Global variations in lung cancer incidence by histological subtype in 2020: a population-based study

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Summary

Background Lung cancer is the second most common cancer worldwide, yet the distribution by histological subtype remains unknown. We aimed to quantify the global, regional, and national burden of lung cancer incidence for the four main subtypes in 185 countries and territories.

Methods In this population-based study, we used data from Cancer Incidence in Five Continents Volume XI and the African Cancer Registry Network to assess the proportions of adenocarcinoma, squamous cell carcinoma, small-cell carcinoma, and large-cell carcinoma among all lung cancers by country, sex, and age group and subsequently applied these data to corresponding national (GLOBOCAN) estimates of lung cancer incidence in 2020. Unspecified morphologies were reallocated to specified subtypes. Age-standardised incidence rates were calculated using the world standard population to compare subtype risks worldwide, adjusted for differences in age composition between populations by country.

Findings In 2020, there were an estimated 2 206 771 new cases of lung cancer, with 1 435 943 in males and 770 828 in females worldwide. In males, 560 108 (39%) of all lung cancer cases were adenocarcinoma, 351 807 (25%) were squamous cell carcinoma, 163 862 (11%) were small-cell carcinoma, and 115 322 (8%) were large-cell carcinoma cases. In females, 440 510 (57%) of all lung cancer cases were adenocarcinoma, 91 070 (12%) were squamous cell carcinoma, 68 224 (9%) were small-cell carcinoma, and 49 246 (6%) were large-cell carcinoma cases. Age-standardised incidence rates for adenocarcinoma, squamous cell carcinoma, small-cell carcinoma, and large-cell carcinoma, respectively, were estimated to be 12·4, 7·7, 3·6, and 2·6 per 100 000 person-years in males and 8·3, 1·6, 1·3, and 0·9 per 100 000 person-years in females worldwide. The incidence rates of adenocarcinoma exceeded those of squamous cell carcinoma in 150 of 185 countries in males and in all 185 countries in females. The highest age-standardised incidence rates per 100 000 person-years for adenocarcinoma, squamous cell carcinoma, small-cell carcinoma, and large-cell carcinoma, respectively, for males occurred in eastern Asia (23·5), central and eastern Europe (17·5), western Asia (7·2), and south-eastern Asia (11·0); and for females occurred in eastern Asia (16·0), northern America (5·4), northern America (4·7), and south-eastern Asia (3·4). The incidence of each subtype showed a clear gradient according to the Human Development Index for male and female individuals, with increased rates in high and very high Human Development Index countries.

Interpretation Adenocarcinoma has become the most common subtype of lung cancer globally in 2020, with incidence rates in males exceeding those of squamous cell carcinoma in most countries, and in females in all countries. Our findings provide new insights into the nature of the global lung cancer burden and facilitates tailored national preventive actions within each world region.

Funding None.

Lancet Oncol 2023

Published Online October 11, 2023 https://doi.org/10.1016/S1470-2045(23)00444-8

See Online/Comment https://doi.org/10.1016/S1470-2045(23)00475-8

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Introduction

With an estimated 2·2 million new cases and 1·8 million deaths in 2020, lung cancer is the second most common cancer and the leading cause of cancer-related death worldwide.[1] Lung cancer incidence varies considerably by geographical region and sex.[1,2] More than half of all new lung cancer cases occur in Asia, and the frequency of occurrence in male individuals is double that of female individuals.[1]

The major histological subtypes of lung cancer are adenocarcinoma, squamous cell carcinoma, small-cell carcinoma, and large-cell carcinoma.[3] The observed geographical patterns and temporal trends in lung cancer incidence by histological subtype vary greatly across countries,[3,4] and these disparities are considered to be related to differences in current and historical smoking patterns, changes in cigarette composition, and exposures to other lung carcinogens.[3,5] Given the recent discovery of a novel causal mechanism linking air pollution to the risk of adenocarcinoma of the lung,[6] a quantification of the proportions of the main histological subtypes at country level could provide improved understanding of the epidemiological profile of lung cancer incidence

Research in context

Evidence before this study

We searched PubMed on Jan 1, 2023, with no date restrictions, using the search terms ("lung cancer") AND ("subtype" OR "subsite" OR "histology") AND ("global" OR "international" OR "worldwide") AND ("incidence" OR "morbidity" OR "mortality" OR "burden") for Articles in English. A previous study reported lung cancer incidence based on histological subtypes from 1973 to 2002 in 11 high and very high human development index countries. However, we identified no publication that had quantified the recent burden of lung cancer incidence by histological subtype on a global scale.

Added value of this study

To our knowledge, we provide for the first time a quantitative assessment of the epidemiological profile of lung cancer incidence by histological subtype in 185 countries and territories, documenting the substantial variations across world regions and their constituent countries. A novel finding is the extent to which adenocarcinoma leads as the most common subtype of lung cancer globally in 2020, with incidence rates among females exceeding those for squamous cell carcinoma in all countries studied. Given the accumulating evidence of causal mechanisms linking air pollution to the risk of adenocarcinoma and the impact of changes in smoking prevalence and cigarette composition on the epidemiological profile of lung cancer, this study aimed to facilitate the national implementation of tailored approaches to lung cancer prevention across the world regions.

Implications of all the available evidence

Understanding the epidemiological profile of lung cancer incidence according to histological subtype can help health specialists gain insights on how to tailor cancer control policies in countries and world regions. Our findings provide important evidence for policy makers seeking to plan appropriate tobacco and other control strategies and optimise the allocation of resources accordingly.

and aid implementation of tailored approaches to primary prevention.

Although a previous study reported the incidence of lung cancer according to histological subtype from 1973 to 2002 in 11 high-income countries,[3] recent and comprehensive epidemiological data on the incidence of lung cancer histological subtypes are still needed. In this study, we provide the first comprehensive assessment of the incidence of lung cancer for the main four histological subtypes at the global, world region, and country level, incorporating incidence data from population-based cancer registries alongside GLOBOCAN estimates of the cancer burden developed at the International Agency for Research on Cancer (IARC) for the year 2020.

Methods

Study design and procedures

In this population-based study, the estimated numbers of new lung cancer cases (International Classification of Diseases, Tenth Revision [ICD-10 C33-34]) by country, sex, and age in 2020 were extracted on Jan 1, 2023, from the GLOBOCAN database as presented in the International Agency for Research on Cancer's Global Cancer Observatory (GCO) for the year 2020. The national estimates were derived for 185 countries and territories with populations of more than 150 000 inhabitants in the same year, and for world regions as defined by the UN Standard Country or Area Codes for Statistical Use and listed in the GCO.[7] To obtain representative site-specific proportions of lung cancer cases by country or by world region when country-specific information was not available, we used data from Cancer Incidence in Five Continents Volume XI (CI5-XI),[8] which contains high-quality cancer incidence data from 2008 to 2012 from 343 cancer registries worldwide, complemented with data submitted from population-based cancer registries used to obtain the national estimates for 2020 compiled in the GLOBOCAN database, and supplemented by updated data from registries for sub-Saharan Africa that are members of the African Cancer Registry Network (AFCRN). In total, incidence data from 95 countries were available.

For the **International Agency for Research on Cancer's Global Cancer Observatory** see https://gco.iarc.fr/today

Data were extracted from the CI5-XI and AFCRN databases on the basis of the third edition of the International Classification of Diseases for Oncology (ICD-O-3) groupings: (1) adenocarcinoma: 8140, 8211, 8230–8231, 8250–8260, 8323, 8480–8490, 8550–8552, 8570–8574, and 8576; (2) squamous cell carcinoma: 8050–8078 and 8083–8084; (3) small-cell carcinoma: 8041–8045; (4) large-cell carcinoma: 8010–8012, 8014–8031, 8035, and 8310; (5) other specified carcinomas, including non-small-cell carcinoma (8046), carcinoid tumours (8240–8245), adenoid cystic (8200), mucoepidermoid (8430), adenosquamous (8560), and large-cell neuroendocrine (8013) carcinomas; (6) sarcoma: 8800–8811, 8830, 8840–8921, 8990–8991, 9040–9044, 9120–9133, 9150, and 9540–9581; (7) other morphology: all remaining histology codes; and (8) unspecified morphology: 8000–8005. To avoid basing calculations on cancer registry data that clearly lacked histological specificity, we excluded registries that had unspecified lung cancer histology for more than 25% of cases, which is consistent with previously published papers.[3,4] The proportions of each histological group according to registry, sex, and 5-year age group were calculated and used to proportionally re-allocate cases with unspecified morphology (group 8) to the known morphological subtypes (groups 1–7). The reallocation procedure has been shown to perform robustly in previous studies.[3,4,9,10]

Ethical approval was not required for this study because it used existing non-identifiable data that were aggregated and population-level.

Statistical analysis

We calculated country-specific, sex-specific, and age-specific (<65 and ≥65 years) proportions of all four histological subtypes, with the sum of all new lung cancer cases as the denominator, based on the CI5-XI and AFCRN databases.[10–12] We selected the age strata used in many previous studies (<65 and ≥65 years)[10,11] to reflect the differences in the distribution of lung cancer subtypes between younger and older age groups while allowing for sufficient numbers in each group. When data were available from more than one cancer registry within a country, they were pooled to obtain national proportions.[2,10–12] National-level proportions could be calculated for 50 countries (appendix pp 3–12).

For the remaining 135 countries without registry data included in the CI5-XI and AFCRN databases, we calculated regional proportions based on aggregated country-level data and then applied to country-specific subsite proportions.[10–12] We calculated the corresponding proportions of each histological subtype on the basis of the sum of all new lung cancer cases as the denominator by world region, sex, and age group (<65 and ≥65 years). These estimates were considered proxies of the true proportion of each lung cancer histological subtype in constituent countries when cancer registry data were not available locally. We included all countries with available data in the defined regions to estimate these regional proportions. Countries were categorised into the following UN-defined world regions:[11,12] northern Europe, western Europe, southern Europe, central and eastern Europe, northern America, south America, the Caribbean and central America, eastern Asia (including China), south-central Asia (including India), south-eastern Asia, western Asia, Oceania, northern Africa, and sub-Saharan Africa (including eastern, middle, southern, and western Africa). The resulting proportions were multiplied by the total number of new lung cancer cases by sex and 5-year age group for each corresponding country in GLOBOCAN 2020 to calculate the number of new lung cancer cases by histological subtype.[10–12] These methods have previously performed well empirically and provide robust estimates of cancer incidence by histological subtype for 185 countries and territories compiled in the GLOBOCAN database.[10–12]

As well as crude incidence rates (CIR, per 100 000 person-years), we calculated age-standardised incidence rates (ASRs; per 100 000 person-years) by sex, using the world standard population[13] for 185 countries and territories and 14 world regions, and we characterised the burden of each subtype across four tiers of Human Development Index (HDI) values (low, medium, high, and very high). Confidence intervals for incidence rates and related ratios could not be calculated because of the absence of data on histological specificity in many countries. The HDI is a composite measure of key dimensions of human development (population health, knowledge, and standards of living).[1] We also presented the findings for selected large countries (China, India, the USA, and Indonesia) and the European Union of 27 member states.

In our post-hoc sensitivity analysis, we compared the case counts and ASRs of lung cancer by histological subtype when registry datasets with more than 75% of cases having unspecified histology were excluded,[9,10] relative to the default exclusion of more than 25%, as applied in the main results in this study.

We did all data management and analyses in R (version 4.0.2). We plotted figures using R (version 4.0.2) and SigmaPlot (version 12.5; Systat Software, San Jose, CA, USA). We plotted maps using ArcGIS (version 10.6; Esri, Redlands, CA, USA).

See Online for appendix

Role of the funding source

There was no funding source for this study.

Results

Lung cancer incidence data by histological subtype were collected from 363 cancer registries from CI5-XI and AFCRN databases (appendix pp 13–22). Considerable variations in the proportions of unspecified lung cancer morphology were noted across registries worldwide, with the mean proportion of cases with unspecified histology being 28·6% (SD 20·3; appendix pp 13–22). 168 (46%) of 363 registries were excluded because the histology of lung cancer was unspecified in more than 25% of cases in these registries, such that 195 (54%) registries were included in the main analysis.

In 2020, an estimated 1 435 943 new cases of lung cancer worldwide occurred in males, of which 560 108 (39%) were adenocarcinoma, 351 807 (25%) were squamous cell carcinoma, 163 862 (11%) were small-cell carcinoma, and 115 322 (8%) were large-cell carcinoma cases (table 1). An estimated 770 828 new cases of lung cancer worldwide occurred in females, of which 440 510 (57%) were adenocarcinoma, 91 070 (12%) were squamous cell carcinoma, 68 224 (9%) were small-cell carcinoma, and 49 246 (6%) were large-cell carcinoma cases (table 2). 1 272 081 (89%) cases in 1 435 943 males and 702 604 (91%) cases in 770 828 females were non-small-cell lung cancer (including adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma, as well as other lung cancer subtypes). Of the four most common subtypes, most cases were diagnosed in males (560 108 [56%] of 1 000 618 adenocarcinoma cases, 351 807 [79%] of 442 877 squamous cell carcinoma cases, 163 862 [71%] of 232 086 small-cell carcinoma cases, and 115 322 [70%] of 164 568 large-cell carcinoma cases).

Adenocarcinoma was the most frequently diagnosed subtype of lung cancer in males across all world regions, except for central and eastern Europe, western Asia, south-eastern Asia, and northern Africa, and was the

	Adenocarcinoma			Squamous cell carcinoma			Small-cell carcinoma			Large-cell carcinoma		
	Proportion of total lung cancer cases, % (n/N)*	Crude incidence rate†	Age-standardised incidence rate†	Proportion of total lung cancer cases, % (n/N)*	Crude incidence rate†	Age-standardised incidence rate†	Proportion of total lung cancer cases, % (n/N)*	Crude incidence rate†	Age-standardised incidence rate†	Proportion of total lung cancer cases, % (n/N)*	Crude incidence rate†	Age-standardised incidence rate†
Global	39% (560 108/1 435 943)	14·3	12·4	25% (351 807/1 435 943)	9·0	7·7	11% (163 862/1 435 943)	4·2	3·6	8% (115 322/1 435 943)	2·9	2·6
Northern Europe	36% (14 120/39 413)	27·1	12·3	29% (11 578/39 413)	22·2	9·5	15% (6003/39 413)	11·5	5·2	5% (1920/39 413)	3·7	1·6
Western Europe	39% (34 635/89 646)	36·2	16·6	31% (27 352/89 646)	28·6	12·3	15% (13 275/89 646)	13·9	6·2	7% (6059/89 646)	6·3	2·8
Southern Europe	34% (24 817/74 009)	33·5	14·9	30% (22 240/74 009)	30·0	12·7	13% (9787/74 009)	13·2	6·0	11% (8349/74 009)	11·3	4·8
Central and eastern Europe	18% (20 093/111 986)	14·6	8·9	36% (40 257/111 986)	29·2	17·5	13% (14 677/111 986)	10·7	6·5	10% (10 750/111 986)	7·8	4·7
Northern America	37% (48 378/129 086)	26·1	13·3	28% (36 042/129 086)	19·4	9·7	13% (17 211/129 086)	9·3	4·8	4% (5150/129 086)	2·8	1·4
South America	33% (14 939/44 878)	7·0	6·2	30% (13 361/44 878)	6·3	5·5	10% (4335/44 878)	2·0	1·8	10% (4478/44 878)	2·1	1·8
Caribbean and central America	40% (4987/12 468)	4·6	4·4	28% (3471/12 468)	3·2	3·0	10% (1286/12 468)	1·2	1·1	8% (1011/12 468)	0·9	0·9
Eastern Asia	47% (317 849/670 827)	38·2	23·5	21% (140 024/670 827)	16·8	10·0	11% (70 902/670 827)	8·5	5·1	3% (16 957/670 827)	2·0	1·2
South-central Asia	36% (31 300/88 130)	3·0	3·4	19% (16 398/88 130)	1·6	1·8	12% (10 670/88 130)	1·0	1·2	17% (14 979/88 130)	1·4	1·7
South-eastern Asia	27% (23 542/85 795)	7·0	7·1	12% (9902/85 795)	2·9	3·0	6% (4997/85 795)	1·5	1·5	43% (36 611/85 795)	10·9	11·0
Western Asia	25% (11 657/47 146)	7·8	10·9	36% (16 805/47 146)	11·2	16·1	16% (7691/47 146)	5·1	7·2	4% (1822/47 146)	1·2	1·7
Oceania	37% (3397/9277)	15·6	10·1	24% (2245/9277)	10·3	6·5	12% (1112/9277)	5·1	3·3	10% (905/9277)	4·2	2·6
Northern Africa	26% (5100/19 310)	4·0	5·5	44% (8475/19 310)	6·7	9·1	5% (869/19 310)	0·7	0·9	23% (4434/19 310)	3·5	4·7
Sub-Saharan Africa	38% (5294/13 972)	1·0	2·1	26% (3657/13 972)	0·7	1·5	7% (1047/13 972)	0·2	0·4	14% (1897/13 972)	0·3	0·8
Very high HDI	34% (206 620/611 867)	27·0	14·0	30% (186 287/611 867)	24·3	12·5	13% (81 999/611 867)	10·7	5·6	7% (40 454/611 867)	5·3	2·8
High HDI	45% (310 870/697 411)	21·3	16·7	20% (140 141/697 411)	9·6	7·5	10% (68 933/697 411)	4·7	3·7	7% (48 251/697 411)	3·3	2·6
Medium HDI	34% (39 297/116 316)	3·3	3·9	20% (22 892/116 316)	1·9	2·3	10% (12 082/116 316)	1·0	1·2	21% (24 958/116 316)	2·1	2·5
Low HDI	34% (3319/9713)	0·7	1·5	26% (2487/9713)	0·5	1·2	9% (848/9713)	0·2	0·4	17% (1661/9713)	0·3	0·7

HDI=Human Development Index. *Row proportion of all lung cancer cases in 2020. †Per 100 000 person-years.

Table 1: **Estimated crude incidence rate, age-standardised incidence rate, and numbers and proportions of lung cancer by subtype in 2020, world region, and HDI, in males**

	Adenocarcinoma			Squamous cell carcinoma			Small-cell carcinoma			Large-cell carcinoma		
	Proportion of total lung cancer cases, % (n/N)*	Crude incidence rate†	Age-standardised incidence rate†	Proportion of total lung cancer cases, % (n/N)*	Crude incidence rate †	Age-standardised incidence rate†	Proportion of total lung cancer cases, % (n/N)*	Crude incidence rate †	Age-standardised incidence rate †	Proportion of total lung cancer cases, % (n/N)*	Crude incidence rate†	Age-standardised incidence rate†
Global	57% (440 510/770 828)	11·3	8·3	12% (91 070/770 828)	2·3	1·6	9% (68 224/770 828)	1·8	1·3	6% (49 246/770 828)	1·3	0·9
Northern Europe	45% (16 120/35 638)	30·2	12·5	19% (6672/35 638)	12·5	4·6	17% (6088/35 638)	11·4	4·6	4% (1531/35 638)	2·9	1·2
Western Europe	51% (29 197/56 814)	29·4	13·1	15% (8646/56 814)	8·7	3·6	16% (9224/56 814)	9·3	4·1	6% (3626/56 814)	3·7	1·6
Southern Europe	51% (15 368/30 382)	19·7	8·4	14% (4169/30 382)	5·4	2·2	11% (3420/30 382)	4·4	1·9	11% (3303/30 382)	4·2	1·7
Central and eastern Europe	27% (10 599/39 646)	6·8	3·1	20% (7875/39 646)	5·1	2·3	16% (6366/39 646)	4·1	2·0	11% (4328/39 646)	2·8	1·2
Northern America	45% (56 167/124 451)	29·8	13·7	19% (23 650/124 451)	12·5	5·4	15% (18 857/124 451)	10·0	4·7	4% (4402/124 451)	2·3	1·0
South America	50% (15 924/31 731)	7·3	5·3	12% (3955/31 731)	1·8	1·3	11% (3514/31 731)	1·6	1·1	9% (2784/31 731)	1·3	0·9
Caribbean and central America	57% (4876/8524)	4·4	3·6	14% (1221/8524)	1·1	0·9	7% (573/8524)	0·5	0·4	6% (494/8524)	0·4	0·4
Eastern Asia	72% (246 803/341 194)	30·6	16·0	7% (23 592/341 194)	2·9	1·4	4% (12 569/341 194)	1·6	0·7	2% (5563/341 194)	0·7	0·3
South-central Asia	47% (15 638/33 239)	1·6	1·6	11% (3748/33 239)	0·4	0·4	9% (3132/33 239)	0·3	0·3	19% (6164/33 239)	0·6	0·6
South-eastern Asia	40% (15 056/37 514)	4·5	3·7	6% (2429/37 514)	0·7	0·6	3% (1312/37 514)	0·4	0·3	37% (13 977/37 514)	4·2	3·4
Western Asia	48% (5427/11 291)	4·0	4·3	14% (1580/11 291)	1·2	1·2	12% (1411/11 291)	1·0	1·1	5% (523/11 291)	0·4	0·4
Oceania	46% (3571/7698)	16·5	10·0	15% (1153/7698)	5·3	3·0	13% (1000/7698)	4·6	2·8	8% (652/7698)	3·0	1·8
Northern Africa	42% (1613/3869)	1·3	1·5	24% (914/3869)	0·7	0·8	3% (97/3869)	0·1	0·1	12% (459/3869)	0·4	0·4
Sub-Saharan Africa	47% (4151/8837)	0·7	1·4	17% (1466/8837)	0·3	0·5	7% (661/8837)	0·1	0·2	16% (1440/8837)	0·3	0·5
Very high HDI	48% (176 286/363 798)	22·5	10·1	16% (58 987/363 798)	7·5	3·2	14% (49 852/363 798)	6·4	2·9	6% (20 524/363 798)	2·6	1·2
High HDI	68% (238 305/350 296)	16·6	11·0	7% (26 008/350 296)	1·8	1·2	4% (14 271/350 296)	1·0	0·6	5% (17 405/350 296)	1·2	0·8
Medium HDI	46% (22 738/49 627)	2·0	2·1	10% (5139/49 627)	0·4	0·5	7% (3663/49 627)	0·3	0·3	20% (10 015/49 627)	0·9	0·9
Low HDI	47% (3182/6705)	0·6	1·2	14% (938/6705)	0·2	0·4	7% (441/6705)	0·1	0·2	19% (1303/6705)	0·3	0·5

HDI=Human Development Index. *Row percentage of all lung cancer cases in 2020. †Per 100 000 person-years.

Table 2: **Estimated crude incidence rate, age-standardised incidence rate, and numbers and proportions of lung cancer by subtype in 2020, world region, and HDI, in females**

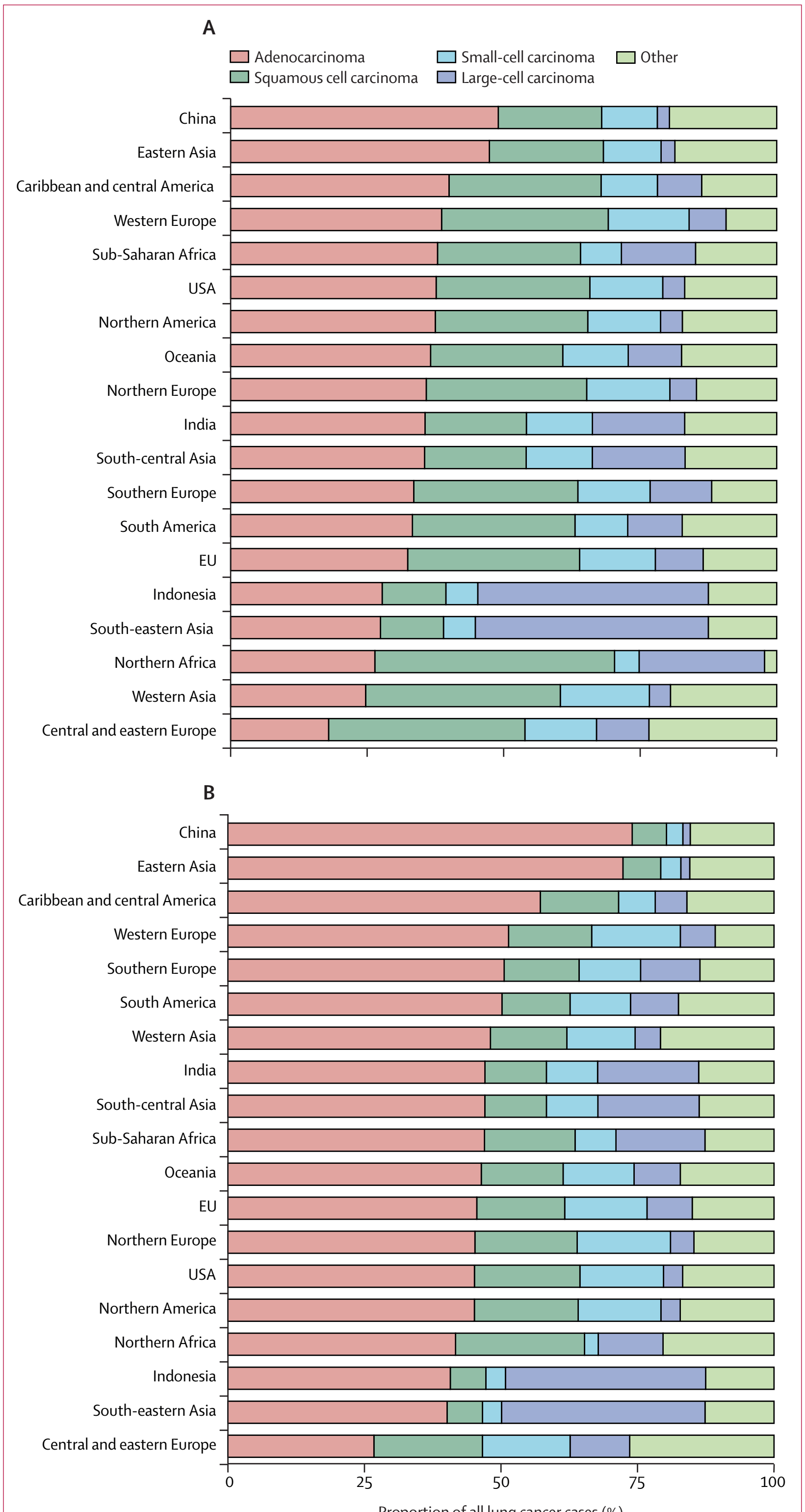


Figure 1: **Proportions of the four histological subtypes of lung cancer by world region, as well as selected countries or region, in males (A) and females (B) in 2020**
EU refers to all 27 countries (excluding the UK) in the European Union as of February, 2020.

most common subtype in females across all world regions (figure 1; tables 1, 2). Squamous cell carcinoma was more common than other subtypes in males in central and eastern Europe, western Asia, and northern Africa (table 1). By region, the greatest number of adenocarcinoma cases in both sexes occurred in eastern Asia (317 849 [57%] of 560 108 adenocarcinoma cases in males globally and 246 803 [56%] of 440 510 cases in females globally), followed by northern America (48 378 [9%] and 56 167 [13%]) and western Europe (34 635 [6%] and 29 197 [7%]; appendix pp 47–48). The largest number of squamous cell carcinoma cases were estimated to occur in eastern Asia (140 024 [40%] of 351 807 world cases), followed by central and eastern Europe (40 257 [11%]) and northern America (36 042 [10%]) in males, and in northern America (23 650 [26%] of 91 070 world cases), followed by eastern Asia (23 592 [26%]) and western Europe (8646 [9%]) in females (appendix pp 47–48).

According to the four-tier HDI grouping, most cases of adenocarcinoma, squamous cell carcinoma, small-cell carcinoma, and large-cell carcinoma (tables 1, 2; appendix pp 49–50) occurred in nations with high and very high HDI values, with these high and very high HDI countries representing 57% (4 447 040 765 of 7 812 143 910) of the world population.

At the national level, in males, due to their large populations and high incidence rates, China, the USA, and Japan were the greatest contributors to the global lung cancer burden for adenocarcinoma, squamous cell carcinoma, and small-cell carcinoma (appendix pp 23–30). However, most large-cell carcinoma cases were observed in China, Indonesia, and India. In females, the largest number of cases by subtype varied by country: most adenocarcinoma cases were found in China, the USA, and Japan; most squamous cell carcinoma cases were found in the USA, China, and the UK; most small-cell carcinoma cases were found in the USA, China, and Germany; and most large-cell carcinoma cases were found in the USA, India, and China.

Estimated ASRs by sex and by cancer subtype are shown in tables 1 and 2. Adenocarcinoma ASRs exceeded those of squamous cell carcinoma in 150 (81%) of 185 countries and territories in males and in all 185 countries and territories in females (appendix p 51). The incidence rates for each histological subtype varied by at least 10 times in both males and females across world regions (figure 2, tables 1, 2). In males, the highest ASRs were seen in eastern Asia for adenocarcinoma, in central and eastern Europe for squamous cell carcinoma, in western Asia for small-cell carcinoma, and in south-eastern Asia for large-cell carcinoma. Sub-Saharan Africa had the lowest ASR for all histological subtypes. In females, the ASRs were highest in eastern Asia for adenocarcinoma, in northern America for squamous cell carcinoma and small-cell carcinoma, and in south-eastern Asia for large-cell carcinoma. The lowest ASRs

 www.thelancet.com/oncology **Published online October 11, 2023 https://doi.org/10.1016/S1470-2045(23)00444-8**

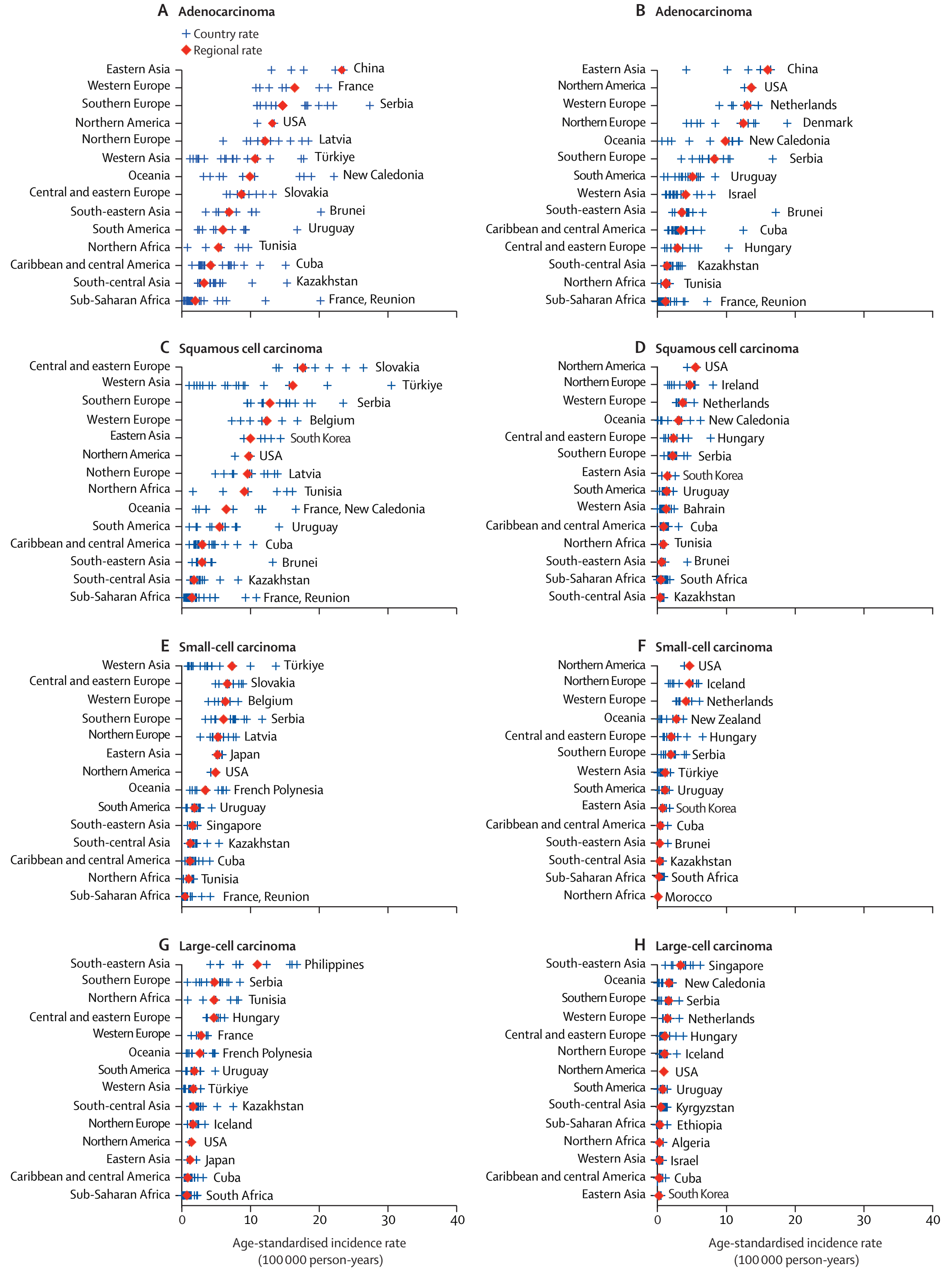
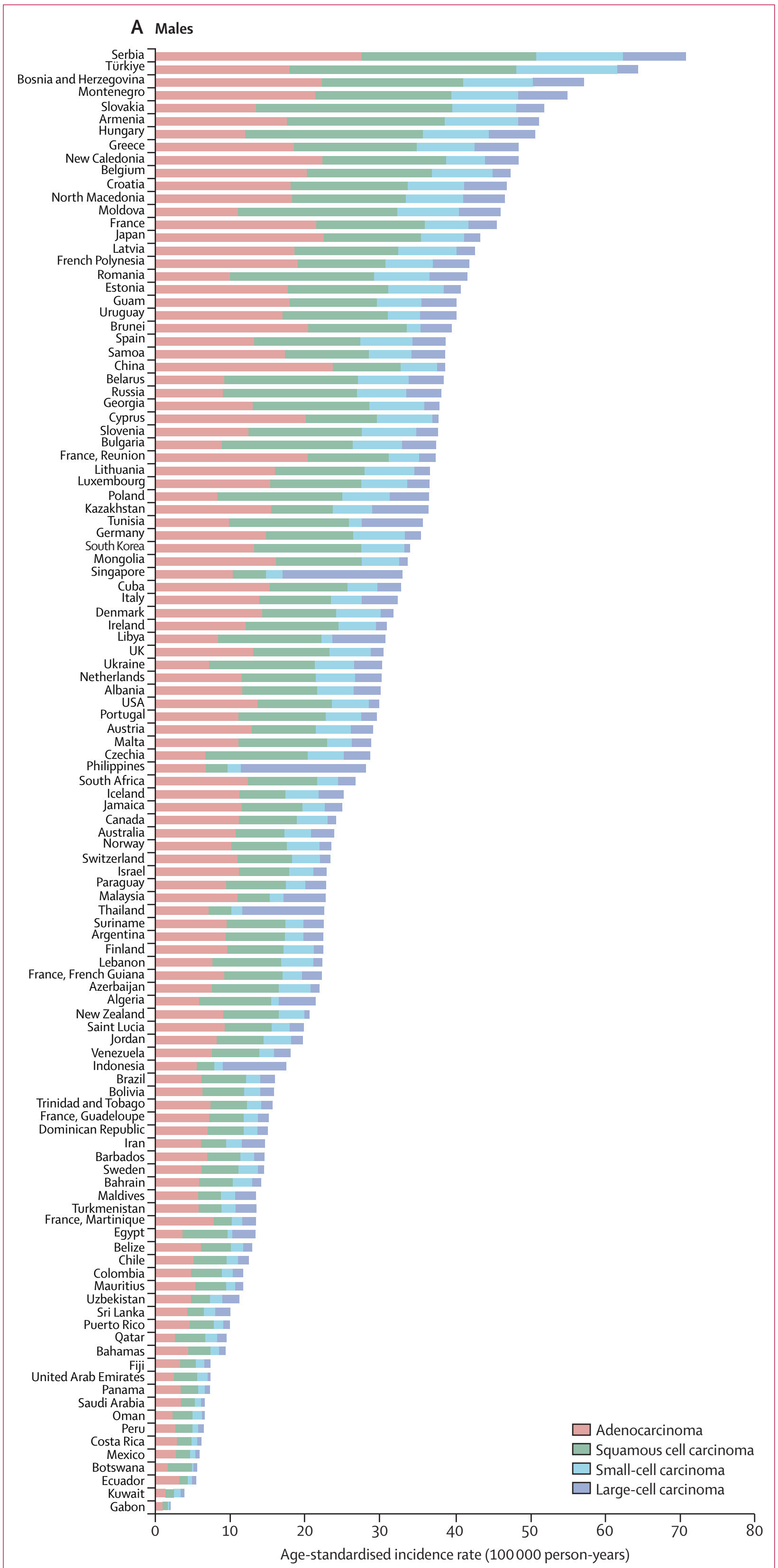


Figure 2: **Age-standardised incidence rate of adenocarcinoma in males (A) and females (B), squamous cell carcinoma in males (C) and females (D), small-cell carcinoma in males (E) and females (F), and large-cell carcinoma in males (G) and females (H), by world region in 2020**
Countries with the highest age-standardised incidence rate within each region are named on each plot.



were found in sub-Saharan Africa for adenocarcinoma, in south-central Asia for squamous cell carcinoma, in northern Africa for small-cell carcinoma, and in eastern Asia for large-cell carcinoma.

Sex-related disparities were also noted across world regions, with the male-to-female ASR ratio ranging from approximately 1·0 in northern America to 3·7 in northern Africa for adenocarcinoma, from 2·1 in northern Europe to 12·9 in western Asia for squamous cell carcinoma, from 1·0 in northern America to 10·5 in northern Africa for small-cell carcinoma, and from 1·4 in northern America to 11·1 in northern Africa for large-cell carcinoma (data not shown).

There were also considerable variations in lung cancer subtype incidence rates between countries within world regions, notably in regions with high incidence rates (figure 2; appendix pp 31–38, 52–53). For example, in eastern Asia, adenocarcinoma ASR ranged from 13·2 per 100 000 person-years in South Korea to 23·7 per 100 000 person-years in China in males, and from 4·4 per 100 000 person-years in Mongolia to 16·4 per 100 000 person-years in China in females.

By HDI group, for both sexes, the incidence rates for all histological subtypes followed a gradient across HDI categories, with the rates generally being substantially higher in countries with very high HDI and high HDI than in those with medium HDI and low HDI values; except for large-cell carcinoma, which had similar ASRs for high HDI and medium HDI countries (tables 1, 2; appendix pp 54–55).

Among high and very high HDI countries, in males, Serbia had the highest ASR for adenocarcinoma (27·5 per 100 000 person-years), Türkiye had the highest ASR for squamous cell carcinoma (30·3 per 100 000 person-years) and for small-cell carcinoma (13·5 per 100 000 person-years), and the Philippines had the highest ASR for large-cell carcinoma (16·8 per 100 000 person-years; figure 3A; appendix pp 31–38). In females, Denmark had the highest ASR for adenocarcinoma (18·8 per 100 000 person-years), Ireland had the highest ASR for squamous cell carcinoma (7·9 per 100 000 person-years), Hungary had the highest ASR for small-cell carcinoma (6·6 per 100 000 person-years), and Singapore had the highest ASR for large-cell carcinoma (6·3 per 100 000 person-years; figure 3B; appendix pp 31–38). In low and medium HDI settings, in males, the highest ASR for adenocarcinoma occurred in the North Korea (17·9 per 100 000 person-years), for squamous cell carcinoma occurred in Morocco (15·2 per 100 000 person-years), for small-cell carcinoma occurred in the occupied Palestinian territory (5·4 per 100 000 person-years), and for large-cell carcinoma occurred in Viet Nam (15·7 per 100 000 person-years;

(Figure 3 continues on next page)

figure 4A and appendix pp 31–38). In females in low and medium HDI settings, the highest ASR for adenocarcinoma occurred in the North Korea (13·2 per 100 000 person-years), for squamous cell carcinoma occurred in North Korea (2·5 per 100 000 person-years), for small-cell carcinoma occurred in North Korea (1·8 per 100 000 person-years), and for large-cell carcinoma occurred in Myanmar (4·8 per 100 000 person-years; figure 4B; appendix pp 31–38).

In post-hoc sensitivity analyses, slight differences were observed in the counts and rates of lung cancer by histological subtype when datasets with more than a 75% unspecified histology proportion were excluded, relative to the default cutoff of more than 25% (appendix pp 3–12, 39–46).

Discussion

We found that, in 2020, adenocarcinoma was the most common subtype of lung cancer globally, with incidence rates exceeding those of squamous cell carcinoma in the majority of countries in males, and in all countries in females. Most lung cancer cases occurred in nations with high and very high HDI values, and the estimated age-standardised incidence rates for each histological subtype followed a gradient across HDI categories, with the lowest rates generally observed in low and medium HDI countries. There was also considerable regional variability, for instance, incidence rates of adenocarcinoma being highest in eastern Asia (including China) in males and females, whereas incidence rates of squamous cell carcinoma were highest in central and eastern Europe in males and northern America in females.

The epidemiological profile of lung cancer incidence according to histological subtype has continued to evolve in recent decades. In a previous study of trends from 1973 to 2002 in 11 high and very high HDI countries (Australia, Austria, Canada, Denmark, France, Iceland, Italy, Spain, Switzerland, the Netherlands, and the USA), declines were reported in the incidence rates of squamous cell carcinoma among males in all 11 studied countries, in contrast with the increasing rates of squamous cell carcinoma in females observed in around half of the studied populations.[3] Incidence rates of adenocarcinoma have stabilised in most countries in men, but increases have been reported in many countries in women.[3,14] Additionally, the international trends study reported that, between 1998 and 2002, the incidence rates of adenocarcinoma in males surpassed those of squamous cell carcinoma in six (Australia, Austria, Canada, Denmark, Iceland, and the USA) of the 11 studied countries, with the gap between

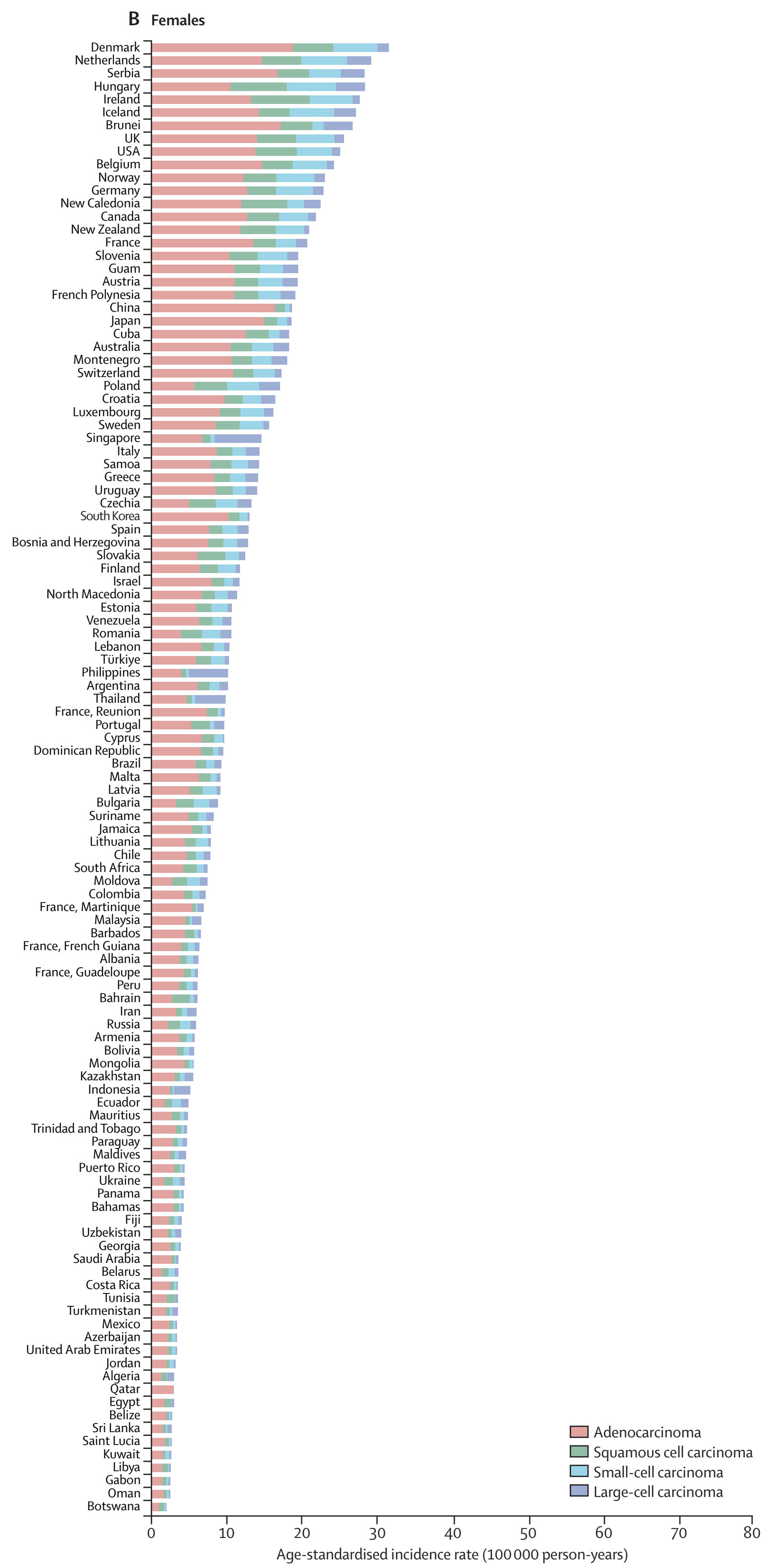
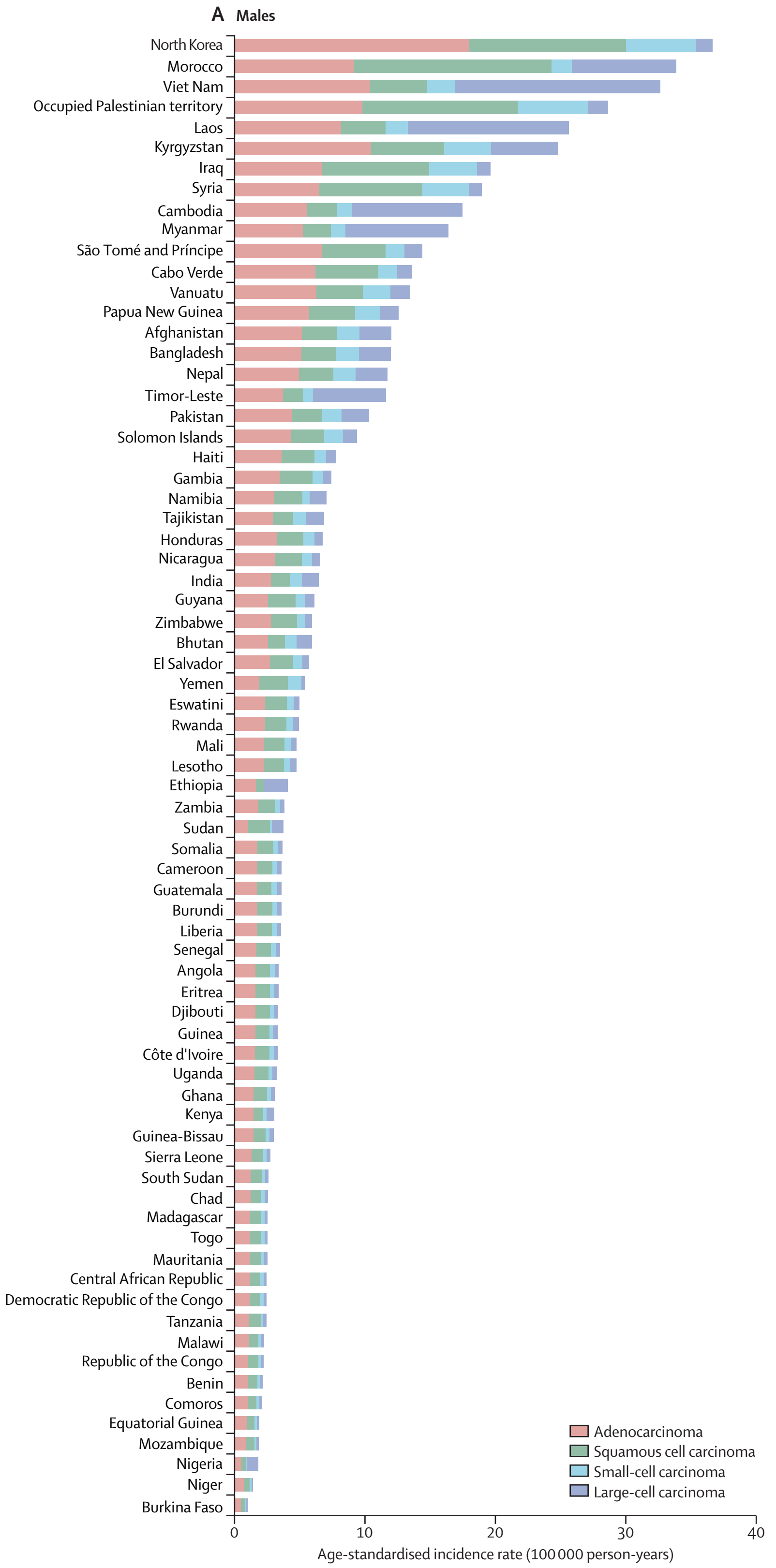


Figure 3: **Age-standardised incidence rate of lung cancer by histological subtype in males (A) and females (B) in high and very high Human Development Index countries, 2020**



(Figure 4 continues on next page)

incidence rates for adenocarcinoma and squamous cell carcinoma narrowing in five (France, Italy, Spain, Switzerland, and the Netherlands) of the 11 studied countries since 1973.[3] Our study updates these findings: incidence rates of adenocarcinoma in males have now surpassed those of squamous cell carcinoma in four (Switzerland, Italy, France, and the Netherlands) of the five countries. In women, adenocarcinoma was the predominant subtype of lung cancer before 1993 in eight (Australia, Austria, Canada, Denmark, Iceland, Italy, Switzerland, and the USA) of the 11 studied countries, and by around 2000, lung adenocarcinomas comprised the highest incidence rates in all of the studied countries.[3] Subsequent studies of individual countries (ie, the USA, the UK, China, and Japan) also showed that adenocarcinoma has become the most common subtype of lung cancer in male and female individuals in the past decade.[15–18] Our study has established adenocarcinoma as the most frequently diagnosed subtype in most countries in males and in all countries in females.

Lung cancer is associated with a socioeconomic gradient and is a major contributor to cancer inequalities overall.[19] In a prospective cohort study in the Nordic countries,[14] a progressive increase in risk of lung cancer with decreasing socioeconomic status was observed across all histological subtypes, and in male and female individuals. Among female individuals, upward temporal trends were seen in all socioeconomic status groups and for all subtypes, although mortality rates increased to a greater extent for low socioeconomic status groups than for high socioeconomic status groups.

The changing global patterns of lung cancer incidence according to histological subtype are related to several factors, including changes in smoking prevalence, cigarette composition, and exposure to environmental carcinogens. The decreased worldwide prevalence of smoking in recent decades might have a larger impact on decreasing the incidence of squamous cell carcinoma, small-cell carcinoma, and large-cell carcinoma given that smoking cessation reduces the risk of these subtypes somewhat more rapidly than adenocarcinoma.[20,21] There has been a shift from central tumours to peripheral tumours over the past 60 years, which has been postulated to be due to the global shift from high-tar, non-filter cigarettes towards low-tar filter cigarettes. This change has resulted in the peripheral deposition of chemical carcinogens and a concomitant shift from central tumours (squamous cell carcinoma and small-cell carcinoma) to peripheral tumours (adenocarcinoma and large-cell carcinoma).[3,4,22] Furthermore, changes in the composition of manufactured cigarettes over the past 60 years have reduced the yield of polycyclic aromatic hydrocarbons, which are inducers of squamous cell carcinoma, and increased the yields of tobacco-specific *N*-nitrosamines, which are inducers of adenocarcinoma.[4]

The distinct variations in lung cancer incidence identified by histological subtype across regions and countries correlate with geographical differences in smoking patterns. For example, increases in adenocarcinoma incidence in north America compared with European regions might relate to an increased predominance of low-tar filtered cigarettes.[22] The higher proportion of females diagnosed with adenocarcinoma over other lung cancer subtypes could also be related to the fact that females often start smoking later in life than do males and mainly smoke low-tar filtered cigarettes, resulting in the peripheral deposition of carcinogens in the lungs, and an overall increased baseline proportion of females among patients diagnosed with adenocarcinoma.[20]

Notably, approximately 25% and 63% of lung cancer deaths among male and female individuals worldwide, respectively, are not attributable to tobacco smoking and lung cancer among people who never smoked is more common among female individuals.[23] Epidemiological studies have shown that the high burden of adenocarcinoma in nations with high and very high HDI values, such as the USA, could be related to living in highly polluted areas.[6,24–26] Indeed, a novel mechanism has been recently postulated, showing how air pollution might cause adenocarcinoma, even among people who never smoked.[6] Thus, the high levels of air pollution recorded in several urban areas worldwide might be among the important underlying reasons of the observed patterns of lung cancer, even in nations with low or medium HDI values. In countries in Asia, such as China, exposure to indoor air pollution produced by second-hand smoke and fuel burning are postulated to be the main factors contributing to lung cancer incidence, particularly affecting women.[27,28] Such factors could explain, at least partially, the global dominance of adenocarcinoma in our study.

The somewhat higher large-cell carcinoma incidence in some world regions and countries might, in part, relate to the implementation of immunohistochemical and histochemical staining that excludes other subtypes before a large-cell carcinoma diagnosis,[29] and hence there might be a relative overdiagnosis of large-cell carcinoma in resource-limited countries where such staining processes are less readily available. The high rates of large-cell carcinoma reported in some countries might also suggest large-cell carcinoma diagnoses are increasingly being made on the basis of small biopsy samples (from patients with advanced stage lung cancer who do not undergo resection) rather than only on resected samples.

To our knowledge, this study is the first to provide a comprehensive epidemiological profile of lung cancer

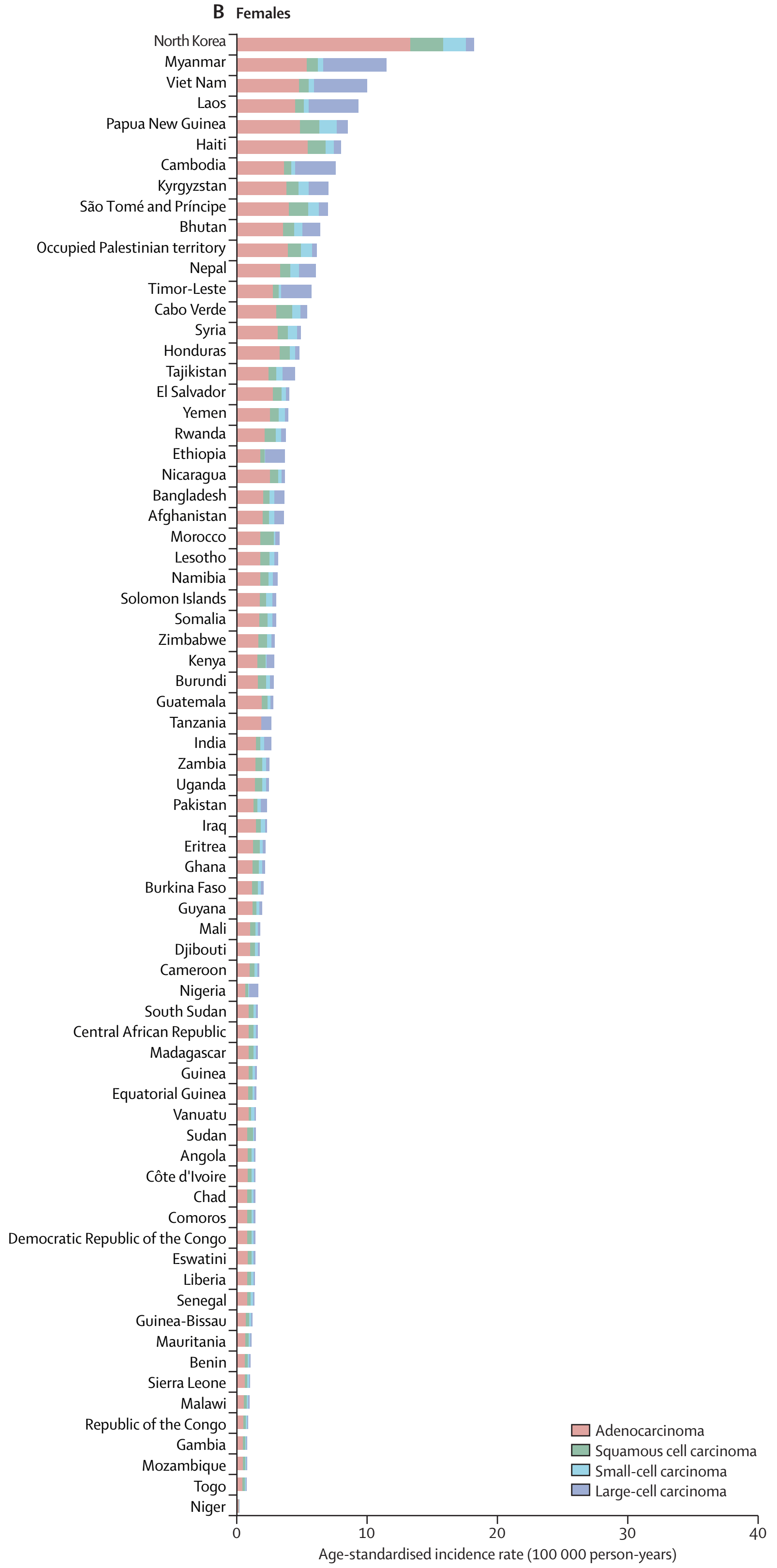


Figure 4: **Age-standardised incidence rate of lung cancer by histological subtype in males (A) and females (B) in low and medium Human Development Index countries, 2020**

incidence according to the main histological subtypes on a global scale. This study is highly relevant for cancer control planning and clinical practice. A 2011 review found that in the USA, adenocarcinoma, squamous cell carcinoma, small-cell carcinoma, and large-cell carcinoma, respectively, represented 38%, 20%, 14%, and 3% of all lung cancer cases for the total population.[30] Although the proportions of lung cancer cases by histological subtype in our study are generally consistent with these findings, there are several important limitations to an analysis involving 185 countries worldwide. We coded the data based on the ICD-O-3, as used by cancer registries worldwide for coding the site (topography) and the histology (morphology) of neoplasms obtained from pathology reports. Nevertheless, a first concern is the persistent finding of a high degree of poorly specified histology (high proportions of unspecified morphology) in many cancer registries, and the variation in proportions across registries not only highlights the challenges in the interpretation of subtype-specific estimates in our study, but also the need for more accurate morphological data worldwide. To enable the development of robust estimates of lung cancer subtypes, we excluded registries that had more than 25% of cases with unspecified lung cancer histology, consistent with previous reports.[3,4] We found no studies that set a lower threshold of acceptance, probably because this would exclude most registries from such an international analysis. We did, however, examine the impact of a less conservative cutoff of more than 75%, finding only slight differences in estimates overall, with somewhat fewer cases, and slightly lower rates of adenocarcinoma.

Second, when country-specific proportions of lung cancer by histological subtype were not available, regional information were aggregated to obtain national estimates; in such cases, the heterogeneity across these countries might not be adequately addressed. Third, data aggregated from multiple cancer registries within one country might not be necessarily representative of the entire national profile. However, our study did use the most recent estimated data from GLOBOCAN alongside recorded registry data from CI5-XI and AFCRN, of which CI5-XI is entirely based on cancer registries with high-quality data. Although the relatively low incidence in some low HDI settings might point to ascertainment issues, it might equally point to the tobacco epidemic being in an earlier phase, and a lower intensity of smoking in constituent countries. Fourth, while of great interest, our study was unable to provide any indication of the proportions of each lung cancer histologic subtype that were associated with smoking status, given the limitations of granularity of the data sources used. Finally, the overall accuracy of the national lung cancer incidence estimates from GLOBOCAN vary according to the corresponding availability and quality of population-based cancer registration in individual countries.

In summary, the geographical distribution of lung cancer incidence according to histological subtype varies substantially across world regions and their constituent countries, and these observations relate to differences in recent and historical smoking behaviour, and possibly to levels of air pollution. Given lung cancer remains the leading cause of cancer death and is associated with considerable geographical disparities by histological subtype, it remains imperative to develop and implement targeted interventions nationally that will reduce the extensive societal and economic burden associated with this highly preventable disease.

Contributors

YZ contributed to conceptualisation, supervision, project administration, data curation, formal analysis, methodology, analysis on the software, data visualisation, data interpretation, and writing (original draft, reviewing and editing) of the manuscript. FB contributed to supervision, methodology, data interpretation, and writing (reviewing and editing) of the manuscript. SV and EM contributed to methodology, data interpretation, and writing (reviewing and editing) of the manuscript. ML and JE contributed to writing (reviewing and editing) of the manuscript. EC, BK, AO, and SSM contributed to data curation. YZ and FB have accessed and verified all the data in the study. All authors had full access to all data in the study, reviewed and approved the manuscript, and accept responsibility for the decision to submit for publication. FB had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

GLOBOCAN 2020 and Cancer Incidence in Five Continents Volume XI datasets are available in a public, open access repository. Data are available on https://gco.iarc.fr/ and on https://ci5.iarc.fr/Default.aspx. Cancer registry data in sub-Saharan Africa are from the members of the African Cancer Registry Network (AFCRN). Processed datasets used in the analysis are available from the corresponding author upon reasonable request.

Acknowledgments

We gratefully acknowledge all cancer registries and their staff who have contributed in sharing the data needed for this study. We thank the AFCRN and all its collaborators for the provision of data. Additionally, we thank Murielle Colombet at the International Agency for Research on Cancer for her help in preparing the AFCRN data. 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.

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