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International differences in lung cancer survival by sex, histological type and stage at diagnosis: an ICBP SUVRMARK-2 study

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Key messages

What is the key question?

Are there international disparities in lung cancer survival by clinically-relevant subgroups in the most recent population level data?

What is the bottom line?

International differences in survival among patients with lung cancer persist in high-income countries, which are partly due to differences in stage at diagnosis or early detection, and to survival difference within stage groups due to cancer management.

Why read on?

This study presents in-depth results of the most-up-to-date differences of lung cancer stage distribution and survival by histological types, age group and sex for each included country, as well as within countries, followed by a discussion of potential causes of the disparities including clinical and data factors.

ABSTRACT

Introduction: Lung cancer has a poor prognosis that varies internationally when assessed by the two major histological subgroups [non-small cell (NSCLC) and small cell (SCLC)].

Method: 236,114 NSCLC and 43,167 SCLC cases diagnosed during 2010-2014 in Australia, Canada, Denmark, Ireland, New Zealand, Norway, and the United Kingdom (UK) were included in the analyses. One- and 3-year age-standardised net survival (NS) was estimated by sex, histological type, stage, and country.

Results: One- and 3-year NS was consistently higher for Canada and Norway, and lower for the UK, New Zealand and Ireland, irrespective of stage at diagnosis. Three-year NS for NSCLC ranged from 19.7% for the UK to 27.1% for Canada for males and was consistently higher for females (25.3% in the UK; 35.0% in Canada) partly because males were diagnosed at more advanced stages. International differences in survival for NSCLC were largest for regional stage and smallest at the advanced stage. For SCLC, 3-year NS also showed a clear female advantage with the highest being for Canada (13.8% for females; 9.1% for males) and Norway (12.8% for females; 9.7% for males).

Conclusion: Distribution of stage at diagnosis among lung cancer cases differed by sex, histological subtype and country, which may partly explain observed survival differences. Yet, survival differences were also observed within stages, suggesting that quality of treatment, healthcare system factors, and prevalence of comorbid conditions may also influence survival. Other possible explanations include differences in data collection practice, as well as differences in histological verification, staging and coding across jurisdictions.

Keywords: Histology, lung cancer, stage at diagnosis, survival, international

INTRODUCTION

Lung cancer is the leading cause of cancer death among men and women worldwide, with an estimated 1.6 million deaths, or nearly 20% of all cancer deaths, occurring in 2018.[1] Lung cancer is categorised into two main histological groups - small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC) - with SCLC patients generally having poorer outcomes compared to NSCLC.[2] Marked sex differences in survival have also been previously reported, with females having a more favourable prognosis.[3-6]

As cancer survival is one of the key measures of performance improvement in health care, international cancer survival comparisons can identify possible causes for observed variations, such as access to early detection or optimal treatments. The International Cancer Benchmarking Partnership (ICBP), a consortium of clinicians, policy-makers, researchers, and cancer data experts, has previously described lung cancer survival differences across high-income countries[7] and concluded that stage at diagnosis and histological type explained some of the international variation in lung cancer survival in 2004-2007.[2] In this study, we extend this prior work by assessing the most up-to-date lung cancer survival statistics by sex and stage at diagnosis for NSCLC and SCLC, using population-based data from seven countries.

METHODS

Data

Data were collected as part of the ICBP SURVMARK-2 project for patients diagnosed during 1995-2014 at ages above 18 years and followed until the end of 2015.[8] ICBP countries were included due to their high-quality population-wide registries, universal access to healthcare with similar healthcare expenditure, and interest in understanding how and why cancer survival differs across countries. For this study, lung carcinoma data from 18 population-based cancer registries in seven countries with at least 50% complete data on stage at diagnosis during 2010-2014, were included (Australia - New South Wales; Canada - Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland, Nova Scotia, Ontario, Prince Edward Island, Saskatchewan; Denmark; Ireland (2010-2013); New Zealand; Norway; and the UK - England, Scotland, Wales, Northern Ireland). Cases diagnosed with an invasive primary malignant tumour of the lung and bronchus (ICD-10: C34) were classified as SCLC, NSCLC, other and unspecified histology (see **Table 1**). Of 393,453 adult lung cancer patients diagnosed during 2010-2014, we excluded cases diagnosed based on death certificate only (DCO) or at autopsy (N=8,105, 2.1%), with inconsistent

dates (N=54, <0.0%), below age 15 or above age 99 (N=127, <0.0%), with second primary cancer in the lung (N=5,034, 1.3%), with incorrect stage information (N=4,557, 1.2%) or classified as neuroendocrine neoplasms (NEN) (N=7,869, 2.0%).

Each participating cancer registry provided information on pre-treatment pathological and clinical stage based on the tumour extent (T), the degree of nodal involvement (N), and the presence of metastases (M), grouped TNM (stages I-IV), and SEER summary stage 2000 (**Supplementary Figure 1A**). A previously developed algorithm[9] was adapted to harmonise individual or grouped TNM information (7th edition[10]) to SEER stage (localised, regional, distant and missing), creating a 'mapped SEER stage' that combines both TNM and SEER stage information; during the stage mapping, pathological T and N, and clinical M information was prioritised if both pathological and clinical data were available (**Supplementary Figure 1B**).

Statistical analyses

We estimated net survival, which is the survival of cancer patients after adjustments for background mortality in the general population using life tables. Life tables were specific to sex, single year of age, geographical region and year of death. Net survival estimates at one and three years after diagnosis were estimated by histological group and sex for each country and jurisdiction, as appropriate, using Pohar Perme estimators.[11] Age-standardisation was carried out using International Cancer Survival Standard weights.[12] The period approach was used to provide short-term predictions of three-year survival for patients diagnosed during 2010-2014. Statistically significant differences in net survival between sexes, histological subgroups, countries or jurisdictions were determined by comparing the 95% confidence intervals (95%CI).

Stage at diagnosis was imputed separately for SCLC and NSCLC patients with missing stage data (SCLC missingness range: 1.1% (Denmark – SEER) to 33.6% (UK – TNM); NSCLC missing range: 1.1% (Denmark –SEER) to 33.3% (UK – TNM). Covariates in the imputation model included age, sex, year of diagnosis, survival time, and the Nelson-Aalen estimator of the cumulative hazard. We ran the imputation model 30 times and combined the results using Rubin's rules.[13] Stage-specific survival estimates using the imputed datasets were then compared with the corresponding results without imputation (**Supplementary Tables 1 & 2**). All analyses were undertaken using Stata 14.[14]

Final results are presented by grouped TNM for all countries except Australia and New Zealand where TNM data were not collected, and mapped SEER stage for all countries, and stratified by histology group. All results relate to imputed stage, unless otherwise noted. For simplicity, we used stages I-IV when referring to TNM stage, and 'localised', 'regional', and 'distant' when referring to mapped SEER stage. Finally, while we focussed on sex-specific estimates, the findings for both sexes combined are presented in **Supplementary Figures 2-5** and **Supplementary Tables 1-10**.

RESULTS

In total, 367,707 patients (93.5%) diagnosed during 2010-2014 were included in the survival analyses (**Table 1**). 280,744 cases (76.4% of eligible cases) were microscopically confirmed, either through cytologic examination, histology of primary tumour or of metastasis. The proportion with NSCLC ranged between 59% (UK) and 76% (Australia) while the proportion with SCLC was largely consistent across all countries at 11-12%, with a slightly larger proportion in Denmark (14%) and Norway (16%). The proportion with unspecified cancers ranged from 11% (Denmark) to 29% (UK). For the remainder of this report we will comment only on results for NSCLC and SCLC cases (n=279,281).

Table 1. Characteristics of patients diagnosed with lung cancer during 2010-2014

	Australia[°]	Canada[†]	Denmark	Ireland[¶]	New Zealand	Norway	United Kingdom[‡]	Total
Number of patients diagnosed during 2010-2014	18,567	90,439	22,828	9,393	10,309	14,538	227,379	393,453
Exclusions								
Diagnosed based on death certificate only (DCO) or autopsy	665 (3.6%)	1,412 (1.6%)	272 (1.2%)	157 (1.7%)	185 (1.8%)	334 (2.3%)	5,080 (2.2%)	8,105 (2.1%)
Quality control[Δ]	48 (0.3%)	5 (0.0%)	None	None	None	None	1 (0.0%)	54 (0.0%)
Age <15 or >99 years	4 (0.0%)	20 (0.0%)	1 (0.0%)	2 (0.0%)	1 (0.0%)	4 (0.0%)	95 (0.0%)	127 (0.0%)
Second or higher order cancers at the same site	89 (0.5%)	1,478 (1.6%)	78 (0.3%)	187 (2.0%)	2 (0.0%)	172 (1.2%)	3,028 (1.3%)	5,034 (1.3%)
Cases with inconsistencies in stage information[*]	None	174 (0.2%)	801 (3.5%)	204 (2.2%)	None	292 (2.0%)	3,086 (1.4%)	4,557 (1.2%)
Neuroendocrine Neoplasms (NENs)[◊]	451 (2.4%)	1,846 (2.0%)	629 (2.8%)	270 (2.9%)	181 (1.8%)	371 (2.6%)	4,121 (1.8%)	7,869 (2.0%)
Total cases eligible for survival analysis	17,310 (93.2%)	85,504 (94.5%)	21,047 (92.2%)	8,573 (91.3%)	9,940 (96.4%)	13,365 (91.9%)	211,968 (93.2%)	367,707 (93.5%)
% Males	59.1%	51.9%	51.1%	56.6%	52.7%	55.2%	54.4%	53.9%
Histological subtype								
SCLC[Ŧ]	1,971 (11.4%)	9,671 (11.3%)	2,991 (14.2%)	1,089 (12.7%)	1,185 (11.9%)	2,097 (15.7%)	24,163 (11.4%)	43,167 (11.7%)
NSCLC[§]	13,115 (75.8%)	59,969 (70.1%)	15,590 (74.1%)	6,006 (70.1%)	6,619 (66.6%)	9,414 (70.4%)	125,401 (59.2%)	236,114 (64.2%)
Other[∂]	44 (0.3%)	119 (0.1%)	62 (0.3%)	19 (0.2%)	23 (0.2%)	30 (0.2%)	403 (0.2%)	700 (0.2%)
Unspecified[Ѧ]	2,180 (12.6%)	15,745 (18.4%)	2,404 (11.4%)	1,459 (17.0%)	2,113 (21.3%)	1,824 (13.6%)	62,001 (29.3%)	87,726 (23.9%)

[†] Canadian provinces included: Alberta, British Columbia, New Brunswick, Manitoba, Newfoundland, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan

[‡] United Kingdom registries included: England, Northern Ireland, Scotland, and Wales

[°] Australia registries included: New South Wales

[¶] Ireland (2010-2013)

[Δ] Includes: data inconsistencies (invalid age, missing/incomplete dates), tumours with non-malignant behavior, tumours with invalid morphological or topographical codes

[*] Stage error or in situ flag

[◊] NENs (ICD-O-3 morphology): 8013 and 8041-8045 (excluding lung cancer), 8150-8158, 8240-8247, 8249, 9091, 8574

[Ŧ] SCLC, small cell lung cancer (ICD-O-3 morphology): 8041-8045

[§] NSCLC, non-small cell lung cancer (ICD-O-3 morphology): 8012, 8014, 8050-8078, 8083, 8084, 8140, 8211, 8230–8231, 8250–8260, 8323, 8480–8490, 8550–8552, 8570–8574, 8576

[∂] Other, specified (ICD-O-3 morphology): 8800-8811, 8830, 8840-8921, 8990, 8991, 9040-9044, 9120-9133, 9150, 9540-9581

[Ѧ] Unspecified (ICD-O-3 morphology): 8000-8005, 8010, 8011

Non-Small Cell Lung Carcinoma

At least 45% of the 236,114 NSCLC cases were diagnosed at the most advanced stage (Stage IV for TNM, distant stage for SEER) for males in all countries, with the largest proportion observed in New Zealand at 59.8% (**Table 2A, Figure 1A**). Compared to males, females had a more favourable stage distribution in all countries, except New Zealand and Denmark (**Table 2B, Figure 1A**).

Table 2A. Number and proportion of male patients with non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC) diagnosed during 2010-2014 by country and stage at diagnosis (TNM and SEER), before and after imputation

	TNM stage									Mapped SEER								
		NSCLC		%		SCLC		%			NSCLC		%		SCLC		%	
	Stage	Number	Median age at diagnosis	Observed	After imputation	Number	Median age at diagnosis	Observed	After imputation	Stage	Number	Median age at diagnosis	Observed	After imputation	Number	Median age at diagnosis	Observed	After imputation
Australia[^]	All patients									c	7,786	71 (63-78)			1,132	70 (63-77)		
	Missing									Missing	820	73 (66-81)	10.5		89	69 (61-77)	7.9	
	I									Localised	1,419	72 (66-78)	20.4	21.2	86	73 (62-79)	8.2	9.3
	II									Regional	1,873	70 (63-77)	26.9	27.0	230	69 (64-75)	22.1	22.0
	III									Distant	3,674	70 (62-77)	52.7	51.8	727	70 (63-77)	69.7	68.7
	IV																	
Canada[†]	All patients	31,142	70 (63-77)			4,862	68 (61-75)			All patients	31,142	70 (63-77)			4,862	68 (61-75)		
	Missing	1,945	71 (64-78)	6.2		202	69 (63-76)	4.2		Missing	1,686	71 (63-78)	5.4		173	69 (62-75)	3.6	
	I	5,401	71 (65-78)	18.5	19.1	126	74 (66-78)	2.7	3.0	Localised	4,289	71 (65-78)	14.6	15.3	107	74 (68-78)	2.2	2.6
	II	3,022	71 (64-77)	10.4	10.5	142	69 (63-76)	3.0	3.3	Regional	10,424	71 (64-77)	35.4	35.2	1,157	68 (62-75)	23.8	25.6
	III	6,137	70 (63-77)	21.0	21.0	984	68 (61-75)	21.1	22.0	Distant	14,743	69 (62-77)	50.1	49.4	3,425	68 (61-75)	70.4	71.7
	IV	14,637	69 (62-77)	50.1	49.5	3,408	68 (61-75)	73.1	71.8									
Denmark	All patients	8,045	70 (64-76)			1,491	70 (63-76)			All patients	8,045	70 (64-76)			1,491	70 (63-76)		
	Missing	216	72 (64-79)	2.7		40	75 (63-82)	2.7		Missing	102	71 (64-78)	1.3		20	79 (63-83)	1.3	
	I	580	70 (65-76)	7.4	8.0	23	71 (59-74)	1.6	1.6	Localised	1,372	71 (65-77)	17.3	18.2	50	71 (66-75)	3.4	3.3
	II	1,396	71 (65-77)	17.8	18.5	47	71 (65-76)	3.2	3.1	Regional	2,054	70 (63-76)	25.9	25.7	192	70 (64-77)	13.1	11.6
	III	1,750	70 (63-77)	22.4	21.3	271	69 (63-75)	18.7	16.6	Distant	4,517	69 (63-76)	56.9	56.1	1,229	70 (63-75)	83.5	85.1
	IV	4,103	69 (63-76)	52.4	52.2	1,110	70 (63-75)	76.5	78.7									
Ireland[¶]	All patients	3,522	70 (63-76)			542	67 (61-74)			All patients	3,522	70 (63-76)			542	67 (61-74)		
	Missing	493	73 (65-79)	14.0		79	70 (62-77)	14.6		Missing	258	72 (65-79)	7.3		36	73 (62-77)	6.6	
	I	286	70 (64-77)	9.4	9.3	9	63 (58-80)	1.9	2.6	Localised	651	71 (64-77)	19.9	20.4	23	63 (57-77)	4.5	5.0
	II	587	70 (64-76)	19.4	19.0	18	68 (62-78)	3.9	4.2	Regional	1,143	70 (63-77)	35.0	34.0	131	68 (62-74)	25.9	24.9
	III	865	69 (62-76)	28.6	28.7	110	67 (62-72)	23.8	23.3	Distant	1,470	68 (61-75)	45.0	45.6	352	67 (61-73)	69.6	70.1
	IV	1,291	68 (61-75)	42.6	43.0	326	67 (61-73)	70.4	69.9									
New Zealand	All patients									All patients	3,493	70 (63-77)			615	68 (61-75)		
	Missing									Missing	1,131	72 (65-79)	32.4		144	69 (61-76)	23.4	
	I									Localised	262	69 (63-74)	11.1	12.3	3	61 (59-83)	0.6	0.6*
	II									Regional	558	70 (62-75)	23.6	27.9	71	68 (62-73)	15.1	15.1*
	III									Distant	1,542	69 (61-76)	65.3	59.8	397	68 (60-75)	84.3	84.3*
	IV																	
Norway	All patients	5,286	70 (64-77)			1,068	69 (63-77)			All patients	5,286	69 (63-77)			1,068	69 (63-77)		
	Missing	1,167	71 (64-79)	22.1		330	69 (63-75)	30.9		Missing	113	75 (67-81)	2.1		36	73 (66-81)	3.4	
	I	514	71 (65-77)	12.5	13.4	16	74 (68-77)	2.2	3.0	Localised	1,167	71 (65-77)	22.6	22.0	80	72 (63-78)	7.8	8.0
	II	810	69 (64-76)	19.7	18.4	46	70 (65-77)	6.2	6.8	Regional	1,717	70 (64-77)	33.2	34.1	271	68 (62-76)	26.3	27.8
	III	1,017	70 (63-77)	24.7	23.1	186	68 (62-76)	25.2	23.7	Distant	2,289	69 (62-77)	44.2	43.9	681	69 (64-77)	66.0	64.2
	IV	1,778	69 (63-76)	43.2	45.1	490	70 (64-77)	66.4	66.6									
United Kingdom[‡]	All patients	71,098	71 (64-78)			12,335	70 (63-76)			All patients	71,098	71 (64-78)			12,335	70 (63-76)		
	Missing	24,093	71 (64-78)	33.9		4,175	70 (63-76)	33.8		Missing	18,958	72 (64-79)	26.7		3,683	70 (63-76)	29.9	
	I	6,285	72 (66-78)	13.4	13.8	179	71 (64-77)	2.2	2.4	Localised	9,563	72 (66-77)	18.3	17.0	258	71 (64-77)	3.0	2.8
	II	5,330	72 (65-78)	11.3	11.0	259	70 (64-78)	3.2	3.1	Regional	14,356	71 (64-77)	27.5	26.4	1,504	70 (64-76)	17.4	17.0
	III	11,278	71 (64-77)	24.0	23.6	1,812	69 (63-75)	22.2	22.3	Distant	28,221	70 (63-77)	54.1	56.7	6,890	70 (63-76)	79.6	80.2

	IV	24,112	70 (63-77)	51.3	51.6	5,910	70 (63-76)	72.4	72.3

† Canadian provinces included: Alberta, British Columbia, New Brunswick, Manitoba, Newfoundland, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan
‡ United Kingdom registries included: England, Northern Ireland, Scotland, and Wales
º Australia registries included: New South Wales
¶ Ireland: 2010-2013
* Model did not converge

Table 2B. Number and proportion of female patients with non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC) diagnosed during 2010-2014 by country and stage at diagnosis (TNM and SEER), before and after imputation

	TNM stage									Mapped SEER								
	NSCLC			%		SCLC		%		NSCLC			%		SCLC		%	
	Stage	Number	Median age at diagnosis	Observed	After imputation	Number	Median age at diagnosis	Observed	After imputation	Stage	Number	Median age at diagnosis	Observed	After imputation	Number	Median age at diagnosis	Observed	After imputation
Australia[º]	All patients									All patients	5,329	69 (62-77)			839	69 (61-76)		
	Missing									Missing	536	72 (64-81)	10.1		69	72 (64-79)	8.2	
	I									Localised	1,095	71 (64-77)	22.8	24.9	83	69 (60-76)	10.8	11.5
	II									Regional	1,272	69 (62-76)	26.5	26.6	206	69 (60-76)	26.8	25.2
	III									Distant	2,426	68 (60-77)	50.6	48.5	481	68 (61-75)	62.5	63.3
	IV																	
Canada†	All patients	28,827	69 (62-76)			4,809	69 (61-75)			All patients	28,827	69 (62-76)			4,809	69 (61-75)		
	Missing	1,745	71 (62-79)	6.1		189	70 (63-78)	3.9		Missing	1,534	71 (62-78)	5.3		155	70 (63-77)	3.2	
	I	6,421	70 (63-76)	23.7	25.0	155	72 (63-77)	3.4	3.8	Localised	5,072	70 (63-77)	18.6	19.8	129	71 (63-77)	2.7	3.1
	II	2,692	70 (62-76)	9.9	10.0	173	70 (64-77)	3.7	4.0	Regional	9,409	69 (62-76)	34.5	34.7	1,438	68 (60-75)	29.9	32.1
	III	5,250	69 (62-76)	19.4	19.5	1,229	68 (60-74)	26.6	27.5	Distant	12,812	68 (60-76)	46.9	45.5	3,087	69 (61-75)	64.2	64.8
	IV	12,719	68 (60-76)	47.0	45.5	3,063	69 (61-75)	66.3	64.7									
Denmark	All patients	7,545	69 (62-76)			1,500	69 (62-76)			All patients	7,545	69 (62-76)			1,500	69 (62-76)		
	Missing	180	74 (67-80)	2.4		44	65 (56-75)	2.9		Missing	74	74 (68-82)	1.0		14	71 (65-77)	0.9	
	I	768	69 (63-76)	10.4	11.8	23	69 (62-76)	1.6	1.9	Localised	1,543	70 (63-76)	20.7	22.5	52	69 (60-76)	3.5	4.0
	II	1,245	69 (62-76)	16.9	17.6	60	69 (62-76)	4.0	4.2	Regional	1,675	69 (62-76)	22.4	21.9	246	68 (62-75)	16.6	17.0
	III	1,450	68 (61-74)	19.7	17.9	327	68 (61-74)	21.8	23.1	Distant	4,253	69 (61-76)	56.9	55.6	1,188	69 (62-76)	79.9	79.0
	IV	3,902	69 (61-76)	53.0	52.7	1,046	69 (62-76)	69.7	70.7									
Ireland¶	All patients	2,484	69 (62-76)			547	68 (61-75)			All patients	2,484	69 (62-76)			547	68 (61-75)		
	Missing	310	73 (64-81)	12.5		96	71 (63-78)	17.6		Missing	148	76 (66-82)	6.0		48	72 (60-79)	8.8	
	I	358	69 (62-75)	16.5	16.9	11	65 (57-73)	2.4	2.6	Localised	632	69 (63-77)	27.1	28.4	27	69 (65-75)	5.4	6.2
	II	433	70 (63-77)	19.9	20.5	33	69 (63-80)	7.3	8.1	Regional	745	69 (62-76)	31.9	31.5	155	69 (62-76)	31.1	30.7
	III	540	69 (62-76)	24.8	24.8	132	68 (61-75)	29.3	30.3	Distant	959	68 (61-75)	41.1	40.1	317	67 (60-74)	63.5	63.1
	IV	843	68 (61-75)	38.8	37.8	275	67 (60-74)	61.0	58.9									
New Zealand	All patients									All patients	3,126	68 (61-75)			570	67 (59-74)		
	Missing									Missing	954	70 (63-77)	30.5		177	68 (59-73)	31.1	
	I									Localised	270	68 (62-73)	12.4	13.3	3	72 (67-75)	0.8	0.8*
	II									Regional	456	67 (60-73)	21.0	24.4	82	67 (58-74)	20.9	20.9*
	III									Distant	1,446	67 (59-75)	66.6	62.3	308	67 (59-74)	78.4	78.4*
	IV																	
Norway	All patients	4,128	69 (62-76)			1,029	68 (61-75)			All patients	4,128	68 (61-75)			1,029	68 (61-75)		
	Missing	895	69 (63-77)	21.7		354	68 (62-75)	34.4		Missing	89	69 (64-78)	2.2		29	75 (67-78)	2.8	
	I	589	68 (63-75)	18.2	17.5	26	65 (60-73)	3.9	3.3	Localised	1,067	69 (64-76)	26.4	25.9	85	68 (59-75)	8.5	8.0
	II	601	69 (63-75)	18.6	17.7	48	65 (59-75)	7.1	6.4	Regional	1,215	69 (62-76)	30.1	31.4	285	67 (60-73)	28.5	30.6
	III	677	69 (62-76)	20.9	20.4	167	67 (59-73)	24.7	26.1	Distant	1,757	68 (61-76)	43.5	42.6	630	68 (62-75)	63.0	61.4

	IV	1,366	68 (61-76)	42.3	44.4	434	68 (62-75)	64.3	64.3									
United Kingdom ‡	All patients	54,303	70 (63-77)			11,828	68 (62-75)			All patients	54,303	70 (63-77)			11,828	68 (62-75)		
	Missing	17,708	71 (63-78)	32.6		3,935	69 (62-76)	33.3		Missing	13,465	71 (64-79)	24.8		3,494	69 (62-76)	29.5	
	I	6,368	71 (64-77)	17.4	18.2	205	70 (63-77)	2.6	2.8	Localised	9,246	70 (64-76)	22.6	21.2	282	70 (63-77)	3.4	3.4
	II	3,856	71 (64-77)	10.5	10.3	269	69 (63-75)	3.4	3.4	Regional	10,429	70 (63-77)	25.5	24.8	1,615	68 (62-75)	19.4	19.0
	III	8,002	70 (63-77)	21.9	21.7	2,086	68 (61-75)	26.4	27.0	Distant	21,163	69 (62-77)	51.8	54.0	6,437	68 (62-75)	77.2	77.6
	IV	18,369	69 (62-77)	50.2	49.9	5,333	69 (62-75)	67.6	66.8									

† Canadian provinces included: Alberta, British Columbia, New Brunswick, Manitoba, Newfoundland, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan
‡ United Kingdom registries included: England, Northern Ireland, Scotland, and Wales
º Australia registries included: New South Wales
¶ Ireland: 2010-2013
* Model did not converge

For all stages combined, the age-standardised 1-year net survival for NSCLC among males was highest for Canada (48.1%) and lowest for Ireland (41.8%), New Zealand (41.5%) and the UK (40.8%) (**Figure 2A, Supplementary Table 11**). The 3-year net survival rates showed a similar pattern (between 19.7% and 27.1%). For females, the range was slightly wider for 1-year and 3-year net survival (between 48.3% and 57.8%, and 25.3 and 35.0%, respectively) (**Figure 2A, Supplementary Table 12**).

Sex-specific net survival varied substantially depending on stage at diagnosis, with little consistency in the ranking of countries at both 1-year and 3-years after diagnosis (**Figure 3A, Supplementary Tables 11-12**). For example, for males, Australia had the lowest 1-year net survival for localised tumours (81.6%), but the highest 1-year net survival for distant tumours (25.6%). Nevertheless, we observed that survival for males and females was consistently high across all (SEER) stages for Canada, whilst Ireland and the UK reported consistently lower survival.

Among males and females, both 1-year and 3-year survival for distant SEER stage was highest for Australia and lowest for the UK, respectively. Further, as seen for overall NSCLC, females had higher 1-year and 3-year net survival for all stages at diagnosis. Notable sex differences (i.e. >10% point difference) were observed at 1-year post diagnosis for regional NSCLC in New Zealand (Δ=10.7% point), Ireland (Δ=12.0% point), and Norway (Δ=11.4% point).

Similar differences in stage-specific net survival were observed when using TNM stage (**Figure 4A, Supplemental Tables 11-12**). Among the five countries that provided TNM stage, 1-year net survival for NSCLC with TNM stages II and III was significantly lower for males in Ireland, at 69.8% and 45.3% respectively, and the UK, at 76.3% (TNM stage II only), compared to Denmark (84.4% for stage II , 56.0% for stage III). Amongst cases diagnosed with stage IV disease, 1-year net survival was lowest at 18.8% for males in the UK, followed by Ireland (19.8%), Denmark (21.2%), Norway (21.8%), and finally Canada (23.6%). As for females, the lowest survival for all stages at both 1-year and 3-years post-diagnosis was observed for the UK and Ireland. The largest absolute differences in net survival between countries were observed for stages II and III, and there was an indication that survival was more homogeneous for stage IV, particularly for 3-year net survival where the absolute difference between Canada (highest) and the UK (lowest) was only 3.7 percentage points.

Small Cell Lung Carcinoma

Approximately 70% of SCLC patients were diagnosed with stage IV or distant disease (**Table 2A and 2B, Figure 1B**), although some variation was observed between countries and sexes; for example, New Zealand had the largest proportion of patients diagnosed with distant disease at 84.3% for males and 78.4% for females. Females had a more favourable stage distribution compared to males.

One-year net survival ranged for males from 25.0% in New Zealand and the UK to 31.8% in Australia, and for females 31.2% in the UK to 39.2% in Canada (**Figure 2B, Supplementary Tables 13-14**). Canada and Norway had the highest 3-year net survival for both males and females, though differences between the seven countries were minimal. There were large disparities in net survival between sexes, in particular at 1-year after diagnosis, with 1-year net survival for females being 6.2 percentage points (UK) to 10.6 percentage points (Canada) higher than that observed for males.

Differences by SEER stage in net survival between the seven countries were also found (**Figure 3B, Supplementary Tables 13-14**). Among males with localised SCLC, 1-year net survival was lower in Australia (58.3%) and Norway (58.6%) than in Canada (82.2%) and Denmark (79.5%). For cases with regional and distant disease, males in Denmark had the highest 1-year net survival at 63.0% and 24.3%, respectively; whereas for regional disease, 1-year survival was lowest for males in Ireland and New Zealand, and Norway and New Zealand had the lowest survival for distant cases. Net survival at 3-years among male patients showed similar patterns. For females, 1-year and 3-year net survival was highest in Denmark for most stages. New Zealand and Norway had lower survival for most stages along with Ireland and the UK, though most notable was the low survival observed for females with localised stage in Australia (62.8%) at one year post diagnosis (**Supplementary Table 14**).

Net survival by TNM stage is shown in **Figure 4B** (**Supplemental Tables 13-14**). In general, similar differences in stage-specific net survival were observed when using TNM stage. For example, for females, 1-year net survival for stage III SCLC ranged from 49.1% in Ireland to 56.3% in Canada; the corresponding 3-year net survival ranged from 15.6% in the UK to 24.2% in Canada. As with NSCLC, the survival differences among the countries investigated were largest for stages II and III.

Within country differences

While it was beyond the scope of this manuscript to explore within-country disparities for NSCLC and SCLC survival in detail, the best outcomes in Canada were generally observed for Manitoba and New Brunswick while the worst outcomes were observed for Prince Edward Island and Nova Scotia, although the differences were not always statistically significant due to low statistical power for the latter jurisdictions (**Supplemental Tables 6-10, 15-20**). In the UK, survival for NSCLC and SCLC appeared to be highest in Scotland for early disease stages, with survival at advanced stages being generally comparable across the four jurisdictions.

DISCUSSION

In this study, discrepancies in lung cancer survival were evident across countries by sex, histological group and stage, with higher survival observed for Canada and Norway, and lower survival in the UK, New Zealand and Ireland. Survival was consistently higher for females (for all stage and histological groups) and for NSCLC. Variations in stage distribution and stage-specific survival estimates were apparent and may partly explain international survival differences. Net survival within stage groups varied across countries whereby survival was consistently higher across stages of disease for Canada and Denmark, and consistently lower for Ireland and the UK.

A previous study of a similar group of countries reported 1-year net survival among lung cancer cases diagnosed from 2004-2007.[2] Despite differences in study methods, generally we obtained similar results with respect to survival differences by histological group and stage, as well as the countries' rankings. Similar findings were also noted in another study investigating lung cancer survival in Europe for 1999-2007, where Ireland and the UK generally exhibited lower survival.[15] Nonetheless, a decade later, we observed improved survival for lung cancer for all countries,[8] as well as higher stage-specific survival particularly for NSCLC in this study. However, the contribution of stage migration to the apparent improvement in stage-specific survival cannot be completely ruled out. For example, the migration due to coding stage III to stage IV disease resulting from increased sensitivity and utilization of novel imaging techniques, such as positron emission tomography.

Our findings show that females generally are diagnosed at an earlier stage and have better survival outcomes than men. This is in line with previous studies[3-6] evaluating the effect of sex on

lung cancer prognosis and several potential reasons for this observation have been proposed. Firstly, adenocarcinoma lung cancer is the predominant subtype of NSCLC and is more common among females than males. As adenocarcinoma lung cancer is associated with being a never smokers[16] and having a better response to treatment[17], we would expect that females would experience better NSCLC survival compared to males because there is a higher proportion of these favourable cases. Secondly, adenocarcinoma that has a wider spectrum of growth rate with some being quite indolent is generally diagnosed at earlier stages compared to other histological types[18], which corresponds with our finding that a higher proportion of females present with early stage disease, though this may also be due to more frequent and earlier medical consultations. Finally, several studies[19-21] have also suggested that female sex may be a positive prognostic factor in itself[21 22], irrespective of age, stage, period of diagnosis and histological groups. Further, mutations in epidermal growth factor receptor have been shown to be more prevalent in females, which may lead to survival advantages.[23,24]

Net survival for SCLC was consistently lower compared to that for NSCLC in all countries. This corresponds with the fact that SCLC tends to grow and spread faster than NSCLC, exemplified by previous research that found larger proportions of individuals with SCLC compared with NSCLC diagnosed at advanced stage or with co-morbid illnesses, which may lead to fewer patients being considered for curative treatment.[25] For example, in Norway, only 1.7% of patients with SCLC received surgery compared to 18.1% of those with any lung cancer in the period 2002-2011.[26] While we observed considerable differences in 1-year net survival across countries for SCLC, disparities were much smaller at 3 years, which may be explained by the high fatality rate of SCLC regardless of available treatments.[27]

Disparities observed for NSCLC between countries may partly relate to varying proportions with squamous cell carcinoma, large cell carcinoma, and adenocarcinoma, together forming the group with NSCLC. For example, for NSCLC, 50% were adenocarcinomas for Canadian males compared with 40% for males in the UK with a similar difference for females (62% versus 51% respectively). As a result, the UK had a larger proportion of squamous cell carcinomas which are associated with lower survival overall compared to adencarcinoma.[28] Unfortunately further stratification of the NSCLC by finer histological groupings was not possible due to insufficient statistical power. Similarly, the UK and New Zealand had larger proportions with NSCLC and SCLC diagnosed at later stages compared to other countries suggesting that countries like

Canada may detect cancers earlier, although a formal recommendation for lung cancer screening was made in Canada after our study period in 2016.[29]

Although differences in stage distribution will account for some of the survival disparities between countries, differences in stage-specific survival were also evident across countries in our study. These absolute differences were most pronounced for localised and regional stage disease, and may relate to the variability in treatment and management. For example, as surgical resection offers the only realistic chance of cure for lung cancer,[30] differences in rates of surgery may partly explain survival differences in patients with localised and regional lung cancer. Differences in prehabilitation prior to lung cancer surgery or age at diagnosis across countries are other factors that may explain the observed survival differences.[31] For example, the median age of patients with NSCLC in the UK was generally higher than that for other countries at each cancer stage. Previous studies have shown that patients at older ages are more likely to have comorbid conditions, which are known predictors of treatment decisions and poorer outcomes including survival.[32] Whilst historically only around 9% of NSCLC patients in the UK underwent surgery, the current percentage is 18% according to the National Lung Cancer Audit 2018 annual report, which is above the national standard.[33] Combined with the other improvements in lung cancer care in the UK, including recent adoption of immunotherapy and increases in pathological confirmation of cancer and overall cancer care[33], we expect to see improvements in stage-specific survival in the next ICBP iteration.

A strength of our study is that all data are from high-quality population-based cancer registries, which were additionally standardised and checked using a predefined protocol. All results were validated and interpreted with the input of local experts, including registry experts, epidemiologists and clinicians from each country. Yet, a number of limitations should be noted. First, there is still a substantial proportion of cases with unknown histology, ranging between 11% and 29% across the seven countries. While survival for these cases is typically lower than for cases with known histology, the size of this group might have affected survival estimates for SCLC and NSCLC. In a complementary paper, we showed that while the proportion of lung cancer cases with unknown histology has an impact on survival estimates for “known” histology groups, the inclusion and/or reallocation of these individuals does not change international rankings or overall patterns we see across countries[34]. Second, when mapping information from different staging systems, there is potential for misclassification, which might have affected the reported stage distributions and corresponding survival estimates. When analyses were restricted to cases with both SEER and

TNM information, discrepancies in the final summary stage were found for 8% of all cases and this affected the estimated survival for localised and regional stage disease only (results not shown). Nonetheless, differences in cancer registration practices and staging systems used should be taken into account when interpreting the results of this paper.[35] Finally, missing information on stage at diagnosis presents another potential concern when conducting survival comparisons by stage across countries. To some extent, we mitigated the issue of differential missingness across countries by running imputation models separately by country (or jurisdiction) and by including measures of survival time in the models. In sensitivity analyses, we showed that both approaches (with and without imputation) led to very similar results. Yet, there are factors that cannot be taken into account in multiple imputation models that may influence missingness of stage information such as differences in registration practices[36] and this may have affected our results. Including information such as comorbidity or performance status may improve the imputation and also further our understanding on the causes of survival difference by stage across countries.

In conclusion, this study provides more recent estimates of stage-specific lung cancer survival for seven high-income countries with comparison for the two main histological types and investigating differences by sex. Whilst wide international disparities in lung cancer survival persist, this study illustrates the favourable prognosis for NSCLC cases and early stage lung cancers for females. It is also evident that differences in stage distribution across sex groups, histological types and countries partly explain better lung cancer survival, yet international differences were also observed for stage-specific survival suggesting that factors linked to disease treatment and management, such as rates of high-quality surgery, utilisation of targeted therapy or rehabilitation with increased focus on smoking and physical activity, may be contributing to international disparities in lung cancer survival. As the largest disparities were noted for regional stage disease, the opportunity for intervention may be greatest for this group. Finally, it is recommended that efforts should be made, and resources allocated, to improve the availability and comparability of stage data across countries. This will enable further research to understand the reasons behind international differences in stage-specific survival, which may fuel policy development and optimise prognosis.

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STATEMENTS

a. Authors contributorship

MAr and MMF-B analysed the data and drafted and revised the paper. MA, MR and AB wrote the statistical analysis plan, monitored data collection for the study, and revised the draft paper, JF prepared the study protocol, monitored data collection and data harmonisation for the study, and revised the draft paper, OB, PD, GE, AG, SK, AL, BM, NSJ, HT, PW, RW prepared the study

protocol, collected the data, contributed to the analytical plan and revised the draft of the paper, DOC, DB, ME, SS commented on the analytical plan, study results and revised the draft of the paper, FB and IS designed study, data collection tools, monitored data collection for the study, wrote the statistical analysis plan, and drafted and revised the paper. IS is the guarantor of the study.

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c. Competing interests
The authors declare no relevant competing interests

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e. Ethics statement
The study has been approved by the IARC ethical committee. Meeting reference: EC 2016-04; and Project reference: 16-36.

DICLAIMER
Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this

article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

LIST OF TABLES AND FIGURES

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