ORIGINAL ARTICLE

Evaluating Prognostic Factors for Sex Differences in Lung Cancer Survival: Findings From a Large Australian Cohort

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ABSTRACT

Introduction: Women tend to survive a lung cancer diagnosis longer than men; however potential drivers of this sex-related disparity remain largely elusive. We quantified factors related to sex differences in lung cancer survival in a large prospective cohort in Australia.

Methods: Participants in the 45 and Up Study (recruited 2006–2009) diagnosed with incident lung cancer were followed up to December 2015. Prognostic factors were identified from questionnaire data linked with cancer registrations, hospital inpatient records, emergency department records, and reimbursement records for government-subsidized medical services and prescription medicines. Hazard ratios (HRs) and 95% confidence intervals (CIs) for lung cancer death for men versus women were estimated using Cox proportional hazard regression in relation to key prognostic factors alone and jointly.

Results: A total of 488 women and 642 men were diagnosed with having lung cancer. Women survived significantly longer (median 1.28 versus 0.77 y; HR for men = 1.43, 95% CI: 1.25–1.64, $p < 0.0001$). The survival disparity remained when each subgroup of major prognostic factors was evaluated separately, including histologic subtype, stage at diagnosis, treatment received, and smoking status. Multivariable analyses revealed that treatment-related factors explained half of the survival difference, followed by lifestyle and tumor characteristics (explaining 28%, 26%, respectively). After adjusting for all major known prognostic factors, the excess risk for men was reduced by more than 80% (HR = 1.06, 95% CI: 0.96–1.18, $p = 0.26$).

Conclusions: The sex-related lung cancer survival disparity in this Australian cohort was largely accounted for by known prognostic factors, indicating an opportunity to explore sex differences in treatment preferences, options, and access.

Keywords: Epidemiology; Lung cancer; Sex; Survival disparities

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Introduction

Incidence rates for lung cancer have historically been higher in men than in women, but in Australia, this gap has been steadily narrowing since the 1980s.[1] As lung cancer in women has become more prevalent, significant sex-based differences in survival have been noted in Australia,[2] with women surviving longer than men. Potential reasons underlying this sex-related disparity remain largely elusive,[3–5] but it has been most often attributed to tumor characteristics and treatment modalities, with women more likely to be diagnosed with having adenocarcinoma and be more responsive to treatment. Nevertheless, the survival disparity has been found to remain even after considering these factors.[5–9] This suggests that other factors, for example, lifestyle characteristics, may also contribute to this sex disparity, but to our knowledge, no study has systematically evaluated all of these factors in one study population. Furthermore, most studies aimed at identifying sex survival differences have been retrospective[2,7,8,10,11] or hospital-based studies,[6,12] which are subject to various biases (e.g., inclusion of patients with certain clinical characteristics related to stage at diagnosis,[6,13] histologic subtypes,[6–8] or type of treatment received,[6,7,13]) and are thus limited in scope.

We used a large prospective, population-based cohort in Australia to simultaneously examine tumor characteristics, treatment modalities, and sociodemographic, health, and lifestyle factors as potential predictors of lung cancer survival disparity between men and women.

Materials and Methods

The Sax Institute's 45 and Up Study is an ongoing Australian prospective cohort study of 267,153 people aged more than or equal to 45 years residing in New South Wales (NSW), Australia, recruited during 2006 to 2009.[14] Prospective participants were randomly sampled from the Services Australia (formerly the Australian Government Department of Human Services) Medicare enrolment database, which provides near complete coverage of the population. People aged more than or equal to 80 years, and residents of rural and remote areas were oversampled. Of those invited, approximately 18% participated in the study, and the sample included approximately 11% of the NSW population aged more than or equal to 45 years. Participants joined the study by completing a mailed health and lifestyle questionnaire and gave consent for linkage of their data to routinely collected heath records.

The 45 and Up Study was approved by the University of NSW Human Research Ethics Committee. This analysis was covered by ethics approval from the NSW Population and Health Services Research Ethics Committee.

Data Linkage

Participants diagnosed with first primary lung cancer were identified by means of linkage to the NSW Cancer Registry (1994–2013). Data on treatments received, comorbidities, and vital status, were ascertained by means of linkage to the NSW Admitted Patient Data Collection, the NSW Emergency Department Data Collection, the Cause of Death Unit Record File from the Australian Coordinating Registry, and reimbursement records for government-subsidized medical services—Medicare Benefits Schedule (MBS), and prescription medicines—Pharmaceutical Benefits Scheme (PBS). Linkage of the 45 and Up cohort to the MBS and PBS (with deterministic matching) was facilitated by the Sax Institute using a unique identifier provided by Services Australia. All other data sets were probabilistically linked by the Centre for Health Record Linkage using a privacy-preserving approach and a matching process known to be highly accurate (false-positive and false-negative rates $< 0.4\%$).[15] The study period ended in December 2015.

Exclusions

Participants with any record of cancer before recruitment (either self-reported or registry-identified) were excluded, along with participants first diagnosed at death or whose survival time was 0 day. Participants whose health care was subsidized by the Australian Government's Department of Veterans' Affairs were excluded as their prescription medicines have a separate billing arrangement which were not available. Those aged more than or equal to 90 years at diagnosis were excluded because misclassification of cause of death has been found to be more common for older patients with cancer.[16]

Outcomes

Relative survival could not be estimated because relevant population lifetables were not available, so lung cancer-specific survival was used as the outcome.[17] The Surveillance, Epidemiology and End Results Program's cause-specific death classification[17] was used to optimize the accuracy of survival estimates as causes of death recorded in population-based registries can be inaccurate.[18] Lung cancer survival was calculated from the date of diagnosis to the date of death from lung cancer, or censored at the date of death from another cause, or at December 2015.

Covariates

Covariates that were previously found to be associated with the risk of lung cancer death were grouped into the following four factor domains: patients'

Table 1. Baseline Characteristics of Participants Aged Less Than 90 Years at Diagnosis in the 45 and Up Study (2006–2009) Diagnosed With Lung Cancer up to December 2013

Characteristic	Total, n (%)	Women, n (%)	Men, n (%)	*p* Value[a]
Participant characteristics	1130	488 (43)	642 (57)	
Marital status				0.0067
Married/de facto	733 (64.9)	295 (60.5)	438 (68.2)	
Single/widowed/divorced/separated	397 (35.1)	193 (39.5)	204 (31.8)	
Private health insurance				0.0018
Yes	478 (42.3)	235 (48.2)	243 (37.9)	
Physical disability needing help with daily tasks				0.72
No	945 (83.6)	405 (83.0)	540 (84.1)	
Highest education level (self-report)				<0.0001
Low	527 (46.6)	267 (54.7)	260 (40.5)	
Medium	260 (23.0)	60 (12.3)	200 (31.2)	
High	308 (27.3)	142 (29.1)	166 (25.9)	
Missing	35 (3.1)	19 (3.9)	16 (2.5)	
nSES[b]				0.0054
nSES 1 (lowest)	390 (34.5)	178 (36.5)	212 (33.0)	
nSES 2	325 (28.8)	122 (25.0)	203 (31.6)	
nSES 3	240 (21.2)	94 (19.3)	146 (22.7)	
nSES 4 (highest)	160 (14.2)	86 (17.8)	74 (11.5)	
Missing	15 (1.3)	8 (1.6)	7 (1.1)	
Remoteness of residence[c]				0.76
Major cities	581 (51.4)	247 (50.6)	334 (52.0)	
Inner regional	394 (34.9)	176 (36.1)	218 (34.0)	
Outer regional or remote/very remote	156 (13.8)	65 (13.3)	90 (14.0)	
Country of birth				0.18
Australian-born	920 (81.4)	408 (83.6)	512 (79.8)	
East Asian-born	41 (3.6)	18 (3.7)	23 (3.5)	
Other migrants	169 (15.0)	62 (12.7)	107 (16.7)	
Family history of lung cancer				0.37
Yes	157 (13.9)	73 (15.0)	84 (13.1)	
Mean height (cm) and SD	169 (7.4)	161 (7.6)	175 (7.2)	<0.0001
Lifestyle factors				
Tobacco smoking				<0.0001
Never smoker	164 (14.5)	112 (23.0)	52 (8.1)	
Past smoker (quit >15 y)	299 (26.5)	110 (22.5)	189 (29.4)	
Past smoker (quit >5–15 y)	186 (16.5)	64 (13.1)	122 (19.0)	
Past smoker (quit ≤5 y)	157 (13.9)	65 (13.3)	92 (14.3)	
Current smoker	313 (27.7)	134 (27.5)	179 (27.9)	
Missing	11 (0.97)			
Passive smoking				0.01
No	502 (44.4)	238 (48.8)	264 (41.1)	
Yes	628 (55.6)	250 (51.2)	378 (58.9)	
Alcoholic drinks (per wk)				<0.0001
0	379 (33.5)	203 (41.6)	176 (27.4)	
1–14	498 (44.1)	227 (46.5)	271 (42.2)	
>14	229 (20.3)	46 (9.4)	183 (28.5)	
Missing	24 (2.1)	12 (2.5)	12 (1.9)	
Physical activity (minutes per wk)				0.11
0	85 (7.5)	40 (8.2)	45 (7.0)	
1–149	215 (19.0)	82 (16.8)	133 (20.7)	
150–299	173 (15.3)	64 (13.1)	109 (17.0)	
≥300	607 (53.7)	278 (57.0)	329 (51.2)	
Missing	50 (4.4)	24 (4.9)	26 (4.0)	
Tumor-related factors				
Age at diagnosis mean (SD), y	71.2 (9.2)	69.2 (9.4)	72.7 (9.0)	<0.0001
Stage at diagnosis				0.17
Localized	219 (19.4)	109 (22.3)	110 (17.1)	

(continued)

Table 1. Continued

Characteristic	Total, n (%)	Women, n (%)	Men, n (%)	*p* Value[a]
Regional	247 (21.9)	101 (20.7)	146 (22.7)	
Distant	552 (48.8)	233 (47.7)	319 (49.7)	
Unknown	112 (9.9)	45 (9.2)	67 (10.4)	
Emergency department presentation				0.42
During 2 wk before diagnosis	178 (15.8)	72 (14.8)	105 (16.5)	
Histologic subtype				<0.0001
Adenocarcinoma	459 (40.6)	249 (51.0)	210 (32.7)	
Small cell carcinoma	117 (10.4)	41 (8.4)	76 (11.8)	
All other NSCLC	554 (49.0)	198 (40.6)	356 (55.5)	
Treatment-related factors				
Any surgery in 6 mo after diagnosis	233 (20.6)	122 (25.0)	111 (17.3)	0.0015
Any systemic therapy in 6 mo after diagnosis	462 (40.9)	208 (42.6)	254 (39.6)	0.30
Any radiotherapy in 6 mo after diagnosis	420 (37.2)	173 (35.5)	247 (38.5)	0.30
Charlson comorbidity index[d]				<0.0001
0	758 (67.1)	360 (73.8)	398 (62.0)	
1	198 (17.5)	71 (15.8)	121 (18.8)	
≥2	174 (15.4)	51 (10.5)	123 (19.2)	

[a]Chi-square test (except for variable "height" for which two-sample *t* tests were used).
[b]On the basis of a composite index of relative socioeconomic disadvantage from the 2011 Australian Census.
[c]On the basis of the Australian Standard Geographic Classification Remoteness Structure.
[d]The Charlson Comorbidity Index were calculated using records up to 5-years prediagnosis in the linked APDC data.
APDC, Admitted Patient Data Collection; nSES, neighborhood socioeconomic status.

characteristics, lifestyle, tumor-related, or treatment-related factors (Table 1). Detailed descriptions of these covariates can be found in the Supplementary Materials.

Sociodemographic and lifestyle factors were ascertained from the study's baseline questionnaire, including marital status, private health insurance, remoteness of residence, education, neighborhood socioeconomic status, physical disability, country of birth, family history of lung cancer, height, tobacco smoking, passive smoking, physical activity, and alcohol consumption.

Tumor-related factors were derived from multiple data sources. Cancer stage at diagnosis as recorded in the registry was reported as localized, regional, distant, or unknown.[19] Using histology codes from the registry, tumor histology was classified as SCLC, adenocarcinoma, or other NSCLC according to the International Agency for Research on Cancer histologic classification.[20] Whether the participant's diagnosis followed an emergency presentation was determined by the date of diagnosis and the date of emergency department departure.

Anticancer treatments relating to lung cancer (surgery, radiation therapy, or systemic treatment) received up to six months after diagnosis were coded as yes or no on the basis of any indication of such treatment recorded in the Admitted Patient Data Collection, MBS, or PBS.[21] The codes to ascertain treatment modalities for lung cancer can be found elsewhere.[22] Comorbidities, for inclusion in the Charlson Comorbidity Index (0, 1, ≥2),[23] were identified using hospitalization records for 5 years before cancer diagnosis.[24]

Statistical Analyses

Sex differences in cause-specific survival were evaluated using Kaplan-Meier curves with log-rank tests for the entire patient cohort and stratified by histologic subtype, cancer stage, receipt of treatment, and smoking status. In the stratified analysis by smoking status (ever versus never smoker), the never smoker category included former smokers who quit more than 15 years ago because their risk of many comorbid conditions is close to that of never-smokers,[25] and because of the small number of never-smokers. In the stratified analysis by receipt of treatment, patients were grouped into the following two categories: participants who had received any anticancer treatments and untreated participants. We also conducted a stratified analysis for adenocarcinoma by smoking status.

To better understand the drivers of disparities in cancer survival,[8,9,13] we evaluated the proportion of the sex disparity accounted for by each covariate domain separately using Cox proportional hazard regressions. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for men relative to women. The basic model was adjusted for age and diagnosis year, and then each domain of covariates was added individually to this basic model, with treatment types included as time-dependent variables. Changes in the HR for men with the addition of each covariate domain to the basic model were used to estimate the individual contribution of each domain to the overall excess mortality for men. The final model, with stratification by histologic subtype

and cancer stage, was selected by removing not significant covariates one by one (in order of descending p value) from the full model until the best fitting model was achieved, on the basis of minimizing the Bayesian Information Criterion. All analyses were performed using SAS version 9.4 (SAS Institute, Inc.). Tests for statistical significance were 2-sided, α equals to 0.05.

Results

Participant Characteristics

Of the 267,153 participants in the 45 and Up Study, 1130 eligible participants were diagnosed with having lung cancer during follow-up (488 women and 642 men). The characteristics of these participants by sex are presented in Table 1. Compared with men, women were, on average, younger at diagnosis, had fewer comorbidities, and were more likely to have a low level of education. Women were also more likely to be never-smokers and less likely to be exposed to passive smoking and were more likely to be diagnosed with having adenocarcinoma and to receive surgery within six months after diagnosis. Of note, there was no significant association between sex and cancer stage.

Survival by Sex: Overall and Stratified Analysis

Lung cancer survival was significantly higher for women (median = 1.28 versus 0.77 y, $p < 0.0001$) (Fig. 1). Stratified analyses revealed that women with lung cancer survived significantly longer than men within each subgroup of major prognostic factors: histologic subtype, cancer stage, cancer treatment, and smoking status (Fig. 2*A–D*). The analysis of adenocarcinoma by smoking status (Supplementary Fig. 1) revealed that women with adenocarcinoma had significantly better survival than men with adenocarcinoma independent of smoking status (logrank, $p = 0.0009$). Survival did not differ significantly by smoking status (logrank, $p = 0.37$); however, never-smokers were older at diagnosis than ever-smokers (mean = age 74 y versus 69 y, $p < 0.0001$) and they had a significantly lower hazard of lung cancer death (HR = 0.84, 95% CI: 0.73–0.98) after adjusting for age.

Multivariable Analyses

In the univariable regression, the hazard of dying from lung cancer was significantly higher for men than women (HR = 1.43, 95% CI: 1.25–1.64, $p < 0.0001$). With minimal adjustment (age and year of diagnosis), the excess risk of dying was reduced to 33% (HR = 1.33, 95% CI: 1.15–1.53) (model 1 in Table 2). After additional, separate adjustment for participants' characteristics, lifestyle, tumor-related factors, or treatment-related factors, the excess risk of death for men reduced considerably, but remained significantly higher than women (models 2–5 in Table 2). Differences in treatment-related factors explained 50% of the sex survival differential, followed by lifestyle and tumor-related factors (28%, 26% respectively). Because of the correlation between these covariate domains, the sum of the domain-specific percentages exceeded 100%. Factors included in the final model together accounted for 81% of the excess risk of dying for men, which did not differ significantly from that for women (HR = 1.06, 95% CI: 0.96–1.18, $p = 0.26$). Results for the final model are presented in Table 3.

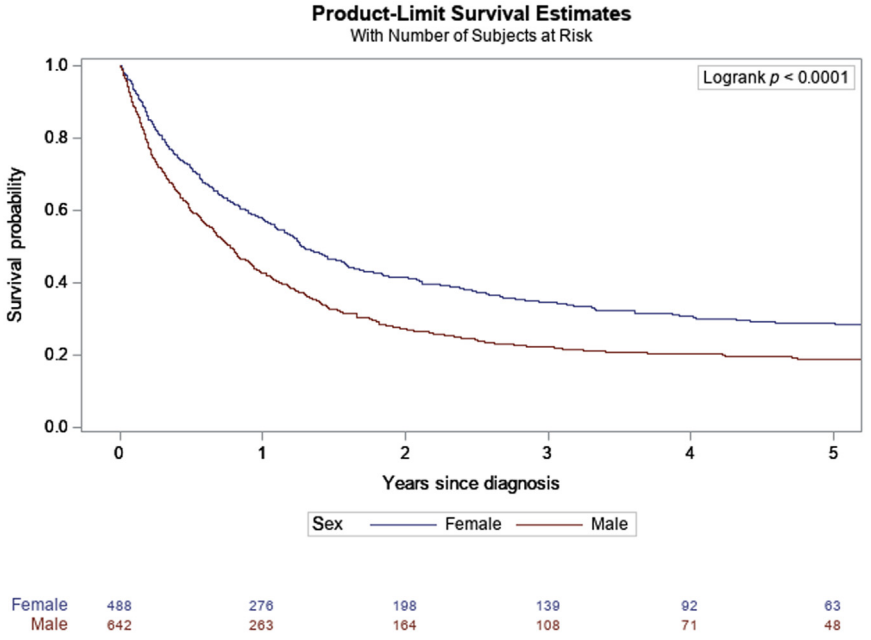

Figure 1. Survival from lung cancer.

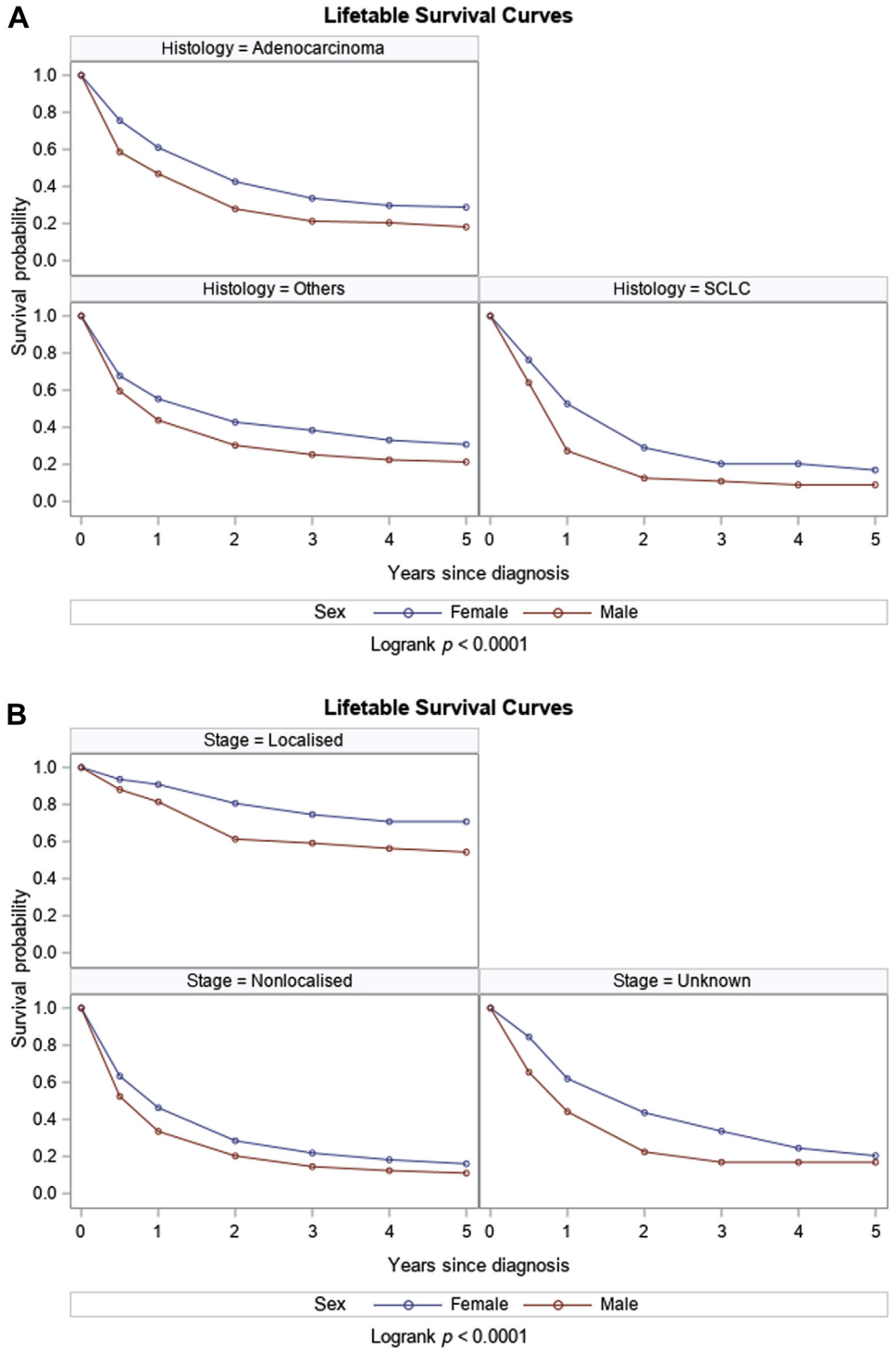

Figure 2. Survival from lung cancer stratified by major prognostic factors: (*A*) histology; (*B*) cancer stage; (*C*) cancer treatment; and (*D*) smoking status.

Discussion

In this first Australian prospective study of lung cancer survival comparing men and women, we found that men had a 43% greater risk of dying from their lung cancer than women. Key prognostic factors including histologic subtype, cancer stage, treatment received, and smoking status were each found to explain some of the survival disparity, but not all. Nevertheless, when all prognostic factors were considered together, most of the survival differential disappeared. These results suggest

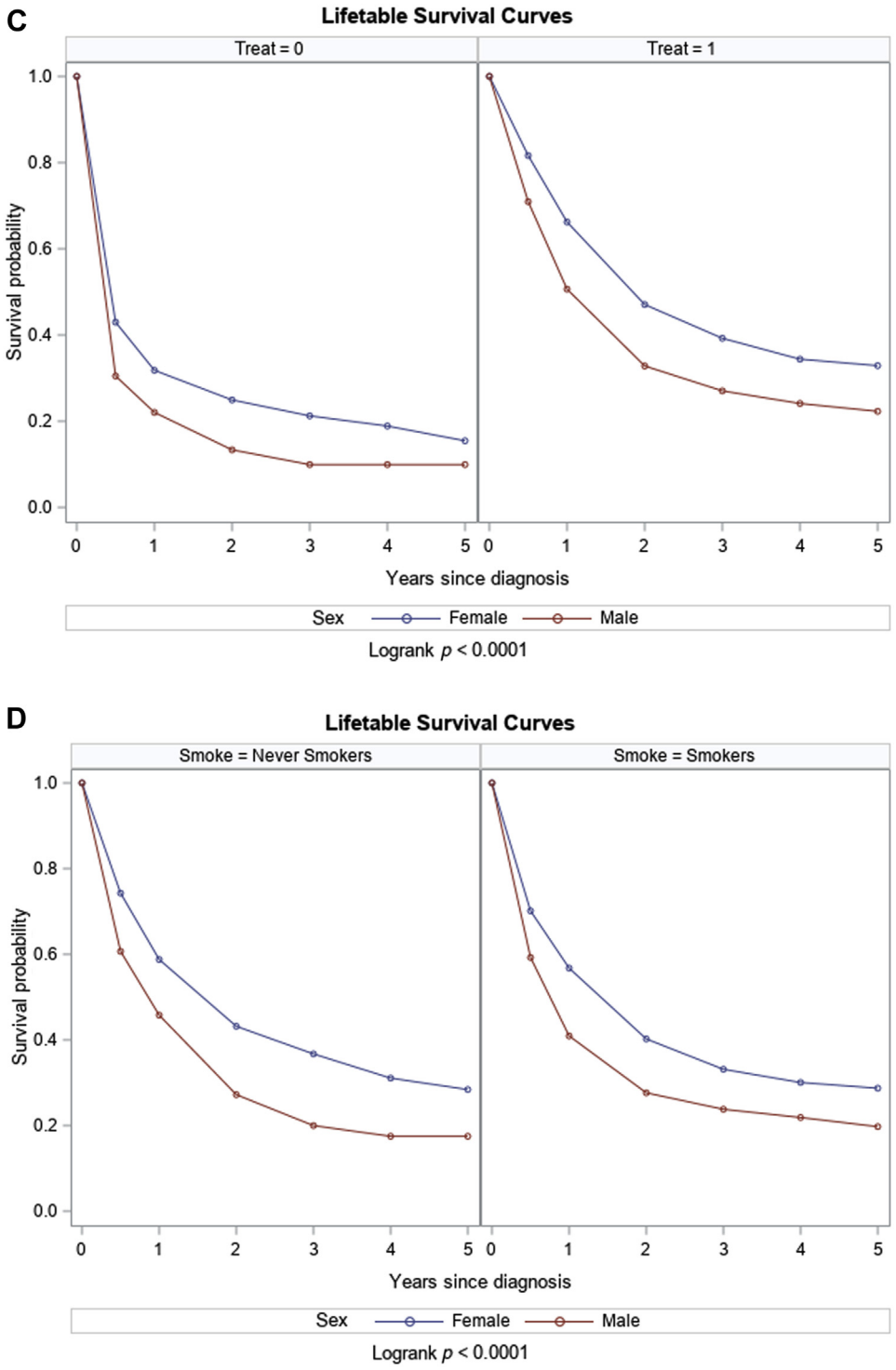

Figure 2. Continued.

that sex differences in lung cancer survival can be largely explained by these known prognostic factors.

Our study has updated and extended the many previous studies on this topic in the past few decades[3,6,7,9,10,12,26,27] by considering four domains of prognostic factors simultaneously in one large comprehensive analysis. In a previous Australian study of a cohort of surgical patients with NSCLC, Wainer et al.[28] found that men had significantly poorer 5-year survival than women, which remained significant after

Table 2. Adjusted HRs for Death From Lung Cancer by Sex and Contributions of Prognostic Factors to Overall Survival Disparity

	Model 1		Model 2		Model 3		Model 4		Model 5		Final Model	
Models	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Women	1.00		1.00		1.00		1.00		1.00		1.00	
Men	1.33	(1.15-1.53)	1.26	(1.02-1.56)	1.24	(1.07-1.44)	1.24	(1.08-1.43)	1.16	(1.06-1.28)	1.06	(0.96-1.18)
p value for sex	<0.0001		0.03		0.005		0.0031		0.0012		0.26	
Contribution to excess mortality, %			19		28		26		50		81	

Note: Model 1: includes sex, age at diagnosis, and diagnosis year. Model 2: model 1 plus patient-related factors (marital status, private health insurance, place of residence, education level, area-based SES, physical disability, country of birth, family history of lung cancer, and height). Model 3: model 1 plus lifestyle factors (smoking status, passive smoking, alcohol consumption, and physical activity). Model 4: model 1 plus disease-related factors (stage at diagnosis, histologic subtype, and emergency presentation). Model 5: model 1 plus treatment-related factors (surgery, systemic therapy, radiotherapy, and comorbidities). Final model: model 1 plus physical disability, education level, family history of lung cancer, country of birth, smoking status, passive smoking, emergency department presentation, Charlson comorbidity score, surgery, systemic therapy, and radiotherapy, stratified by cancer stage at diagnosis and histologic subtype.

CI, confidence interval; HR, hazard ratio; SES, socioeconomic status.

accounting for age, stage, histology, smoking history, and performance status (HR = 1.54, 95% CI: 1.10–2.16). A more recent population-based study extended this previous study by including patients with all stages and histologic subtypes and found that men with lung cancer had significantly poorer 5-year survival than women (11.7% versus 15.2%) after adjusting for age and years since diagnosis.[2] Nevertheless, these previous Australian studies were either hospital based and included patients treated with curative intent only[28] or did not include information on cancer stage and treatment or smoking history.[2] Similarly, many studies from other countries either included only patients with certain clinical characteristics,[6,7,9,10,13] so that their findings may apply only to certain patient groups or did not include important data on prognostic factors (e.g., tobacco smoking history),[5–7,10,12,13] and thereby did not have the ability to explain the sex differences in lung cancer survival. Longer survival in women with lung cancer was also observed after adjustment for age and performance status in large pooled chemotherapy trials for both adenocarcinoma[27] and SCLC[29] where uniform treatment was provided. Although these clinical trials[27,29] provide the highest level of clinical evidence, our real-world data provide more insights into clinical outcomes and supplement clinical trials by addressing some of their limitations (e.g., disparities in access, narrow external generalizability,[30] and lack of data on lifestyle factors).[27,29] The uniqueness of this study is that we used comprehensive health-related data linked with longitudinal data from the largest cohort study in Australia, offering findings that are likely to be robust and reflect a wider population base.

We found that approximately half of the observed sex survival disparity was explained by differences in receipt of anticancer treatments within six months after diagnosis. This could partly be due to a lower proportion of men having surgery within six months than women (17% versus 25%), which may be due to patient-related factors that also correlate with poorer survival. Men are older at diagnosis, less likely to be never-smokers, and have more comorbidities (Table 1), which might prevent them from having surgery. Besides surgery, women with lung cancer may respond to chemotherapy better than men,[4,6] as we found that the survival advantage was observed across all three broad stage of disease categories. In addition, the finding that the sex disparity remained even among those who did not receive any treatment for their cancer within six months suggests that lung cancer in women may have a different natural history.[13] Immunologic differences are a potential explanation for the observed survival disparity among untreated patients. A recent study[31] found that the densities of memory B cells, which play a prominent role in human antitumor immunity, were higher in the lung adenocarcinoma tissues of female patients. The different natural history, together with the characteristics of women in our study (younger at diagnosis, less likely to be smokers, and more likely to have adenocarcinoma relative to men), suggests that lung cancers in women may have different genetic profiles from those in men.[32,33] Evidence suggests that there are differences in the expression and mutation rates of several related genes between sexes, including the *EGFR*, *K-ras*, and *p53*.[26,33] These biological differences may be a factor in women's better response to chemotherapy and radiotherapy for both SCLC[34] and NSCLC,[27] which in turn may explain some of the sex survival disparity observed in this study.

Smoking history at baseline was identified as a significant contributing factor to the sex survival disparity, explaining approximately 28% of the overall disparity.

Table 3. Adjusted HRs for Death From Lung Cancer in the Final Model, Among 45 and Up Study Participants, NSW Australia

Characteristic	HR	95% CI	*p* Value
Sex			0.26
Women	1.00		
Men	1.06	0.96-1.18	
Age at diagnosis	0.99	0.99-1.00	0.012
Year of diagnosis	1.00	0.97-1.02	0.74
Highest education level			0.30
Low	1.00		
Medium	1.01	0.89-1.15	
High	1.09	0.97-1.23	
Physical disability			0.12
Yes	1.00		
No	1.14	0.97-1.35	
Family history of lung cancer			0.068
Yes	1.00		
No	1.14	0.99-1.30	
Country of birth			0.42
Australian-born	1.00		
East Asian-born	0.84	0.63-1.11	
Other migrants	0.97	0.84-1.11	
Tobacco smoking			0.0008
Never smoker	1.00		
Past smoker (quit >15 y)	1.43	1.21-1.70	
Past smoker (quit >5 to 15 y)	1.37	1.13-1.65	
Past smoker (quit ≤5 y)	1.41	1.15-1.72	
Current smoker	1.29	1.08-1.54	
Passive smoking			0.79
Yes	1.00		
No	0.99	0.89-1.09	
Emergency presentation			0.14
Yes	1.00		
No	0.90	0.78-1.03	
Charlson comorbidity index			0.11
0	1.00		
1	0.87	0.75-0.99	
≥2	1.00	0.85-1.16	
Surgery in 6 mo after diagnosis			<0.0001
Yes	1.00		
No	3.96	3.21-4.89	
Systemic therapy in 6 mo after diagnosis			<0.0001
Yes	1.00		
No	2.30	2.00-2.64	
Radiotherapy in 6 mo after diagnosis			<0.0001
Yes	1.00		
No	1.37	1.20-1.55	

Note: Stratified by cancer stage at diagnosis and histologic subtype.
CI, confidence interval; HR, hazard ratio; NSW, New South Wales.

This is likely because more women were never-smokers compared with men (23% versus 8%) and never-smokers are more likely to receive aggressive or complete treatment[27] and to respond well to treatment.[3,6,26] Numerous studies have revealed that lung cancers have heterogeneous genetic profiles, with tumors in never-smokers that grow more slowly and have a higher rate of *EGFR* mutation than those in smokers,[35] and therefore likely have a better prognosis.

Tumor-related factors were other important contributors to the sex disparity in survival, which together explained approximately 26% of the overall sex disparity. That the proportion of cases with adenocarcinoma was higher for women than men in this study (51% versus 33%) is consistent with the literature,[5–7,10–12,27,28] and thus, the higher survival for those with adenocarcinoma may explain some of the survival disparity between the sexes. In addition, our finding that women

with adenocarcinoma had significantly longer survival than men with adenocarcinoma after adjusting for smoking status suggests that sex differences in tumor biology may play a role in explaining the sex survival differential in addition to smoking status and histologic subtype. Previous studies indicated that *EGFR* mutations have been found to be most prevalent among never-smoking women, and in adenocarcinoma cases.[36,37] As those with adenocarcinomas and *EGFR* kinase domain mutations were found to respond favorably to tyrosine kinase inhibitors (TKIs),[38] better overall survival would be expected for women because of TKI therapy. Nevertheless, our follow-up was up to 2015 and targeted therapy for *EGFR* mutated tumors only became commonplace after 2014. As TKIs are ineffective in unselected patients, they were unlikely to have been a major contributor to the observed survival difference.

A potential confounder for the observed survival differences could be that men are generally at greater risk than women of dying from causes other than lung cancer, in which case misclassification in cause of death could affect men more than women. We tried to minimize this bias using multiple approaches. First, to account for potential misclassification in the cause of death, we used the Surveillance, Epidemiology and End Results cause-specific death classification,[17] which has been found to produce reliable survival estimates.[39] Second, we excluded patients aged more than or equal to 90 years at diagnosis from our analysis, as misclassification of cause of death is more prevalent among older patients with cancer.[16] Third, we considered smoking status, comorbidities, and age in our multivariable analyses, to reduce the probability of differences in competing-risk mortality between sexes. For all these reasons, sex differences in cause of death are unlikely to explain the observed sex survival differences after lung cancer diagnosis in this study.

This study has some limitations. First, smoking history was self-reported at recruitment, which means that true smoking habits were possibly under-reported[40]; thus, there may be some residual confounding by smoking. Second, it may still be possible that lung cancer was incorrectly registered as the cause of death on the death certificate,[41] although efforts were made to minimize its impact in our analysis. Third, the study population was limited to the participants in the 45 and Up Study, and the low participation rate (18%) in that study means that our results may not be representative of the entire NSW population. Nevertheless, a previous study has indicated that reasonable estimates of relative differences can be obtained from the cohort.[42] Finally, other potential limitations include the lack of data on participant's treatment preferences and performance status at diagnosis, as they were not available for analysis. There are likely to be differences in the way men and women respond to a lung cancer diagnosis and their preferences for treatment and care.[43] There may also be sex differences in the types of treatments offered and whether or not they are accessible.

An understanding of the drivers of the sex differences in lung cancer survival is critical to the improvement of outcomes for both men and women with lung cancer. Given that treatment differences are an important factor even when adjusting for age and comorbidities, qualitative studies to evaluate the interactive roles of patients' and family members' choices and perceptions of treatment could yield some insights on additional drivers for these survival differences. In addition, lifestyle modification including education/advocacy around smoking cessation, particularly for men, is another crucial step to reduce survival differences between the sexes.

In conclusion, in this large contemporary Australian cohort, we found that most of the female survival advantage for lung cancer was accounted for by treatment-related factors, suggesting a need for better understanding around sex differences regarding treatment access and patient choice.

CRediT Authorship Contribution Statement

Xue Qin Yu: Conceptualization, Methodology, Statistical analysis, Writing - original draft preparation, had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Xue Qin Yu, Mei Ling Yap, Elvin S. Cheng, Preston J. Ngo, Pavla Vaneckova, Deme Karikios, Karen Canfell, Marianne F. Weber: Writing - Critical revision of the manuscript for important intellectual content review and editing.

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Supplementary data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2022.01.016.

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