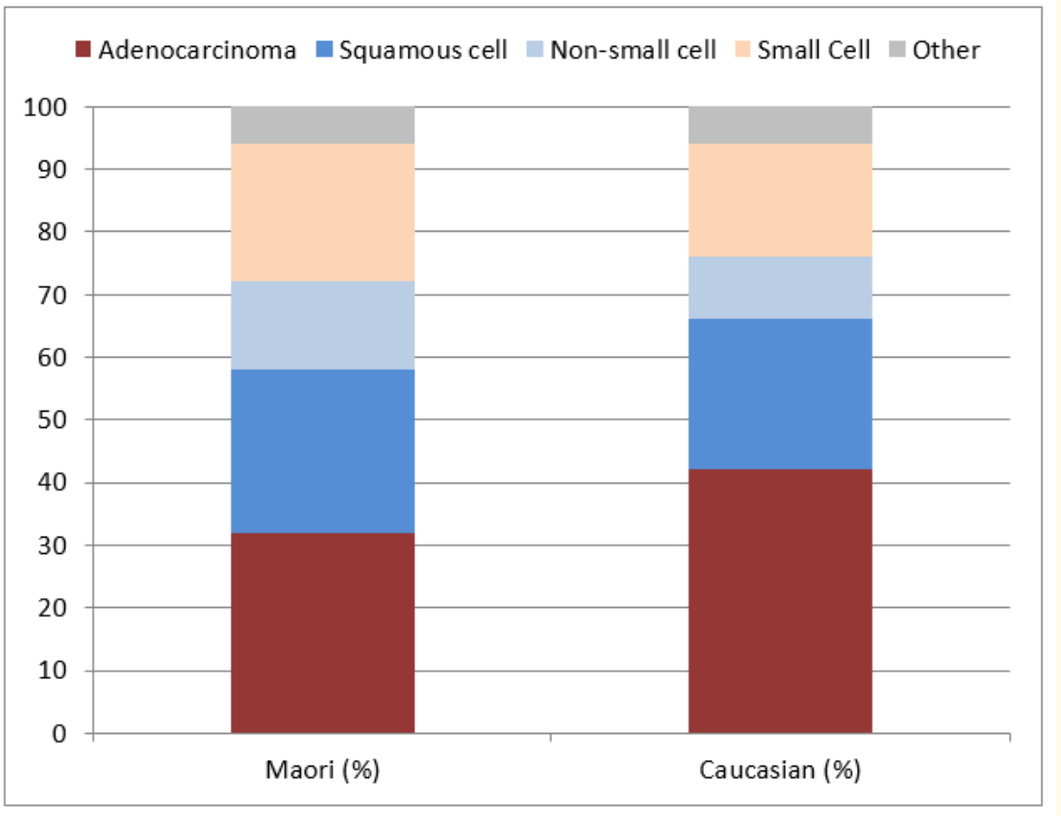
Demographic Variable	Māori COPD N = 208	Caucasian COPD N = 166	Maori No COPD N = 118	Caucasian No COPD N = 91
Mean age at diagnosis (SD) Range	64 yrs 42 - 83 yrs	69y rs 40 - 92 yrs	59 yrs 32 - 87 yrs	65 yrs 43 - 89 yrs
Male (%)	96 (46%)	85 (51%)	42 (36%)	44 (48%)
Smoking History				
Smoking at diagnosis (%) Current Ex-smoker Never smoker Unknown	 135 (65%) 69 (33%) 1 (0.5%) 3 (1%)	 58 (35%) 104 (63%) 4 (2%) -	 81 (69%) 33 (28%) 2 (1%) 2 (1%)	 20 (22%) 59 (65%) 12 (13%) -
Mean Pack years Men Women Total	 41 38 40	 46 41 44	 44 34 37	 39 34 37
Lung function				
% available	100%	100%	100%	100%
Mean FEV_1 (SD)	1.56 (0.48)	1.59 (0.50)	1.99 (0.85)	2.22 (0.87)
Mean FEV_1% predicted	59%	63%	74%	86.5%
Mean FEV_1/FVC	0.57	0.56	0.76	0.78
COPD status				
No COPD	0	0	118	91
GOLD 1 GOLD 2 GOLD 3 GOLD 4	27 (13%) 122 (59%) 51 (24%) 8 (4%)	32 (19%) 90 (54%) 32 (19%) 12 (7%)	- - - -	- - - -
Total COPD	208	166	0	0
Histology				
Adenocarcinoma* Squamous Cell Non-small Cell Small Cell	68 (33%) 71 (34%) 22 (11%) 34 (16%)	69 (42%) 53 (32%) 17 (10%) 12 (7%)	39 (33%) 37 (31%) 16 (14%) 14 (12%)	50 (55%) 26 (29%) 6 (7%) 5 (5%)
Other/Unknown	13 (6%)	15 (9%)	12 (10%)	4 (4%)
Lung Cancer Stage				
NSCLC Stage 1# NSCLC Stage 2 NSCLC Stage 3 NSCLC Stage 4	49 (24%) 28 (13%) 48 (23%) 49 (24%)	58 (35%) 26 (16%) 41 (25%) 28 (17%)	32 (27%) 12 (10%) 30 (25%) 30 (25%)	28 (31%) 15 (16%) 23 (25%) 19 (21%)
Small Cell - Limited Small Cell - Extensive	13 (6%) 21 (10%)	4 (2%) 8 (5%)	9 (8%) 5 (4%)	3 (3%) 2 (2%)

Table 6: *Demographic variables in the Māori and Caucasian lung cancer cases - stratified by COPD status.*

**P = 0.01, # P < 0.00001.*



(a) GOLD Severity



(b) Histology

Figure 3: *Distribution of lung function (mean FEV_1%predicted and FEV_1/FVC ratio) and prevalence of COPD, according to smoking exposure (pack years) and ethnicity.*

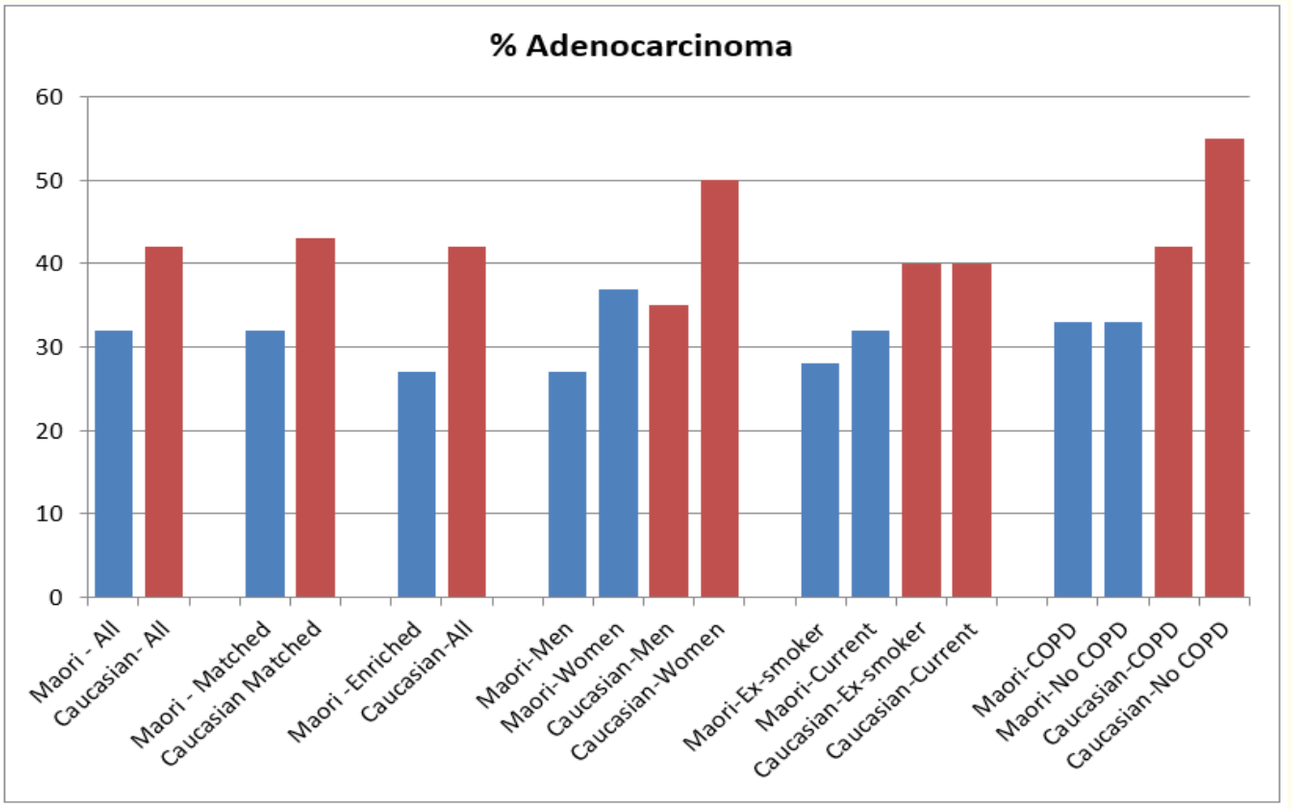


Figure 4: *Proportion of lung cancer cases having Adenocarcinoma histology subtype according to ethnicity, before and after stratification by gender, smoking status and presence of COPD.*

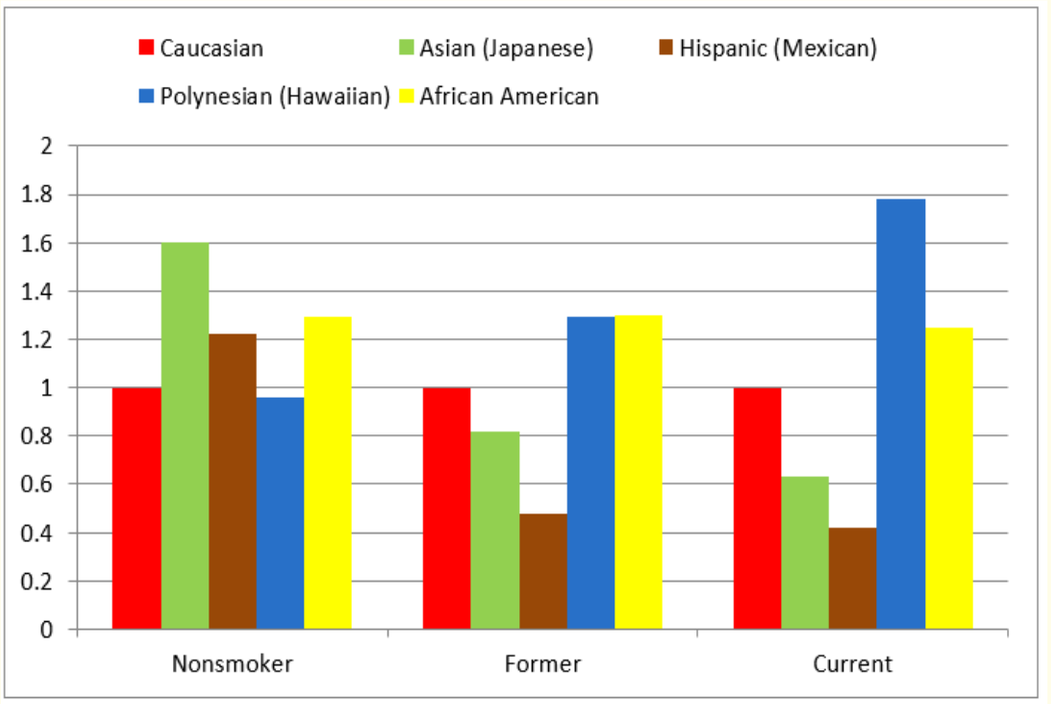


Figure 5: *Risk of lung cancer according to smoking status and ethnicity in the US (Caucasian referent) (data taken from reference [6,8].*

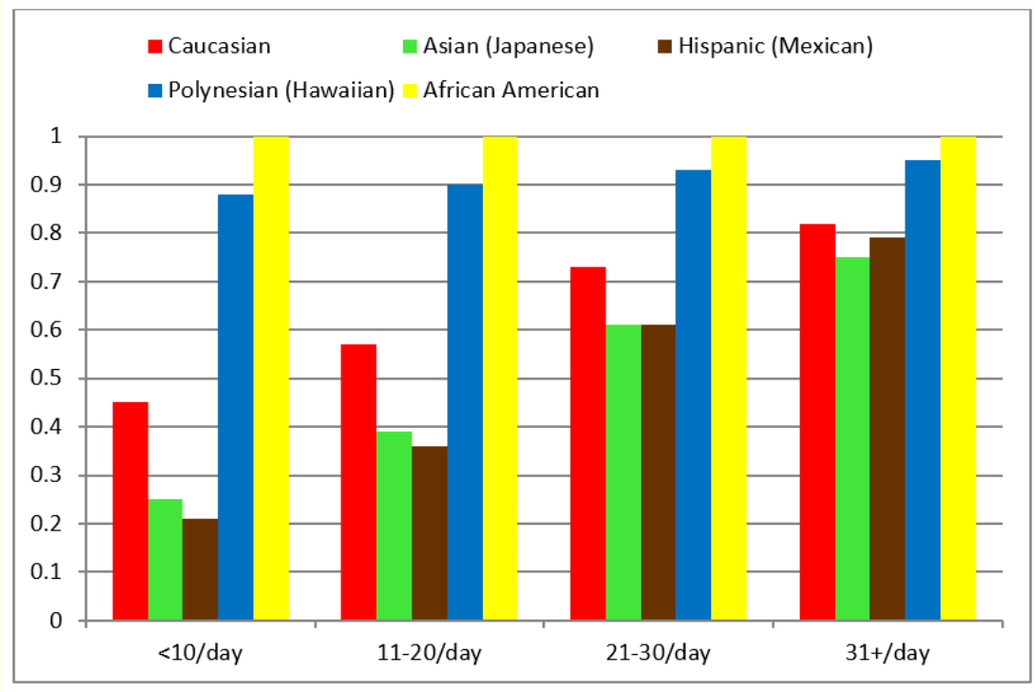


Figure 6: *Risk of lung cancer according to smoking intensity (cigarettes/day) and ethnicity in the US (African-American referent) (data taken from reference [5]).*

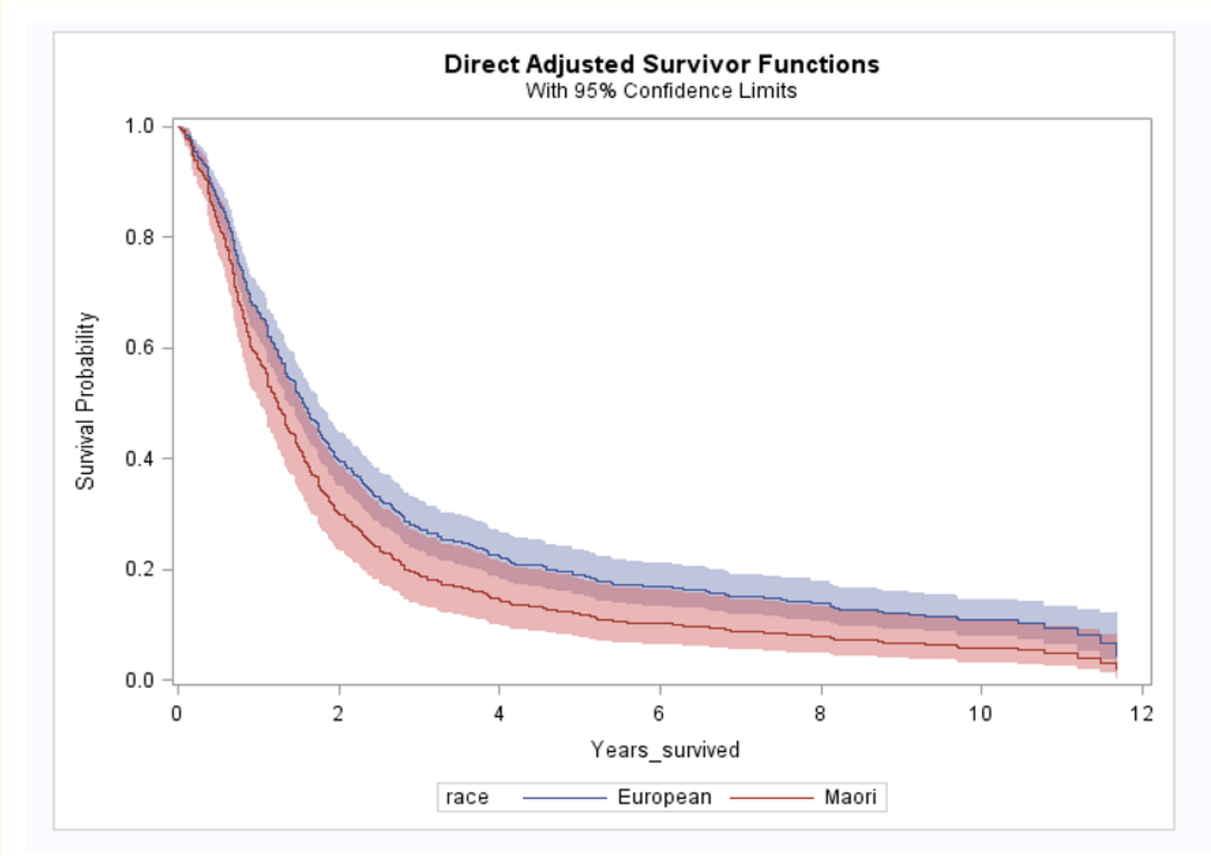


Figure 7: *Cox-proportional hazard ratio analyses for lung cancer mortality in Māori and Caucasian lung cancer cases series diagnosed between 2004 - 2007.*

were more likely to have squamous cell, small cell and non-small cell histology and less likely to have adenocarcinoma histology, relative to Caucasians (Figure 3). These inter-ethnic differences in histology were most apparent according to gender and COPD status (Figure 4 and tables 3-6), where more aggressive histological subtypes have been reported in the latter [23]. Collectively these findings suggest that not only do Māori appear more susceptible to getting lung cancer, they have worse airflow limitation and more aggressive subtypes of lung cancer. The results of these two studies suggest lung cancer in Māori manifests differently to that in Caucasians and raises the questions, "Could this greater susceptibility to lung cancer in Māori be mediated through a greater susceptibility to COPD?" and "Could the greater incidence of lung cancer in Māori stem in part from a greater overall susceptibility to smoking?".

The first novel finding of our study is that at all levels of smoking exposure, Māori with lung cancer have greater airflow limitation (lower FEV1/FVC and FEV1% predicted) compared to Caucasian lung cancer cases (Figure 2a and 2b). More importantly, at low levels of smoking exposure, Māori had a two-fold greater COPD prevalence (Figure 2c). Indeed when smoking dose and prevalence of COPD was compared between Māori and Caucasian lung cancer cases, the expected dose-response relationship evident for Caucasians at lower smoking exposure (< 30 pack years) is lost in Māori (Figure 2c). This finding bares similarities with that found in Hawaiian suggesting an important ethnicity-smoking interaction which is most evident at lower smoking exposure levels (Figures 5 and 6) [8]. We propose that at these low exposure levels, Polynesians (and possibly African-Americans) have a heightened responsiveness to smoking not seen to the same degree in Caucasians [5,6,8]. In another US-based study, it was found that compared to Caucasians with the same severity of COPD, African-Americans were younger, smoked less and had greater lung function decline [25]. In Caucasians and other ethnic groups, where the dose-response relationship is evident [5,6,8], high smoking exposures (> 30 pack years or > 30 cigarettes/day, figure 2c, 5 and 6) presumably overwhelm the innate capacity of smokers to tolerate smoke exposure at these higher exposures [2,3]. In the introduction to this paper we outline the results of the study by Haiman., *et al.* showing that in contrast to never smokers, where the risk of lung cancer in Polynesians (Hawaiians) and Caucasians is comparable (Figure 5), Polynesian current and former smokers had approximately 1.2 and 1.8 fold greater risk of lung cancer respectively than Caucasians [5]. After consideration of other demographic data, Haiman., *et al.* suggest that an important smoking-by-ethnicity effect exists independent of smoking exposure, education and diet. On re-analysis of their data [8], it has been shown that the expected dose-response effect of increasing lung cancer risk with increased smoking exposure dose seen for Caucasians (and Asians and Hispanics) was lost for Polynesians (Figure 6). This suggests a greater propensity to lung cancer in Hawaiians relative to Caucasians, especially at lower smoking exposure. When lung cancer rates were calculated according to histology and gender, in heavy smokers Polynesian (regardless of gender) had greater squamous cell cancers and small cell cancers than corresponding Caucasians [5]. On this basis we decided to examine the difference in histology according to gender, smoking status and the presence of COPD using a stratified approach (Tables 4-6). Such an analysis underpins our view that important differences underlying lung cancer susceptibility may be missed if stratification for important contributing variables is not examined [26].

The second novel finding of this study is the relative decrease in the proportion of lung cancer cases in Māori that were adenocarcinomas (generally less aggressive biology) (Figure 4), especially in those with no COPD (Table 6) and of female gender (Table 4). Compensatory increases were seen in Māori for squamous cell, non-small cell and small cell lung cancer, where the latter two histological subgroups contributed independently to greater all-cause mortality along with Māori ethnicity, age, male gender and stage (Figure 7). This is in contrast to our finding no differences according to severity of COPD (GOLD grade) and clinical stage at diagnosis (Tables 3-6). We found that the proportion of adenocarcinomas in Māori was less than for Caucasians, and that the proportion of other lung cancers such as squamous cell, non-small cell and small cell were correspondingly greater. This was the case despite comparable smoking exposure history (Tables 1-6), matching age (Table 2) and stratifying by gender (Table 4), smoking status (Table 5) and the presence of COPD (Table 6). In contrast, we found no difference in the severity of COPD (GOLD grade) or the clinical stage, either before or after stratifying for the effects of gender, smoking status and COPD, or matching for age. This suggests that these differences in histology, where the prevalence of adenocarcinoma is reduced in Māori while other lung cancer histological subgroups are greater (Figure 4), is not the result of differences in age, gender, smoking status (current vs ex-smokers), smoking exposure or lung function. Differences in histology extended to small cell cancer where the prevalence was 2-fold greater in Māori relative to Caucasians stratified by the presence of COPD suggesting an ethnicity-by-COPD interaction (Table 6). We suggest that these differences in the lung cancer histology, reflects differences in the pathobiology of lung cancer in Māori. Our finding that Māori with lung cancer have worse lung function than Caucasians, at low smoking exposure, suggests Māori may be more "susceptible" to the adverse effects of smoking. Indeed, Māori have roughly 2-fold greater rates of COPD than Caucasians [10]. We and others have shown that in Caucasians with lung cancer, the presence of COPD is associated with more aggressive lung cancer such squamous cell, non-small cell and small cell cancers [23]. Interestingly in the US study [5], inter-ethnic differences between Polynesians

and Caucasians were greatest for adenocarcinomas and small cell cancers. Interestingly, in our study Small cell cancer prevalence was 1.5 fold greater in current smokers compared to ex-smokers (Table 5), suggesting an interaction between histology and smoking status as previously described [27]. Based on our current study, we believe that the higher prevalence of more aggressive lung cancer histological subtypes in Māori may also be related to overlapping pathogenic pathways underlying airway remodelling (or COPD) [19]. Although the current study cannot prove this relationship, our robust finding that differences in lung cancer histology exists between Māori and Caucasians requires further analyses. These apparent differences in the biology of lung cancer in Māori compared to Caucasian have important implications. Below we outline the results of an analysis on all-cause mortality in lung cancers diagnosed during this study.

The significantly younger age at diagnosis in Māori might also indicate a greater susceptibility although ethnic differences in aging, age structure and age-specific mortality may be relevant here [personal communication with Dr T Blakely, NZ Epidemiologist [15,16]]. In the US-based lung cancer study [5], Hawaiian were noted to have the youngest mean age at diagnosis consistent with our finding in Māori, although this was only a small difference compared with other US-based ethnicities. Assuming that age of initiation of daily smoking is similar between Māori and Caucasian in New Zealand (16 yrs old) [22] and the pack year exposure history is comparable in our lung cancer case series (Table 1), it appears unlikely that differences in smoking exposure per se (i.e. cigarette consumption) account for the differences we observed. Further support for our hypothesis comes from New Zealand data showing after adjustment for age and smoking, Māori are two-fold more likely to get COPD than Caucasians [10]. Indeed, two studies reported several decades ago showed that Māori men who smoked had worse lung function than their Caucasian counterparts suggesting greater susceptibility in Māori [28,29]. Collectively, these findings demonstrate that the greater propensity to lung cancer in Polynesians relative to other ethnic groups is unrelated to lifetime differences in smoking exposure. Instead these differences result from a greater inherent susceptibility to the adverse effects of smoking on the lungs generally [5,6,8]. The basis of this hypothesis is discussed below.

As the increased incidence of lung cancer in Māori appears to be associated with earlier onset of disease, greater airflow limitation and a greater propensity to COPD at lower smoking exposure, we are of the view that Māori may be inherently at greater risk of lung cancer through as yet unknown pathogenic or sociocultural mechanisms. Differences in the metabolism of nicotine has been proposed to explain inter-ethnic differences, but the data are inconclusive [30]. In studies including Native Hawaiians, no significant difference in CYP2A enzyme activity was found compared to Caucasians [31]. Hawaiians have shared genetic ancestry with Māori and have the highest incidence of lung cancer in the United States [3,5,9] suggesting shared genetic factors may in part underlie this increased susceptibility [5,6]. Further studies will be needed to test this hypothesis. Another possibility is the effect of high rates of maternal smoking among Māori women of reproductive age compared to Caucasian women [32]. Maternal smoking rates in Māori have been historically high for several decades relative to Caucasians, a feature of smoking prevalence shared with Hawaiian women. The contribution of marijuana smoking to lung cancer in Māori is also a possibility although this has been shown to be relevant in only a small proportion of lung cancer cases (primarily those < 50 yr old, ≈10%) so unlikely to explain our observations (Figure 1) [33]. Differences in the innate immune response to smoking and downstream exaggerated inflammation has been suggested as another possible mechanism underlying inter-ethnic differences in susceptibility to lung cancer [5,8,34]. We propose that the most likely factor underlying our observed differences are secondary to the biological difference in susceptibility of Māori to cigarette smoke, where Māori are more sensitive to one or combination of the addictive, carcinogenic or pro-inflammatory substances in smoke, compared to NZ Caucasians. Collectively, poorer lung function, higher COPD prevalence at low pack years, more aggressive subtypes of lung cancer and earlier age at lung cancer diagnosis [35-38], suggest that Māori have a different biological susceptibility to lung cancer than NZ Caucasians.

We found that mean age at diagnosis was significantly lower in Māori compared to Caucasians (61 vs 67 yrs old, table 1) comparable to the study by Stevens., *et al* [18]. This difference persisted in our stratified comparisons, first using Māori enriched for Māori ancestry (Māori surname, table 3), and second after stratification for gender and the presence of COPD (Tables 4 and 6). Interestingly, after stratification by smoking status (Table 5), we found age at diagnosis was lower in Māori by 4 years in current smokers (60 vs 64 yrs old) and 5 years in ex-smokers (64 vs 69 yrs old). It is notable that the mean age at diagnosis is younger in current smokers, consistent with the literature [39], with Māori current smokers being on average 9 years younger than Caucasian ex-smokers (60 vs 69 yrs old). However after stratification by smoking status, we found the difference in age at diagnosis was reduced. Studies comparing Native Hawaiian with "non-Native Hawaiian" have also shown a younger age at diagnosis of about 5 - 6 years [40]. As previously noted, these age differences may reflect ethnic differences in age structure across each ethnic group. Unexpectedly, age was not a strong predictor of all-cause mortality in our study and this may be due to the strong independent effects we found for ethnicity (Māori), aggressive histology (Small cell and

Non-small cell), propensity to COPD at low smoking exposure and advanced clinical stage (see later). Our matched comparison (Table 2) was primarily done to match for age, in addition to gender and smoking exposure, where we found the most notable difference between Māori and Caucasian was for histology despite the smaller numbers (P = 0.07). We acknowledge that while surname has been used to help "enrich" ancestry in studies of indigenous peoples [41], where varying degrees of genetic admixture has occurred following colonisation, it remains inferior to formal genetic testing.

In order to minimise biases from variation in the investigation and treatment of lung cancer, or variations in temporal trends or institutional policy on lung cancer management, we compared the all-cause mortality of Māori and Caucasian lung cancer cases diagnosed from our single institution between 2004 and 2007. While it is unlikely that Māori lung cancer patients diagnosed in our hospital have been missed, lung cancers diagnosed in the community or on post-mortem may not have been included in this study. However the same can be said for our comparator population of NZ Caucasian lung cancer patients. Based on the results from 312 Caucasian cases and 81 Māori cases (recruited between 2004 - 2007), we found the mean survival in months was significantly less in Māori 29.2 months (SE 3.2 months) compared to Caucasians (35.3 months (SE2.3) ($p < 0.05$)). In a Cox-Proportional analyses we found that the Hazard Ratios (HR) for all-cause mortality were; ethnicity (Māori = 1.4, 95% Confidence Limits (95% CI) = 1.0 - 1.9, P = 0.03); gender (female HR = 0.8, 95% CI = 0.6 - 0.9, P = 0.04), advanced clinical stage (NSCLC Stage 4 or Small Cell-extensive = 2.6, 95% CI 2.0 - 3.4, P < 0.0001), and histology (small cell or non-small cell relative to adenocarcinoma = 1.4, 95% CI = 1.0 - 2.1, P = 0.04). Similar findings have been described for lung cancer mortality in Hawaii where Hawaiian ancestry conferred a hazard risk of 1.4 [40]. Importantly in our study, age, smoking status and COPD status were not significant contributors to all-cause mortality (Figure 7). We note that while clinical stage was an important determinant of all-cause mortality, it was not very different between Māori and Caucasian lung cancer cases. We do note that the non-significant deficit in early stage 1 disease in Māori (Table 1, 18% vs 22%, P > 0.05) is magnified in those with COPD (Table 6, 24% vs 35%, P < 0.05). This likely reflects that Māori ethnicity, advanced stage and aggressive histology independently obscure any effects of COPD on mortality. This observation casts some doubt on the currently accepted view that Māori lung cancer cases have greater mortality because of demographic variables such as smoking and presenting late due to poor access to doctors [18]. A similar conclusion was proposed from the study in Hawaiians [40]. Our results suggest poor outcomes for lung cancer may be in part related to both differences in the biology of the lung cancers (more aggressive histological subtypes) and greater disposition to airflow limitation, where non-respiratory mortality (cardiovascular disease and other cancers) has been shown to be greater [42]. Such an observation may have implications in the use of computed tomography for lung cancer screening or early case finding [23]. One reason for the ethnic differences in lung cancer susceptibility may be differences in how nicotine or carcinogens are absorbed or metabolised by different racial groups. With regards to absorption, one explanation may be that Māori smoke cigarettes differently to NZ Europeans, inhaling deeper per cigarette as has been proposed amongst African-Americans [30,31,43]. This behaviour has been associated with genetic polymorphisms of CYP2A enzymes, which are responsible for nicotine metabolism and activation of carcinogenic substances in cigarette smoke [30,31,44,45]. Increased CYP2A enzyme activity has been correlated to increased smoking depth, and consequently an increased dose of the carcinogen NNK per cigarette [30,44,45]. Differences in smoking depth and nicotine metabolism remain possible explanations for greater susceptibility of lung cancer and COPD in Māori. Differences in nicotine addiction have been examined in different ethnic groups in Hawaii and, based on studies assessing nicotine consumption relative to nicotine metabolism, concluded that Hawaiians were more addicted to nicotine secondary to a higher rate of metabolism [46]. This was supported by an earlier study correlating higher addiction rates in Native Hawaiian compared to Caucasians [47]. Based on these studies, we propose that the one possible factor underlying greater "susceptibility" of Māori to cigarette smoke stems from Māori being more sensitive to the addictive properties of smoking relative to NZ Caucasians. Another possibility has been differences in diet such as fruit and vegetables which have been linked to lower rates of lung cancer [48]. However, in the study by Haiman and colleagues they could find no effect from the intake of fruit and vegetables to account for the ethnic differences they reported [5]. However, it also remains possible that through shared ancestry [49], Hawaiian and Māori have an exaggerated immune response to smoking in the lungs [5,6,8]. We conclude that any one, or combination, of these various factors could contribute to the greater rates of current smoking, earlier age of onset of lung cancer, worse airflow limitation and greater tendency to more aggressive forms of lung cancer in Māori relative to Caucasians. Regardless of the basis of these important differences, aggressive tobacco control measures are required if disparities between Māori and Caucasians are to be addressed.

We acknowledge that this study has several limitations. First, while the Caucasian lung cancer cases were collected prospectively from 2004 - 2008, our Māori lung cancer cases were identified using a retrospective design. However, the Māori cases were identified from the same tertiary hospital, serving the same geographical region and during an overlapping time interval. Second, only about two thirds of our lung cancer case series had spirometry before or around the time of diagnosis. This is likely to introduce some bias but, as discussed above, it likely affects both groups equally and remains the more accurate way to report COPD prevalence compared to using COPD history as stated in medical notes [18]. Third, Māori ancestry was self-reported and was not confirmed (or quantified) on a genetic basis. It is likely that a large proportion of our 'Māori' population has a variable quantity of NZ Caucasian genetic ancestry (estimated to be about 30% on average). This means our results might actually underestimate these ethnic differences compared to a study using genetically defined ancestry. To test this hypothesis, we re-examined our results using only Māori lung cancer cases with a Māori surname and found the differences were slightly more marked with Adenocarcinoma prevalence of 27% in Māori compared to 42% in Caucasian (Figure 4 and table 3). While this approach has strengthened our original findings (rather than diluting them), we cannot be more definitive about this observation in the absence of using genetic ancestry markers to better assign ancestry. Given the retrospective recruitment of Māori lung cancer cases, we were not able to capture ancestry in their grandparents as we did for Caucasians. That said, it is likely we have captured a strongly Caucasian population and compared them to a Māori lung cancer cases series of variable Māori-Caucasian ancestry. Fourth, our case-case study design is inferior to a cohort study where lung cancer cases can be identified prospectively, with relevant demographic data collected prior to the diagnosis of lung cancer.

Conclusion

In conclusion, our results suggest that Māori who smoke may be at greater risk of lung cancer, and possibly COPD, than their Caucasian counterparts. The finding that Māori have worse airflow limitation and more aggressive lung cancer is novel to this study, as is the finding that Māori ethnicity and histology independently contribute to all-cause mortality. Regardless of the basis of this heightened susceptibility, tobacco control measures aimed at substantially reducing all exposure to smoking are indicated if disparities in outcomes for New Zealand Māori are to be successfully addressed [6,20].

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Competing Interest

None to declare in relation to this manuscript.

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