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ORIGINAL ARTICLE

Tracheal, Bronchial, and Lung Cancer Disease Burden and Risk Factors in China, Japan, and Southeast Asia from 1990 to 2021: Results from the Global Burden of Disease 2021 Study

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Abstract

Background: Tracheal, bronchial, and lung cancer (TBL cancer) is the leading cause of cancer mortality in numerous Asian countries, we analyzed time-based trends in the disease burden of TBL cancer, as well as its associated risk factors, in China, Japan, and Southeast Asia.

Methods: We first obtained TBL cancer data from the 2021 Global Burden of Disease Study. We then investigated longitudinal trends in TBL cancer disease burden in China, Japan, and Southeast Asia from 1990 to 2021 by calculating estimated annual percentage change (EAPC) values through linear regression modeling. We next used an autoregressive integrated moving average (ARIMA) model to predict future disease burden (for 2022-2050). Finally, we analyzed risk factors for TBL cancer.

Results: In 2021, there were 814364 TBL cancer-related deaths in China (95% UI:652636-987795), 92119 (95% UI:78912-98959) in Japan, and 134949 (95% UI: 110670-155974) in Southeast Asia. Between 1990 and 2021, ASDR (EAPC: 0.42 (95% UI: 0.25-0.6)) and age-standardized disability-adjusted life years (DALYs; EAPC: 0.07 (95% UI: -0.08-0.21))for TBL cancer in China increased, but decreased in both Japan and Southeast Asia. In these regions, TBL disease burden remains much greater in men than in women. The main risk factor for TBL cancer in all three regions was smoking, but, over time, the proportion of risk attributable to smoking gradually decreased, and the proportion of other risk factors related to air pollution gradually increased.

Conclusions: Over the past 30 years, the disease burden of TBL cancer has been generally decreasing in Japan and Southeast Asia, but generally increasing in China. The composition of the major risk factors contributing to TBL cancer has also changed significantly over this time period, meaning that more effective efforts are needed to reduce the burden of TBL, improve treatments, and to help achieve each region's public health and development goals.

Keywords: TBL cancer, Autoregressive integrated moving average model, ASDR, DALYs, ASIR, ASPR

Introduction

Tracheal, bronchial, and lung cancers (TBL cancers) are malignant tumors with high morbidity and mortality rates. Recent global cancer data show that there were 2.5 million new cases of TBL cancer in 2022 (affecting 12.4% of the world's population), as well as 1.8 million TBL-cancer-related deaths (affecting 18.7% of the world's population) [1]. More than 55% of TBL cancer cases and associated mortality occur in Asian countries, and nearly 60% of the global lung cancer burden is in Asian countries [2]. Although immunotherapy and other targeted therapies have significantly improved survival for lung cancer patients, high treatment costs continue to place a heavy financial burden on patients' families [3].

TBL cancers refer to malignant tumors that originate from the tissues in the respiratory system. They are strongly associated with smoking, air pollution, occupational exposure, radiation, and individual genetic susceptibility, and have geographic and gender-specific morbidity, mortality, and survival rates, with the highest incidence in Central and Eastern Europe (53.5 per 100,000) and East Asia (50.4 per 100,000). Incidence is also much higher amongst men than women [4]. Additionally, a growing body of research suggests that there are racial differences in TBL cancer incidence and mortality. Previous studies have shown that the annual incidence of TBL cancer is highest among Black patients, followed by white patients and Asian/Pacific Islanders [5], and that non-Hispanic white (22%) and non-Hispanic Asian (23%) patients have higher two-year overall survival rates compared to non-Hispanic Black patients (15%) [6].

These differences can also shape treatment outcomes and contribute to racial disparities in clinical care. For example, a recently developed first-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor showed better efficacy in East Asian patients compared to white patients, presumably because of the higher frequency of EGFR mutations in Asian populations. However, the treatment had worse efficacy amongst Black patients, a population with lower EGFR mutation frequency [7]. Environmental factors are also important etiologic contributors that drive the occurrence of TBL cancer, and environmental exposure varies greatly across geographic regions. For example, differences in economic development between Western and Eastern countries can lead to a profound divergence in the type of environmental exposure patients are exposed to, driving both ethnic/racial and geographic disparities in TBL cancer-related morbidity and mortality.

TBL cancer incidence and mortality are increasing globally, with Asian populations leading the way. The burden of disease associated with TBL cancer varies significantly by race and geography. Therefore, a comprehensive understanding of TBL cancer-related incidence, morbidity, and mortality in Asian countries is particularly important for developing new prevention and treatment strategies. However, previous studies have mainly focused on describing TBL cancer epidemiology in different Asian countries, with few studies directly comparing disease burdens between China, Japan, and Southeast Asia. Thus, here, we aim to analyze and compare the number of TBL cancer-related deaths, TBL-cancer related disability-adjusted life years (DALYs), disease incidence and prevalence, and corresponding age-standardized mortality rates (ASRs) between China, Japan, and Southeast Asian countries from 1990 to 2021. We analyze Global Burden of Disease (GBD) data published in 2021 to assess historical trends and then generate a model to predict trends for the next 25 years. We also describe the attributable risk factors for TBL cancer from 1990 to 2019 in each of the three regions. We hope our work will provide groundwork for the development of targeted screening and prevention measures for TBL cancer, as well as the elimination of associated risk factors.

2. Materials and Methods

Data Source

The 2021 GBD study used the most recent epidemiological data and standardized methodologies to assess the effects of 371 different health conditions, injuries, and impairments, as well as 88 contributing factors, across 204 countries and regions. The findings are accessible via the Global Health Data Exchange

query tool (http://ghdx.healthdata.org/gbd-results-tool), which divides the globe into 27 distinct geographic sectors, and allows users to filter results by various categories, including region, sex, and country. To assess the burden of TBL cancer in China, Japan, and Southeast Asia, we obtained data from the Global Health Data Exchange (https://ghdx.healthdata.org/gbd-resultstool) on Gastrointestinal tract cancer cases, DALYs, incidence, mortality, and prevalence (with corresponding 95% uncertainty certainty intervals) as well as other information.

To monitor TBL cancer prevalence and mortality rates, we used age-standardized rates (ASR) and estimated annual percentage changes (EAPC). ASRs are crucial for identifying shifts in disease prevalence across various communities, which helps in formulating targeted preventive strategies for TBL cancer. EAPCs summarize the evolution of ASR across different demographics over specified time frames.

The GBD initiative employs DisMod-MR 2.1 software, a Bayesian meta-regression tool, to estimate disease incidence through a systematic cascade process. Prior to analysis, several adjustments are made to enhance data accuracy, including disaggregating non-specific age and sex data and applying a Meta-Regression-Bayesian, Regularized, Trimmed (MR-BRT) approach to ensure consistent comparisons across different study configurations and definitions. Detailed information regarding these adjustments and specific disease corrections can be found in the GBD 2019 capstone report [8].

We also thoroughly investigated the impacts of secondary and tertiary risk factors, particularly those linked to TBL cancer mortality and DALYs, such as alcohol and drug consumption, smoking, chewing tobacco, fasting plasma glucose, high-sodium diets, and body mass index. These risk factors were chosen based on World Cancer Research Fund guidelines, which highlight significant associations between specific risks and health outcomes using a comparative risk assessment model. For comprehensive methodologies related to each risk factor, please refer to the 2021 GBD risk factors capstone report [9].

Statistical Analysis

We analyzed TBL cancer data from the 2021 GBD, including TBL cancer-related mortality, DALYs, incidence and prevalence rates, and ASRs in 2021. Age standardization is necessary when comparing several populations with different age structures or when comparing populations at the same time. Data were disaggregated by age group and sex. To predict future trends in TBL cancer-related disease burdens in China, Japan, and Southeast Asia, we used an AutoRegressive Integrated Moving Average (ARIMA) model. This model requires the transformation of time series data into a stationary state through differencing prior to analysis. The model itself is also characterized by three key parameters: p (autoregressive order), d (differencing order), and q (moving average order). These parameters were determined using analysis tools, including the autocorrelation function (ACF) and the partial autocorrelation function (PACF). Forecasting was conducted using the forecast and tseries packages in R, enabling both predictions and graphical representations of the results. To ensure forecast accuracy, we applied several validation techniques, including assessing the independence of forecast errors with Ljung-Box Q-tests, verifying the normal distribution of residuals with a mean of zero using Shapiro-Wilk tests, and evaluating the homoscedasticity of residuals through visual inspection and Breusch-Pagan tests. Finally, risk factors for TBL cancer were analyzed. Statistical significance was defined as P-values less than 0.05. Data were processed and analyzed using R software (version 4.3.2).

Patient and Public Involvement

The GBD Study is a scientific, collaborative effort involving over 7,500 participants from ~150 countries. Our study excluded patient participation, as we used secondary data from the 2021 GBD Study. Because the present research questions were not focused on TBL cancer management or related patient concerns, patients were not engaged in formulating the research questions, collecting or analyzing data, interpreting results, or writing the manuscript.

3. Results

3.1 Changes in the burden of disease and future trends for TBL cancer in China, 1990-2021

We found that the number of TBL cancer-related

deaths in China in 2021 was 814364 (95% UI:652636-987795), 545962 (95% UI:403556-702866) of which were in men and 268402 (95% UI:211859-331292) of which were in women. The highest number of deaths occurred in the 70-74 age group. The corresponding age-standardized death rate (ASDR) was 38.98 (95%UI:31.4-47.06)/100,000 (**Table 1**).

Table 1 Number of deaths and age-standardized deaths rates due to TBL cancer in 1990 and 2021, and trends in China from 1990 to 2021.

Characteristics	Number of deaths cases (95% UI) in 1990	The age-standardized deaths rate/100 000 (95% UI) in 1990	Number of deaths cases (95% UI) in 2021	The age-standardized deaths rate/100000 (95% UI) in 2021	EAPC (95% CI)
China	278,226 (238,194-318,827)	34.74(29.96-39.52)	814,364 (652,636-987,795)	38.98 (31.4-47.06)	0.42 (0.25-0.6)
Sex					
Female	85,817 (70,530-103,029)	20.91 (17.36-25.18)	268,402 (211,859-331,292)	24.42 (19.3-30.11)	0.25 (0.09-0.4)
Male	192,409 (152,808-231,623)	51.45 (41.44-61.14)	545,962 (403,556-702,866)	56.45 (41.89-71.82)	0.5 (0.29-0.71)
Age					
15-19 years	537 (451-641)	0.42 (0.36-0.51)	179 (141-220)	0.24 (0.19-0.29)	-2.34 (-2.61--2.06)
20-24 years	798 (669-945)	0.6 (0.51-0.72)	378 (293-469)	0.52 (0.4-0.64)	-0.91 (-1.2--0.62)
25-29 years	1,203 (1,027-1,429)	1.1 (0.93-1.3)	862 (691-1,051)	1 (0.8-1.21)	-0.5 (-0.74--0.27)
30-34 years	2,411 (2,049-2,823)	2.73 (2.32-3.2)	2,901 (2,308-3,506)	2.39 (1.9-2.89)	-0.67 (-0.85--0.48)
35-39 years	5,662 (4,809-6,557)	6.2 (5.26-7.18)	5,284 (4,179-6,532)	4.99 (3.94-6.16)	-1.22 (-1.44--0.99)
40-44 years	9,371 (7,891-10,827)	13.97 (11.76-16.14)	10,023 (7,812-12,446)	10.95 (8.53-13.6)	-1.14 (-1.33--0.96)
45-49 years	12,538 (10,525-14,689)	24.29 (20.39-28.46)	21,190 (16,314-26,363)	19.21 (14.79-23.9)	-0.78 (-0.97--0.59)
50-54 years	23,963 (19,641-28,347)	50.23 (41.17-59.41)	47,774 (37,410-59,885)	39.53 (30.95-49.55)	-1.02 (-1.2--0.83)
55-59 years	35,872 (29,460-42,341)	82.71 (67.93-97.63)	74,308 (56,355-94,029)	67.59 (51.26-85.53)	-0.63 (-0.76--0.5)
60-64 years	42,758 (35,829-49,966)	121 (101.39-141.4)	85,351 (67,657-106,008)	116.91 (92.67-145.21)	0.04 (-0.08-0.16)
65-69 years	47,139 (39,778-55,018)	172.79 (145.81-201.67)	138,084 (109,832-169,174)	180.02 (143.19-220.56)	0.14 (-0.03-0.3)
70-74 years	43,291 (37,031-49,343)	230.05 (196.79-262.22)	148,245 (118,008-181,281)	278.15 (221.42-340.14)	0.64 (0.39-0.89)

75-79 years	30,502 (26,445-34,790)	268.02 (232.37-305.69)	121,165 (97,675-146,752)	365.85 (294.92-443.11)	1.2 (0.93-1.47)
80-84 years	14,609 (12,628-16,669)	275.79 (238.4-314.68)	86,351 (70,848-103,481)	436.3 (357.97-522.85)	1.74 (1.46-2.02)
85-89 years	6,046 (5,207-6,916)	358.41 (308.69-409.97)	52,879 (43,503-61,957)	555.12 (456.69-650.42)	1.47 (1.19-1.74)
90-94 years	1,381 (1,191-1,582)	450.22 (388.24-515.51)	16,330 (13,037-19,356)	556.96 (444.65-660.15)	0.51 (0.34-0.68)
95+ years	145 (116-172)	357.45 (286.33-424.79)	3,061 (2,301-3,703)	478.88 (360.06-579.41)	0.6 (0.45-0.74)

The DALYs associated with, incidence of, and prevalence of TBL cancer were 18920203 (95%UI. 15100681-23111519), 934704 (95% UI:750040-1136938), and 1262275 (95% UI:1005551-1545341), respectively. The ASR of DALY, age-standardized incidence rate (ASIR), and age-standardized prevalence rate (ASPR), were 878.24 (95% UI:703.53-1068.71)/100,000, 44.01 (95% UI:35.45-53.35)/100,000, and 57.95 (95% UI:46.2-70.78)/100,000, respectively (**Tables 2-4**).

Table 2 Number of DALYs and age-standardized DALYs rates due to TBL cancer in 1990 and 2021, and trends in China from 1990 to 2021.

Characteristics	**Number of DALYs cases (95% UI) in 1990**	**The age-standardized DALYs rate/100000 (95% UI) in 1990**	**Number of DALYs cases (95% UI) in 2021**	**The age-standardized DALYs rate/100000 (95% UI) in 2021**	**EAPC (95% CI)**
China	7,762,374 (6,610,051-8,947,038)	863.54 (738.86-991.39)	18,920,203 (15,100,681-23,111,519)	878.24 (703.53-1,068.71)	0.07 (-0.08-0.21)
Sex					
Female	2,358,325 (1,915,033-2,852,516)	522.43 (426.02-628.98)	6,088,330 (4,755,094-7,606,766)	553 (431.58-690.27)	-0.1 (-0.25-0.04)
Male	5,404,050 (4,264,070-6,544,173)	1,230.74 (979.34-1,478.69)	12,831,873 (9,352,167-16,730,756)	1,235.03 (905.79-1,600.15)	0.17 (-0.01-0.34)
Age					
15-19 years	39,058 (32,792-46,615)	30.84 (25.89-36.8)	12,998 (10,271-15,984)	17.41 (13.75-21.41)	-2.34 (-2.62--2.06)
20-24 years	54,247 (45,470-64,243)	41.1 (34.45-48.67)	25,641 (19,869-31,804)	35.04 (27.15-43.46)	-0.92 (-1.21--0.63)
25-29 years	76,011 (64,802-90,297)	69.17 (58.97-82.17)	54,258 (43,491-66,152)	62.74 (50.29-76.49)	-0.5 (-0.74--0.27)
30-34 years	139,509 (118,511-163,555)	158.09 (134.3-185.34)	168,211 (133,740-203,283)	138.84 (110.39-167.79)	-0.66 (-0.85--0.48)

35-39 years	300,668 (255,285-348,000)	329.18 (279.49-381)	281,315 (222,961-347,592)	265.48 (210.41-328.03)	-1.21 (-1.44--0.98)
40-44 years	451,716 (380,152-522,672)	673.25 (566.59-779.01)	482,771 (376,817-598,962)	527.42 (411.67-654.36)	-1.15 (-1.34--0.96)
45-49 years	541,869 (455,068-635,246)	1,049.75 (881.59-1,230.64)	914,838 (704,875-1,137,357)	829.25 (638.93-1,030.95)	-0.78 (-0.97--0.59)
50-54 years	919,780 (752,887-1,089,229)	1,927.82 (1,578.02-2,282.98)	1,837,756 (1,439,244-2,302,028)	1,520.58 (1,190.84-1,904.72)	-1.01 (-1.18--0.83)
55-59 years	1,211,543 (9,942,93-1,430,106)	2,793.56 (2,292.63-3,297.52)	2,518,385 (190,8241-3,183,122)	2,290.64 (1,735.67-2,895.26)	-0.62 (-0.75--0.49)
60-64 years	1,244,978 (1,044,185-1,454,899)	3,523.11 (2,954.9-4,117.16)	2,483,628 (1,969,096-3,081,518)	3,401.99 (2,697.2-4,220.96)	0.05 (-0.08-0.17)
65-69 years	1,155,074 (974,154-1,348,656)	4,233.86 (3,570.71-4,943.42)	3,388,114 (2,695, 937-4,147,382)	4,417.16 (3,514.75-5,407.03)	0.15 (-0.01-0.32)
70-74 years	873,670 (746, 304 -995,713)	4,642.82 (3,965.98-5,291.38)	2,999,641 (2,3 86, 015-3,664, 160)	5,628.22 (4,476.87-6,875.06)	0.64 (0.4-0.89)
75-79 years	494,239 (428, 634 -563,916)	4,342.79 (3,766.33-4,955.02)	1,960,770 (1,584, 738-2,371,654)	5,920.39 (4,784.99-7,161.02)	1.19 (0.92-1.45)
80-84 years	185,495 (160,5 3 7-211,427)	3,501.8 (3,030.65-3,991.35)	1,090,998 (894,973-1,306,700)	5,512.36 (4,521.93-6,602.21)	1.72 (1.45-2)
85-89 years	61,181 (52,651-69,974)	3,626.91 (3,121.26-4,148.17)	532,230 (438,442-623,105)	5,587.28 (4,602.7-6,541.27)	1.46 (1.19-1.73)
90-94 years	12,127 (10,471-13,862)	3,952.46 (3,412.86-4,518.03)	143,362 (114,406-169,997)	4,889.59 (3,902.01-5,798.01)	0.51 (0.34-0.68)
95+ years	1,210 (970-1,439)	2,988.62 (2,395.71-3,554.08)	25,285 (18,996-30,470)	3,956.34 (2,9 72. 29-4,767.6)	0.56 (0.42-0.71)

Table 3 Number of incidence and age-standardized incidence rates due to TBL cancer in 1990 and 2021, and trends in China from 1990 to 2021.

Characteristics	**Number of incidence cases (95% UI) in 1990**	**The age-standardized incidence rate/100000 (95% UI) in 1990**	**Number of incidence cases (95% UI) in 2021**	**The age-standardized incidence rate/100000 (95% UI) in 2021**	**EAPC (95% CI)**
China	274,752 (234,741-315,112)	33.11 (28.47-37.79)	934,704 (750,040-1,136,938)	44.01 (35.45-53.35)	1.03 (0.89-1.17)
Sex					
Female	84,507 (69,112-101,782)	19.97 (16.45-23.98)	311,944 (245,717-387,211)	28.16 (22.22-34.9)	0.93 (0.81-1.05)
Male	190,245 (150,986-229,441)	48.46 (38.94-57.75)	622,760 (460,105-803,234)	62.63 (46.5-79.9)	1.08 (0.9-1.26)
Age					
15-19 years	550 (462-660)	0.43 (0.36-0.52)	210 (167-254)	0.28 (0.22-0.34)	-1.89 (-2.18--1.6)

20-24 years	789 (660-935)	0.6 (0.5-0.71)	426 (331-524)	0.58 (0.45-0.72)	-0.45 (-0.75--0.14)
25-29 years	1,303 (1,114-1,542)	1.19 (1.01-1.4)	1,069 (861-1,293)	1.24 (1-1.49)	-0.03 (-0.28-0.22)
30-34 years	2,650 (2,248-3,100)	3 (2.55-3.51)	3,650 (2,911-4,396)	3.01 (2.4-3.63)	-0.2 (-0.38--0.02)
35-39 years	6,555 (5,555-7,589)	7.18 (6.08-8.31)	7,009 (5,587-8,631)	6.61 (5.27-8.14)	-0.75 (-0.97--0.53)
40-44 years	10,409 (8,764-12,073)	15.51 (13.06-17.99)	13,087 (10,266-16,145)	14.3 (11.22-17.64)	-0.58 (-0.75--0.41)
45-49 years	13,634 (11,436-16,007)	26.41 (22.15-31.01)	27,450 (21,243-34,220)	24.88 (19.26-31.02)	-0.17 (-0.34--0.01)
50-54 years	25,782 (21,145-30,519)	54.04 (44.32-63.97)	61,912 (48,850-77,912)	51.23 (40.42-64.47)	-0.36 (-0.52--0.2)
55-59 years	37,627 (30,976-44,454)	86.76 (71.43-102.5)	94,702 (72,340-119,138)	86.14 (65.8-108.36)	0.07 (-0.04-0.17)
60-64 years	43,782 (36,643-51,069)	123.9 (103.7-144.52)	107,234 (84,923-132,324)	146.89 (116.32-181.25)	0.76 (0.64-0.87)
65-69 years	46,545 (39,356-54,301)	170.61 (144.26-199.04)	167,029 (132,932-202,930)	217.76 (173.31-264.56)	0.85 (0.71-0.99)
70-74 years	40,616 (34,747-46,286)	215.84 (184.65-245.97)	170,445 (135,365-207,534)	319.81 (253.98-389.39)	1.36 (1.14-1.58)
75-79 years	26,915 (23,370-30,740)	236.5 (205.35-270.11)	130,924 (106,200-158,244)	395.31 (320.66-477.8)	1.93 (1.69-2.17)
80-84 years	11,929 (10,302-13,591)	225.2 (194.48-256.57)	85,372 (70,010-101,519)	431.35 (353.73-512.93)	2.45 (2.19-2.71)
85-89 years	4,610 (3,959-5,270)	273.26 (234.73-312.4)	48,779 (40,269-57,117)	512.08 (422.73-599.6)	2.17 (1.93-2.42)
90-94 years	966 (829-1,106)	314.97 (270.27-360.48)	13,455 (10,770-16,030)	458.91 (367.32-546.74)	1.1 (0.97-1.23)
95+ years	90 (72-107)	222.51 (178.9-263.68)	1,949 (1,459-2,364)	305.02 (228.25-369.87)	0.68 (0.53-0.82)

Table 4 Number of prevalence and age-standardized prevalence rates due to TBL cancer in 1990 and 2021, and trends in China from 1990 to 2021

Characteristics	Number of prevalence cases (95% UI) in 1990	The age-standardized prevalence rate/100000 (95% UI) in 1990	Number of prevalence cases (95% UI) in 2021	The age-standardized prevalence rate/100000 (95% UI) in 2021	EAPC (95% CI)
China	301,999 (257,252-347,798)	33.74 (28.9-38.65)	1,262,275 (1,005,551-1,545,341)	57.95 (46.2-70.78)	1.91 (1.81-2.02)

Sex					
Female	92,191 (74,676-111,671)	20.46 (16.68-24.66)	425,701 (333,642-533,493)	38.34 (30.09-48.08)	1.92 (1.82-2.03)
Male	209,808 (165,996-254,011)	48.13 (38.43-57.83)	836,574 (616,941-1,085,694)	79.57 (58.95-102.56)	1.92 (1.78-2.07)
Age					
15-19 years	996 (836-1,195)	0.79 (0.66-0.94)	468 (373-565)	0.63 (0.5-0.76)	-1.17 (-1.49--0.85)
20-24 years	1,461 (1,222-1,733)	1.11 (0.93-1.31)	978 (759-1,207)	1.34 (1.04-1.65)	0.32 (0-0.65)
25-29 years	3,337 (2,851-3,956)	3.04 (2.59-3.6)	3,271 (2,647-3,952)	3.78 (3.06-4.57)	0.62 (0.34-0.89)
30-34 years	6,786 (5,759-7,947)	7.69 (6.53-9.01)	11,217 (8,956-13,573)	9.26 (7.39-11.2)	0.45 (0.26-0.64)
35-39 years	12,878 (10,911-14,910)	14.1 (11.95-16.32)	17,316 (13,872-21,213)	16.34 (13.09-20.02)	0.04 (-0.19-0.28)
40-44 years	14,120 (11,883-16,382)	21.05 (17.71-24.42)	23,733 (18,694-29, 320)	25.93 (20.42-32.03)	0.41 (0.24-0.58)
45-49 years	18,462 (15,498-21,682)	35.77 (30.02-42)	49,605 (38,837-61,939)	44.96 (35.2-56.14)	0.82 (0.68-0.96)
50-54 years	34,842 (28,530-41,246)	73.03 (59.8-86.45)	114,055 (90,118-143,236)	94.37 (74.56-118.51)	0.73 (0.58-0.88)
55-59 years	47,895 (39,438-56,653)	110.44 (90.94-130.63)	168,981 (128,874-213,643)	153.7 (117.22-194.32)	1.26 (1.16-1.36)
60-64 years	49,129 (41,175-57,250)	139.03 (116.52-162.01)	175,025 (138,993-214,177)	239.74 (190.39-293.37)	2.06 (1.94-2.18)
65-69 years	46,978 (39,784-54,918)	172.2 (145.83-201.3)	244,932 (195,688-297,680)	319.32 (255.12-388.09)	2.15 (2.03-2.27)
70-74 years	34,947 (29,870-39,873)	185.71 (158.74-211.89)	211,680 (168,164-257,299)	397.18 (315.53-482.77)	2.65 (2.44-2.86)
75-79 years	19,516 (16,938-22,273)	171.48 (148.83-195.71)	131,073 (104,745-159,579)	395.76 (316.27-481.84)	3.06 (2.82-3.3)
80-84 years	7,541 (6,511-8,567)	142.36 (122.92-161.74)	69,094 (55,945-82,728)	349.1 (282.67-417.99)	3.34 (3.08-3.61)
85-89 years	2,557 (2,195-2,923)	151.59 (130.12-173.27)	32,058 (26,328-37,475)	336.54 (276.39-393.4)	2.76 (2.53-2.99)
90-94 years	508 (436-582)	165.52 (142.06-189.55)	7,806 (6,245-9,306)	266.22 (212.99-317.4)	1.43 (1.32-1.53)
95+ years	45 (36-53)	111.42 (89.59-132.04)	982 (735-1,190)	153.63 (114.96-186.28)	0.7 (0.55-0.84)

Overall, TBL cancer-related deaths, DALYs, incidence rates, and prevalence rates increased with increasing age, peaking in the 65-74 age group (**Figure 1A**), and the burden of TBL cancer-related disease was significantly higher in

men than in women (**Figure 1B**).

Between 1990 and 2021, TBL cancer-related deaths, DALYs, incidence, and prevalence in China increased by 192.7%, 143.7%, 240.2%, and 318%, respectively. ASDR, ASR of DALYs, ASIR, and ASPR increased by 12.2%, 1.7%, 32.9% and 71.8%, respectively. These trends suggest that the burden of TBL cancer-related disease has continued to grow in China (**Figure 1C**).

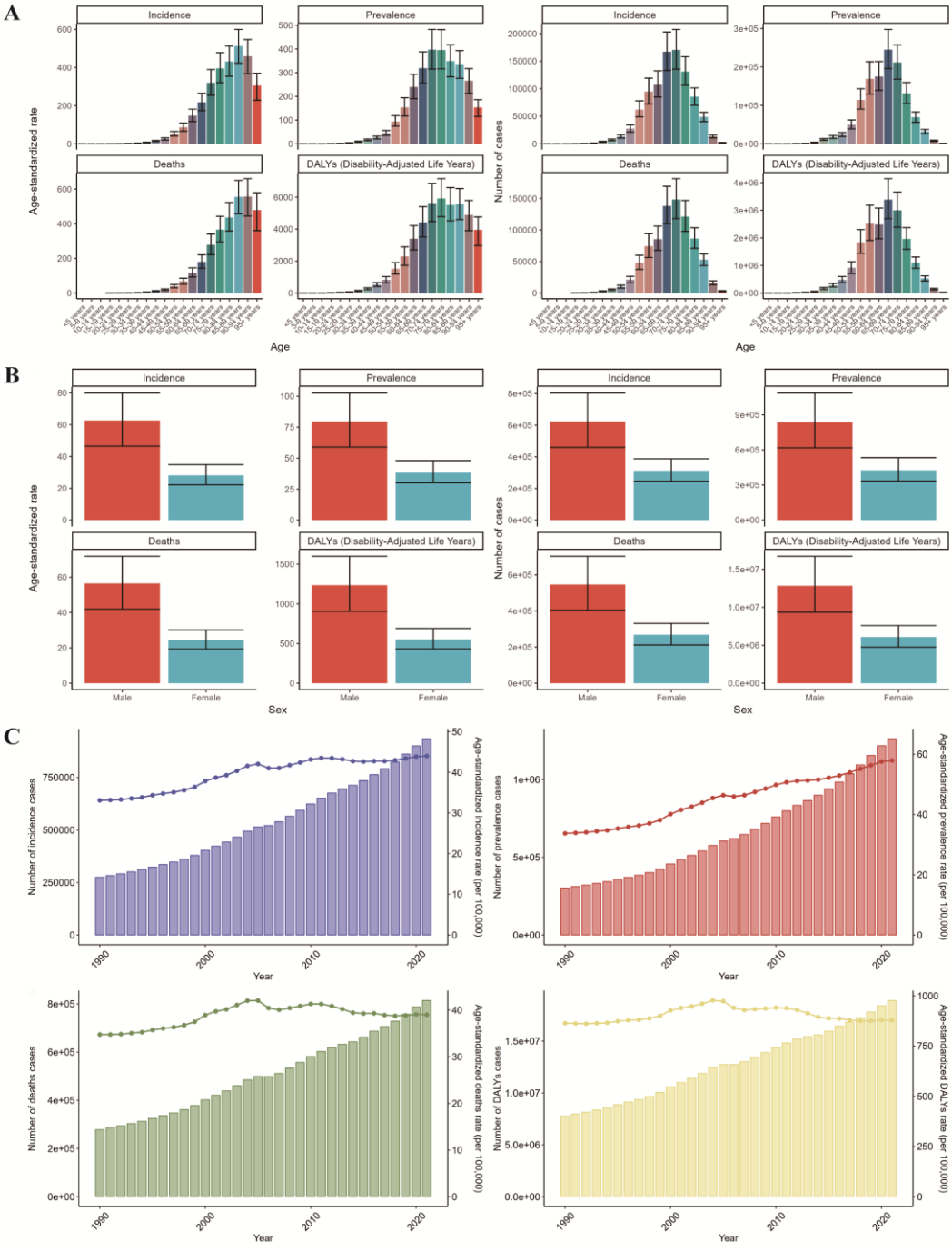

Figure 1 (A-B) Distribution of TBL cancer disease burden by age and sex in China in 2021.（C）Trends in the burden of disease for TBL cancer in China, 1990-2021.

During this time period, the largest increase in the number of deaths occurred in the 70-74 age group, and the ASDR was consistently highest in the 90-94 age group. The largest increase in the number of DALYs was in the 65-69 age group, and the largest increase in the ASR of DALYs was in the 75-79 age group (**Figure 2A**). The growth was greater for men than women in all cases (**Figure**

2B). According to our ARIMA prediction model, the number of TBL cancer-related deaths in China is expected to continue to increase and will reach 1450,989 by 2050. However, both ASDR and ASR of DALYs showed decreasing trends, especially among men (**Figure 2C**).

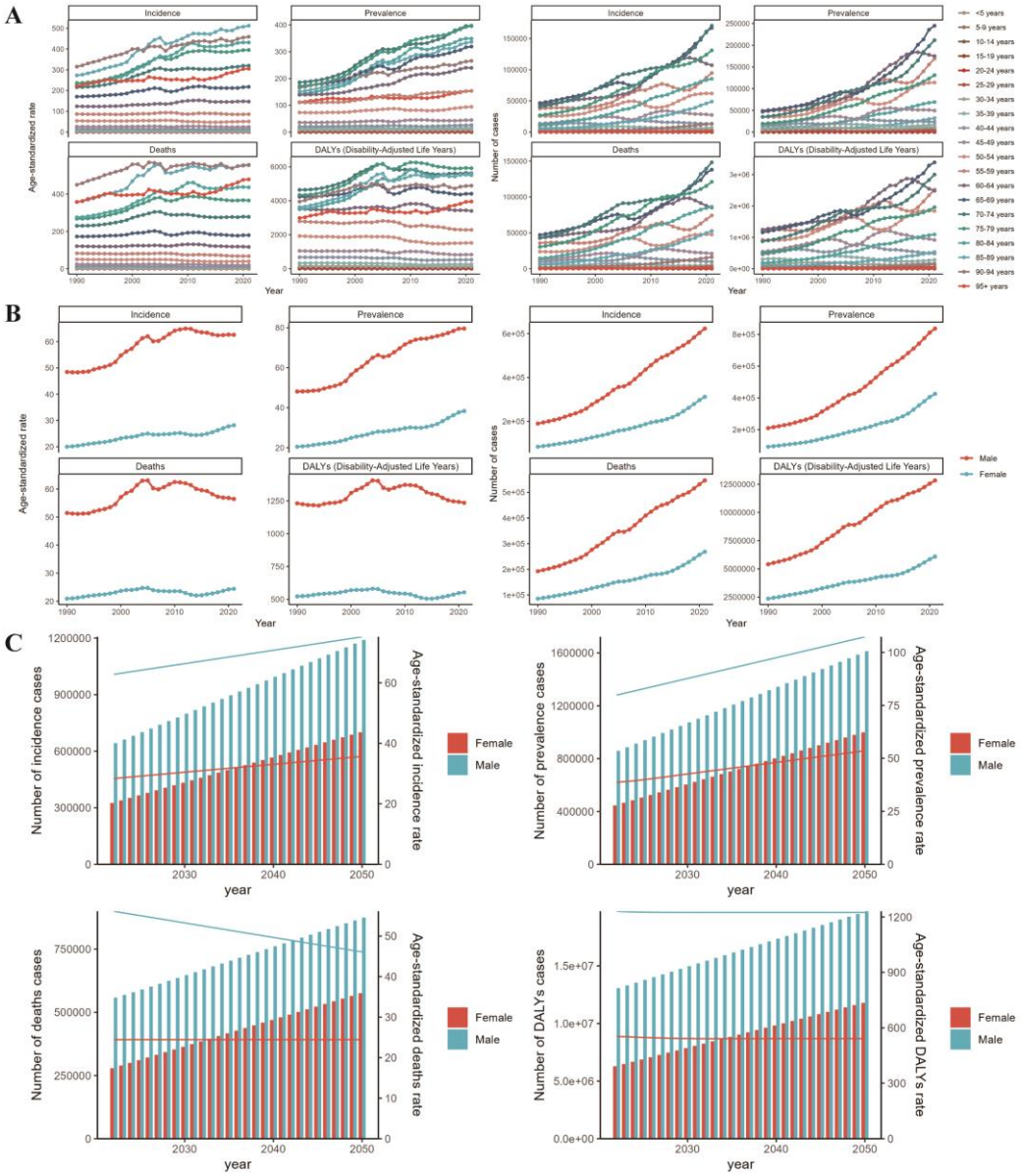

Figure 2 (A-B) Trends in the Burden of Disease for TBL cancer by age and sex in China, 1990-2021.（C）Trends in TBL cancer disease burden in China through 2050 as projected by the ARIMA Predictive Model.

We also analyzed the risk factors for TBL cancer and found that smoking and household air pollution from solid fuels dominated in 1990. By 2021, although smoking still accounted for the largest risk proportion, its relative contribution had decreased over time, as had the risk proportion attributable to household air pollution from solid fuels. In contrast to these declines, the contributions from ambient particulate matter pollution increased significantly over this time period (**Figure 7A-D**).

3.2 Changes in the burden of disease and future trends for TBL cancer in Japan, 1990-2021

In 2021, the number of TBL cancer deaths in Japan was 92,119 (95% UI:78,912-98,959), including 64,188 (95% UI:57,963-67,475) in men

and 27,931 (95% UI:21031-3,819) in women. The highest number of deaths occurred in the 80-84 year age group (**Figure 3A**).

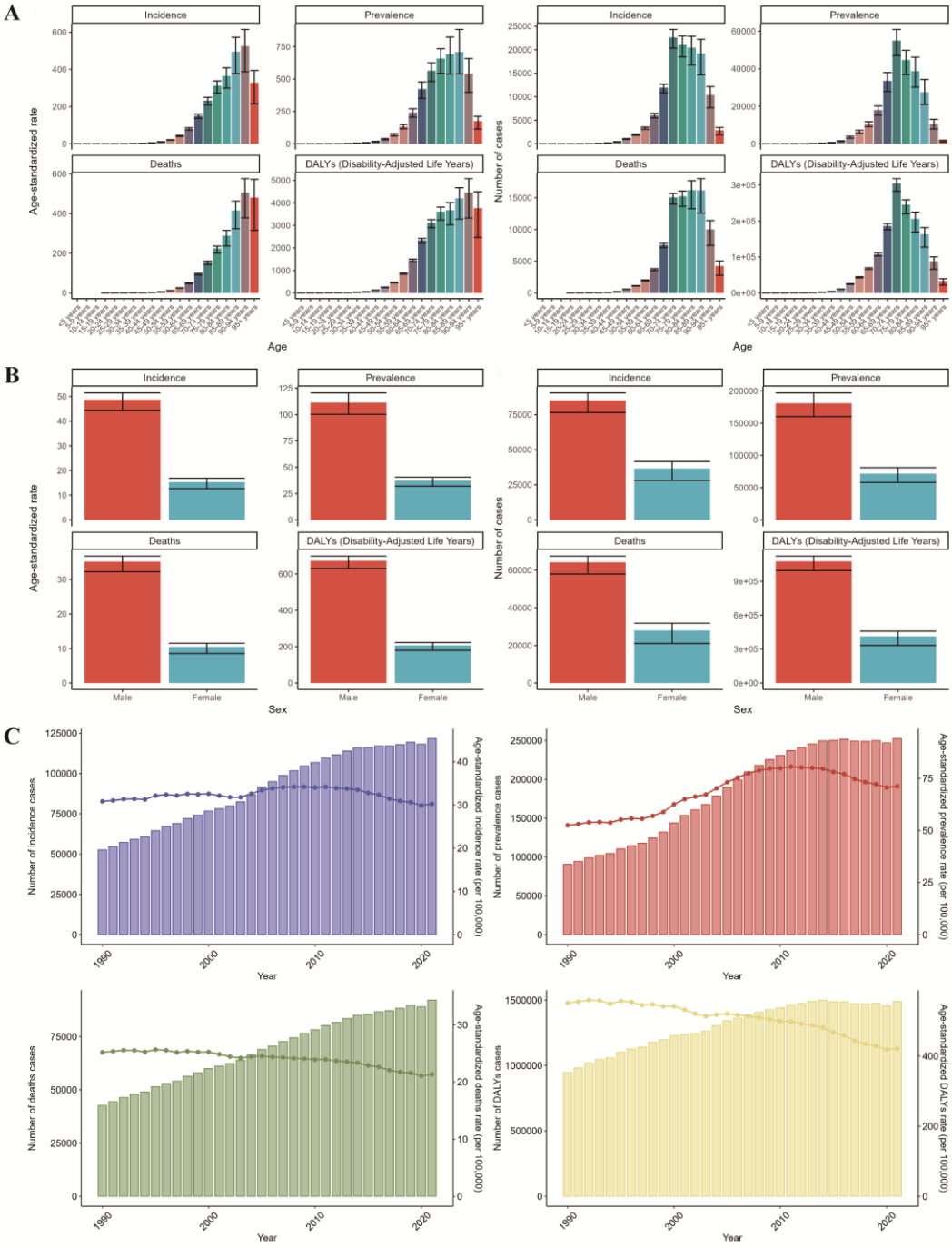

Figure 3 (A-B) Distribution of TBL cancer disease burden by age and sex in Japan in 2021.（C）Trends in the burden of disease for TBL cancer in Japan, 1990-2021

TBL cancer-related ASDR was 21.33 (95% UI:19.06-22.57)/100,000, overall, including 35.19 (95% UI:32.29-36.8)/100,000 in men and 10.48 (95% UI:8.57-11.55)/100,000 in women (**Table S1**).

Table S1 Number of deaths and age-standardized deaths rates due to TBL cancer in 1990 and 2021, and trends in Japan from 1990 to 2021.

Characteristics	Number of deaths cases (95% UI) in 1990	The age-standardized deaths rate/100000 (95% UI) in 1990	Number of deaths cases (95% UI) in 2021	The age-standardized deaths rate/100000 (95% UI) in 2021	EAPC (95% CI)
Japan	42,675 (40,404-43,980)	25.2 (23.77-25.99)	92,119 (78,912-98,959)	21.33 (19.06-22.57)	-0.57 (-0.65--0.49)
Sex					
Female	11,610 (10,581-12,196)	11.94 (10.88-12.55)	27,931 (21,031-31,819)	10.48 (8.57-11.55)	-0.48 (-0.55--0.41)
Male	31,064 (29,854-31,929)	44.34 (42.39-45.61)	64,188 (57,963-67,475)	35.19 (32.29-36.8)	-0.8 (-0.9--0.69)
Age					
15-19 years	7 (7-7)	0.07 (0.07-0.07)	3 (3-3)	0.05 (0.04-0.05)	-1.86 (-2.11--1.61)
20-24 years	12 (12-13)	0.14 (0.13-0.14)	6 (6-6)	0.09 (0.09-0.1)	-1.22 (-1.51--0.92)
25-29 years	28 (27-29)	0.34 (0.33-0.35)	12 (12-13)	0.2 (0.19-0.21)	-1.82 (-2.08--1.57)
30-34 years	86 (83-89)	1.08 (1.04-1.11)	34 (33-35)	0.51 (0.5-0.53)	-2.51 (-2.71--2.31)
35-39 years	254 (245-263)	2.75 (2.66-2.85)	77 (74-80)	1.02 (0.98-1.06)	-3.05 (-3.3--2.8)
40-44 years	602 (585-621)	5.52 (5.36-5.69)	214 (207-222)	2.57 (2.48-2.65)	-2.87 (-3.09--2.64)
45-49 years	1,037 (1,002-1,076)	11.28 (10.89-11.71)	572 (551-595)	5.77 (5.55-6)	-2.52 (-2.82--2.22)
50-54 years	1,665 (1,616-1,717)	20.28 (19.68-20.91)	1,126 (1,081-1,165)	12.01 (11.54-12.43)	-1.79 (-2.18--1.4)
55-59 years	3,136 (3,046-3,236)	40.22 (39.06-41.5)	1,997 (1,922-2,066)	25.29 (24.35-26.18)	-1.24 (-1.56--0.92)
60-64 years	5,046 (4,894-5,201)	74.26 (72.03-76.56)	3,685 (3,504-3,819)	49.41 (46.99-51.21)	-0.95 (-1.2--0.7)
65-69 years	6,003 (5,775-6,160)	116.7 (112.26-119.75)	7,554 (7,131-7,822)	95.06 (89.73-98.43)	-0.73 (-0.89--0.57)
70-74 years	7,105 (6,832-7,332)	184.71 (177.61-190.61)	15,040 (13,969-15,664)	154.14 (143.16-160.53)	-0.79 (-0.91--0.67)
75-79 years	7,934 (7,442-8,213)	261.24 (245.03-270.42)	15,217 (13,630-16,044)	224.01 (200.63-236.17)	-0.76 (-0.88--0.64)
80-84 years	5,827 (5,238-6,177)	315.95 (284.02-334.91)	16,193 (13,258-17,667)	288.86 (236.5-315.17)	-0.25 (-0.39--0.1)
85-89 years	2,958 (2,548-3,172)	353 (304.05-378.54)	16,151 (12,571-17,988)	415.78 (323.61-463.07)	0.63 (0.53-0.73)
90-94 years	834 (685-913)	322.52 (264.92-353.26)	10,002 (7,492-11,396)	505.35 (378.53-575.75)	1.49 (1.39-1.59)
95+ years	139 (104-159)	266.13 (197.89-303.42)	4,236 (2,780-5,049)	480.29 (315.24-572.54)	2.51 (2.3-2.72)

The number of DALY-affected cases was 1489327 (95% UI:1328623-1576188) overall, including 1076103 (95% UI:994596-1123108) in men and 413224 (95% UI:333214-458206) in

women. The peak number of DALY-affected cases was observed in the 70-74 year age group. The DALY ASR was 420.77 (95% UI:387.54-440.11)/100,000 overall, including 671.8 (95% UI:629.67-697.78)/100,000 in men and 207.22 (95% UI:179.44-222.98)/100,000 in women (**Table S2**).

Table S2 Number of DALYs and age-standardized DALYs rates due to TBL cancer in 1990 and 2021, and trends in Japan from 1990 to 2021

Characteristics	Number of DALYs cases (95% UI) in 1990	The age-standardized DALYs rate/100000 (95% UI) in 1990	Number of DALYs cases (95% UI) in 2021	The age-standardized DALYs rate/100000 (95% UI) in 2021	EAPC (95% CI)
Japan	946,447 (908,261-971,956)	550.8 (527.84-565.86)	1,489,327 (1,328,623-1,576,188)	420.77 (387.54-440.11)	-0.9 (-1--0.79)
Sex					
Female	250,807 (234,301-260,720)	264.8 (248-274.84)	413,224 (333,214-458,206)	207.22 (179.44-222.98)	-0.86 (-0.96--0.77)
Male	695,640 (674,016-712,667)	929.85 (898.31-953.79)	1,076,103 (994,596-1,123,108)	671.8 (629.67-697.78)	-1.07 (-1.19--0.96)
Age					
15-19 years	525 (508-546)	5.11 (4.95-5.31)	192 (185-200)	3.32 (3.19-3.46)	-1.85 (-2.1--1.6)
20-24 years	841 (810-872)	9.28 (8.94-9.63)	398 (380-415)	6.43 (6.15-6.71)	-1.21 (-1.51--0.92)
25-29 years	1,768 (1,704-1,846)	21.36 (20.59-22.3)	783 (750-820)	12.41 (11.89-13)	-1.81 (-2.06--1.55)
30-34 years	5,001 (4,832-5,170)	62.66 (60.55-64.77)	1,986 (1,921-2,057)	29.99 (29-31.05)	-2.49 (-2.69--2.29)
35-39 years	13,455 (12,990-13,955)	145.86 (140.82-151.28)	4,106 (3,944-4,263)	54.7 (52.55-56.8)	-3.03 (-3.28--2.78)
40-44 years	29,110 (28,217-29,991)	266.91 (258.72-274.99)	10,364 (9,987-10,708)	124.06 (119.55-128.17)	-2.84 (-3.07--2.61)
45-49 years	44,844 (43,341-46,606)	487.67 (471.33-506.83)	24,887 (23,901-25,889)	251.01 (241.06-261.11)	-2.5 (-2.8--2.2)
50-54 years	64,111 (62,160-66,172)	780.95 (757.18-806.05)	43,653 (41,968-45,173)	465.74 (447.77-481.96)	-1.77 (-2.16--1.38)
55-59 years	106,207 (103,186-109,546)	1,362.04 (1,323.3-1,404.87)	67,878 (65,371-70,218)	859.86 (828.1-889.5)	-1.22 (-1.54--0.9)
60-64 years	147,609 (143,099-152,018)	2,172.51 (2,106.12-2,237.4)	108,018 (102,813-112,014)	1448.38 (1378.58-1501.95)	-0.94 (-1.19--0.7)
65-69 years	148,317 (142,673-	2,883.3 (2,773.58-	186,093 (175,434-	2341.74 (2207.6-	-0.73 (-0.89--0.57)

	152,295)	2,960.65)	192,798)	2426.11)	
70-74 years	143,625 (138,035-148,051)	3,733.62 (3,588.3-3,848.68)	304,782 (282,780-317,758)	3123.58 (2898.08-3256.56)	-0.77 (-0.89--0.65)
75-79 years	128,356 (120,640-132,956)	4,226.24 (3,972.19-4,377.7)	245,417 (219,859-259,022)	3612.68 (3236.46-3812.96)	-0.75 (-0.87--0.63)
80-84 years	74,248 (66,894-78683)	4,025.66 (3,626.92-4,266.12)	206,108 (169,399-224,948)	3676.7 (3021.86-4012.78)	-0.24 (-0.39--0.1)
85-89 years	29,969 (25,896-32,175)	3,576.27 (3,090.17-3,839.47)	163,247 (127,263-181,585)	4202.59 (3276.24-4674.66)	0.62 (0.52-0.72)
90-94 years	7,325 (6,013-8,027)	2,832.57 (2,325.16-3,103.99)	88,187 (65,899-100,499)	4455.45 (3329.38-5077.46)	1.51 (1.41-1.61)
95+ years	1,136 (847-1,295)	2,170.05 (1,618.09-2,473.68)	33,227 (21,780-39,674)	3767.5 (2469.53-4498.47)	2.43 (2.2-2.66)

Case incidence was 121731 (95% UI:105282-131198), and ASIR was 30.24 (95% UI:27.16-32.13)/100,000 (**Table S3**).

Table S3 Number of incidence and age-standardized incidence rates due to TBL cancer in 1990 and 2021, and trends in Japan from 1990 to 2021

Characteristics	**Number of incidence cases (95% UI) in 1990**	**The age-standardized incidence rate/100000 (95% UI) in 1990**	**Number of incidence cases (95% UI) in 2021**	**The age-standardized incidence rate/100000 (95% UI) in 2021**	**EAPC (95% CI)**
Japan	52,644 (49,939-54,525)	30.83 (29.21-31.96)	121,731 (105,282-131,198)	30.24 (27.16-32.13)	0.03 (-0.12-0.18)
Sex					
Female	14,648 (13,351-15,474)	15.08 (13.75-15.92)	36,608 (28,144-41,595)	15.28 (12.67-16.86)	0.02 (-0.11-0.16)
Male	37,996 (36,480-39,177)	53.05 (50.7-54.76)	85,123 (76,451-90,438)	48.63 (44.4-51.4)	-0.18 (-0.34--0.02)
Age					
15-19 years	9 (9-10)	0.09 (0.09-0.1)	5 (4-6)	0.08 (0.07-0.1)	-0.43 (-0.84--0.02)
20-24 years	16 (15-16)	0.17 (0.16-0.18)	10 (9-12)	0.16 (0.15-0.19)	0.19 (-0.33-0.71)
25-29 years	39 (37-41)	0.47 (0.44-0.49)	24 (21-27)	0.37 (0.33-0.43)	-0.4 (-0.88-0.08)
30-34 years	120 (115-127)	1.51 (1.44-1.59)	66 (58-76)	0.99 (0.88-1.14)	-1.11 (-1.51--0.71)
35-39 years	374 (356-394)	4.05 (3.86-4.27)	155 (139-176)	2.06 (1.85-2.35)	-1.7 (-2.16--1.23)

40-44 years	861 (822-902)	7.89 (7.54-8.27)	402 (361-443)	4.81 (4.32-5.3)	-1.82 (-2.17--1.47)
45-49 years	1,412 (1,343-1,480)	15.36 (14.6-16.09)	1,022 (936-1,111)	10.3 (9.44-11.2)	-1.43 (-1.87--0.98)
50-54 years	2,314 (2,203-2,436)	28.19 (26.84-29.67)	1,937 (1,791-2,062)	20.66 (19.11-22)	-0.94 (-1.41--0.48)
55-59 years	4,406 (4,180-4,652)	56.51 (53.61-59.66)	3,344 (3,084-3,555)	42.37 (39.07-45.03)	-0.49 (-0.89--0.08)
60-64 years	7,054 (6,728-7,421)	103.82 (99.02-109.22)	6,052 (5,499-6,458)	81.15 (73.74-86.59)	-0.28 (-0.59-0.02)
65-69 years	7,936 (7,498-8,369)	154.27 (145.76-162.69)	11,940 (10,836-12,685)	150.25 (136.36-159.62)	-0.03 (-0.21-0.14)
70-74 years	8,736 (8,264-9,212)	227.09 (214.84-239.48)	22,629 (20,342-24,339)	231.91 (208.47-249.44)	-0.08 (-0.22-0.06)
75-79 years	9,112 (8,551-9,612)	300.03 (281.53-316.49)	21,191 (18,497-22,951)	311.94 (272.28-337.85)	0 (-0.17-0.17)
80-84 years	6,225 (5,517-6,662)	337.53 (299.11-361.23)	20,445 (16,767-22,891)	364.71 (299.1-408.35)	0.47 (0.29-0.66)
85-89 years	3,236 (2,776-3,539)	386.11 (331.29-422.34)	19,227 (14,657-22,245)	494.98 (377.31-572.68)	0.96 (0.85-1.08)
90-94 years	703 (568-776)	271.69 (219.61-300)	10,386 (7,664-12,172)	524.75 (387.22-614.97)	2.26 (2.18-2.33)
95+ years	91 (68-104)	174.13 (129.03-199.09)	2,897 (1,899-3,472)	328.51 (215.33-393.69)	2.67 (2.44-2.91)

ASDR, ASR of DALYs, and ASIR all peaked in the 90-94 year age group (Figure 3A). Case prevalence was 252645 (95% UI:221384-274788) and ASPR was 71.23 (95% UI:64.39-76.51)/100,000 (**Table S4**), with the highest prevalence in the 85-89 age group. Similarly to China, the disease burden was much greater in men than in women (**Figure 3B**).

Table S4 Number of prevalence and age-standardized prevalence rates due to TBL cancer in 1990 and 2021, and trends in Japan from 1990 to 2021

Characteristics	**Number of prevalence cases (95% UI) in 1990**	**The age-standardized prevalence rate/100000 (95% UI) in 1990**	**Number of prevalence cases (95% UI) in 2021**	**The age-standardized prevalence rate/100000 (95% UI) in 2021**	**EAPC (95% CI)**
Japan	90,620 (85,893-94,263)	52.5 (49.7-54.62)	252,645 (221,384-274,788)	71.23 (64.39-76.51)	1.41 (1.09-1.73)
Sex					
Female	25,982 (23,950-27,686)	27.07 (25.03-28.77)	71,838 (58,176-81,016)	37.18 (32.06-40.53)	1.1 (0.75-1.45)
Male	64,638 (61,183-67,529)	86.57 (81.66-90.53)	180,807 (160,137-196,861)	111.33 (100.25-120.53)	1.35 (1.03-1.67)
Age					
15-19 years	23 (21-24)	0.22 (0.21-0.24)	17 (14-21)	0.29 (0.24-0.36)	1.09 (0.41-1.76)

20-24 years	38 (36-41)	0.42 (0.39-0.45)	36 (31-43)	0.58 (0.5-0.7)	1.69 (0.91-2.49)
25-29 years	124 (117-132)	1.5 (1.41-1.6)	101 (87-119)	1.6 (1.37-1.89)	0.76 (0.07-1.46)
30-34 years	389 (364-413)	4.88 (4.56-5.18)	284 (243-334)	4.28 (3.67-5.04)	0.06 (-0.56-0.68)
35-39 years	977 (916-1,052)	10.59 (9.93-11.4)	585 (495-692)	7.79 (6.6-9.22)	-0.19 (-0.93-0.55)
40-44 years	1,951 (1,803-2,115)	17.89 (16.53-19.4)	1,321 (1,112-1,554)	15.82 (13.31-18.6)	-0.34 (-0.98-0.3)
45-49 years	3,031 (2,791-3,294)	32.97 (30.35-35.82)	3,450 (2,942-4,008)	34.79 (29.67-40.43)	0.51 (-0.27-1.29)
50-54 years	5,153 (4,792-5,644)	62.77 (58.38-68.75)	6,466 (5,580-7,275)	68.99 (59.53-77.62)	0.77 (0.09-1.44)
55-59 years	9,958 (9,104-10,902)	127.7 (116.76-139.81)	10,533 (9,164-11,767)	133.42 (116.09-149.06)	1 (0.41-1.6)
60-64 years	15,528 (14,084-17,054)	228.54 (207.29-251)	17,960 (15,235-20,136)	240.82 (204.28-270)	1.06 (0.64-1.49)
65-69 years	15,471 (14,177-17,053)	300.76 (275.61-331.52)	33,566 (27,879-37,992)	422.38 (350.81-478.08)	1.47 (1.25-1.7)
70-74 years	14,334 (13,054-15,735)	372.62 (339.34-409.05)	55,039 (47,010-61,006)	564.07 (481.78-625.23)	1.34 (1.07-1.61)
75-79 years	12,550 (11,350-13,834)	413.21 (373.7-455.49)	44,687 (36,918-49,859)	657.82 (543.45-733.96)	1.73 (1.39-2.07)
80-84 years	7,122 (6,159-7,962)	386.13 (333.96-431.68)	38,774 (30,151-46,211)	691.68 (537.85-824.34)	2.56 (2.3-2.82)
85-89 years	3,371 (2,850-3,828)	402.24 (340.15-456.84)	27,548 (20,963-34,308)	709.18 (539.66-883.22)	2.18 (2.01-2.35)
90-94 years	553 (446-626)	213.75 (172.53-241.95)	10,740 (7,876-13,029)	542.59 (397.92-658.24)	3.32 (3.23-3.41)
95+ years	46 (34-53)	88.46 (65.54-101.1)	1,539 (1,002-1,864)	174.48 (113.58-211.32)	2.81 (2.59-3.03)

From 1990 to 2021, TBL cancer-related deaths in Japan increased from 42675 (95% UI:40404-43980) to 92119 (95% UI:78912-98959), an increase of 115.9%. However, the corresponding ASDR decreased over time (EAPC, -0.57 (95% UI:-0.65--0.49)). The number of DALY-affected cases increased from 946447 (95% UI:908261-971956) to 1489327 (95% UI:1328623-1576188), but the ASR of DALYs decreased over time (EAPC, -0.9 (95% UI:-1--0.79)). Case incidence and prevalence both increased significantly over time, and the corresponding ASIR (EAPC, 0.03 (95% UI:-0.12- 0.18)) and ASPR (EAPC, 1.41 (95% UI:1.09-1.73)) also increased (**Table 5-8, Figure 3C**).The fastest increase in mortality was observed in the 85-89 year age group, and the fastest increase in the number of DALYs, incidence, and prevalence was observed in the 70-74 year age group (**Figure 4A**). The most significant downward trends in ASDR (EAPC, -0.8 (95% UI:-0.9--0.69)) and number of DALY-affected cases (EAPC, -1.07 (95% UI:-1.19--0.96)) were seen amongst men (**Figure 4B**).

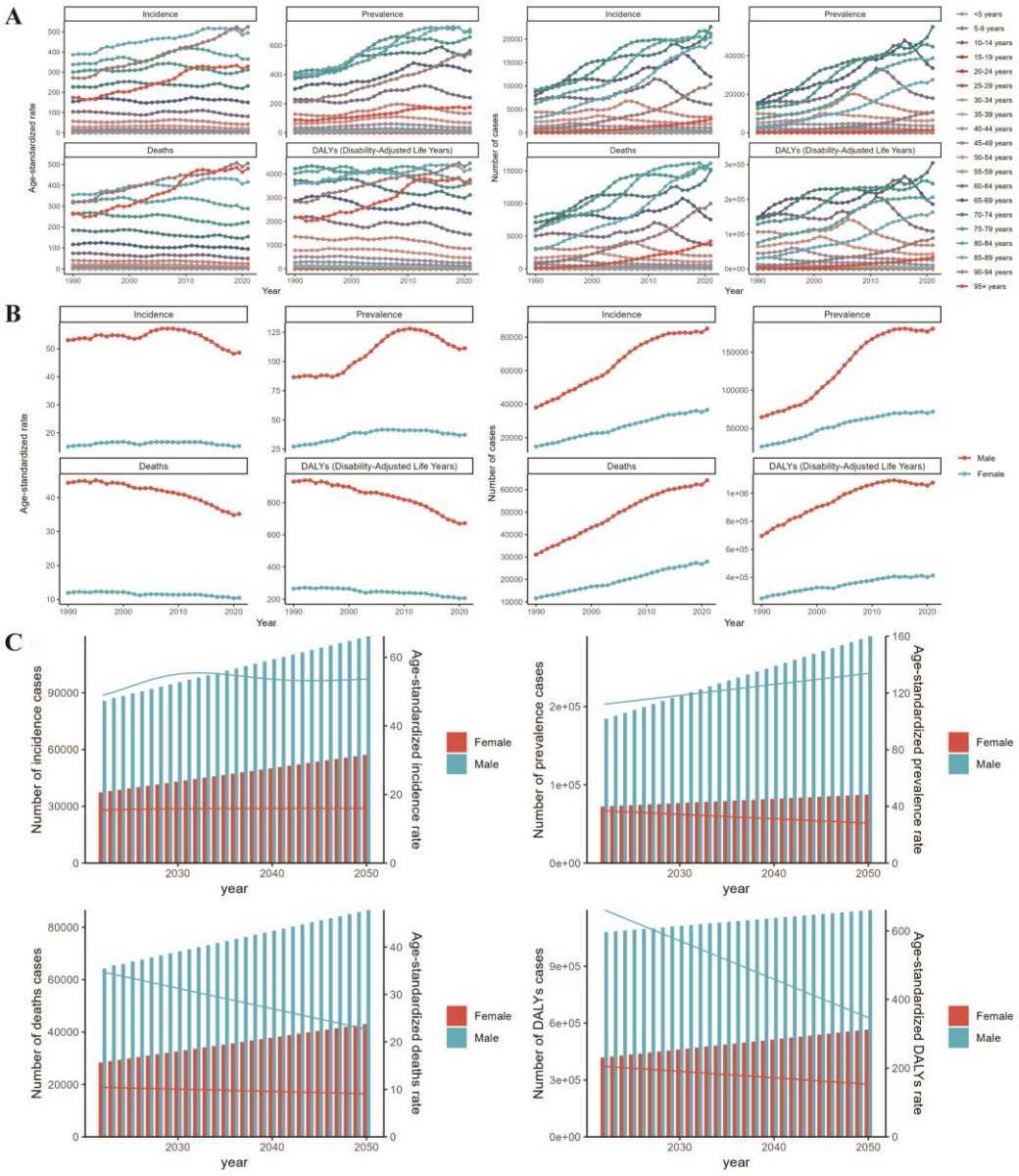

Figure 4 (A-B) Trends in the Burden of Disease for TBL cancer by age and sex in Japan, 1990-2021.（C）Trends in TBL cancer disease burden in Japan through 2050 as projected by the ARIMA Predictive Model

Our model projected that DALY-related ASDR and DALY-related ASR would continue to decline through 2050 in Japan despite an increase in mortality and DALYs. We also analyzed risk factors associated with TBL cancer-related disease burden in Japan and found that, from 1990 to 2021, the greatest risk factor was smoking, but the proportion of risk attributable to smoking gradually decreased over time, while the proportion of risk attributable to occupational exposure to asbestos gradually increased (**Figure 7A-D**).

3.3 Changes in the burden of disease and future trends for TBL cancer in Southeast Asia, 1990-2021

In 2021, the number of TBL cancer-related deaths in Southeast Asia was 134,949 (95% UI: 110670-155,974) overall, including 91,884 (95% UI: 76399-108,062) for men and 43,065 (95% UI: 95% UI: 33,425-51,659) for women. The ASDR was 21.17 (95%UI: 17.34-24.41)/100,000 overall, 31.74 (95%UI: 26.49-36.96)/100,000 for men, and 12.57 (95%UI: 9.8-15.01)/100,000 for women (**Table S5**).

Table S5 Number of deaths and age-standardized deaths rates due to TBL cancer in 1990 and 2021, and trends in Southeast Asia from 1990 to 2021.

Characteristics	Number of deaths cases (95% UI) in 1990	The age-standardized deaths rate/100000 (95% UI) in 1990	Number of deaths cases (95% UI) in 2021	The age-standardized deaths rate/100000 (95% UI) in 2021	EAPC (95% CI)
Southeast Asia	49,571 (43,828-55,536)	20.01 (17.62-22.48)	134,949 (110,670-155,974)	21.17 (17.34-24.41)	-0.03 (-0.12-0.07)
Sex					
Female	13,883 (11,833-16,579)	10.41 (8.89-12.44)	43,065 (33,425-51,659)	12.57 (9.8-15.01)	0.31 (0.17-0.45)
Male	35,688 (30,782-41,886)	31.41 (26.9-36.68)	91,884 (76,399-108,062)	31.74 (26.49-36.96)	-0.14 (-0.22--0.05)
Age					
15-19 years	101 (80-117)	0.2 (0.16-0.24)	131 (102-160)	0.23 (0.18-0.28)	0.38 (0.31-0.45)
20-24 years	158 (128-184)	0.36 (0.29-0.41)	226 (182-282)	0.4 (0.32-0.5)	0.16 (0.04-0.27)
25-29 years	234 (196-269)	0.58 (0.49-0.67)	364 (293-443)	0.64 (0.51-0.78)	-0.11 (-0.38-0.16)
30-34 years	410 (351-467)	1.18 (1.01-1.34)	701 (561-856)	1.27 (1.02-1.55)	-0.12 (-0.43-0.19)
35-39 years	716 (614-814)	2.53 (2.17-2.87)	1,331 (1,057-1,611)	2.54 (2.02-3.08)	-0.24 (-0.44--0.03)
40-44 years	1,298 (1,124-1,470)	6.01 (5.2-6.8)	2,872 (2,291-3,474)	5.85 (4.67-7.08)	-0.23 (-0.36--0.11)
45-49 years	2,442 (2,145-2,787)	13.58 (11.93-15.5)	5,786 (4,629-7,008)	13.03 (10.42-15.78)	-0.29 (-0.4--0.18)
50-54 years	4,510 (3,923-5,131)	28.51 (24.79-32.43)	10,685 (8,512-12,895)	26.52 (21.12-32)	-0.34 (-0.41--0.28)
55-59 years	6,577 (5,814-7,547)	49.69 (43.93-57.02)	16,132 (13,049-19,267)	46.3 (37.45-55.3)	-0.38 (-0.44--0.32)
60-64 years	8,657 (7,462-9,807)	81.73 (70.45-92.59)	21,953 (17,741-25,792)	76.88 (62.13-90.33)	-0.45 (-0.53--0.37)
65-69 years	8,711 (7,422-9,916)	114.64 (97.68-130.5)	23,939 (19,502-28,037)	113.56 (92.51-133)	-0.28 (-0.38--0.17)
70-74 years	6,989 (6,111-7,994)	139.17 (121.7-159.18)	20,018 (16,355-23398)	147.41 (120.43-172.29)	-0.05 (-0.15-0.05)
75-79 years	4,531 (3,873-5,204)	147.78 (126.32-169.71)	14,181 (11,571-16,478)	171.6 (140.02-199.4)	0.3 (0.19-0.41)
80-84 years	2,551 (2,204-2,969)	144.48 (124.81-168.13)	9,476 (7,571-11,177)	196.32 (156.87-231.57)	0.75 (0.62-0.88)

85-89 years	1,304 (1,092-1,515)	165.61 (138.69-192.41)	4,868 (3,923-5,869)	208.91 (168.36-251.87)	0.67 (0.58-0.76)
90-94 years	318 (258-375)	147.12 (119.39-173.27)	1,787 (1,338-2,195)	213.19 (159.7-261.96)	0.78 (0.59-0.98)
95+ years	65 (49-84)	108.93 (82.84-141.68)	498 (353-629)	208.67 (147.96-263.48)	1.89 (1.58-2.21)

The number of DALYs, case incidence, and case prevalence were 3556362 (95% UI: 2921602-4139203), 131740 (95% UI: 108216-152398), 142581 (95% UI: 117611-165258), respectively, and the corresponding ASR of DALYs, ASIR, and ASPR were 511.56 (95% UI: 420.51-593.15), 20.13 (95%UI: 16.5-23.18), and 20.6 (95%UI: 16.94-23.81), respectively (**Tables S6-8**).

Table S6 Number of DALYs and age-standardized DALYs rates due to TBL cancer in 1990 and 2021, and trends in Southeast Asia from 1990 to 2021.

Characteristics	**Number of DALYs cases (95% UI) in 1990**	**The age-standardized DALYs rate/100000 (95% UI) in 1990**	**Number of DALYs cases (95% UI) in 2021**	**The age-standardized DALYs rate/100000 (95% UI) in 2021**	**EAPC (95% CI)**
Southeast Asia	1,387,855 (1,230,913-1548,882)	504.76 (447.39-564.57)	3,556,362 (2,921,602-4,139,203)	511.56 (420.51-593.15)	-0.16 (-0.25--0.07)
Sex					
Female	396,607 (334,799-473,957)	268.83 (228.57-321.29)	1,125,883 (864,995-1,373,015)	306.46 (237-371.82)	0.11 (-0.03-0.26)
Male	991,248 (858,926-1162,004)	774.08 (669.14-907.78)	2,430,479 (2,006,733-2,890,119)	750.39 (622.03-887.13)	-0.27 (-0.34--0.19)
Age					
15-19 years	7,326 (5,816-8,489)	14.9 (11.83-17.27)	9,522 (7,415-11672)	16.82 (13.1-20.62)	0.38 (0.31-0.45)
20-24 years	10,759 (8,711-12,503)	24.14 (19.55-28.06)	15,365 (12,345-19,104)	27.29 (21.92-33.93)	0.16 (0.04-0.27)
25-29 years	14,764 (12,339-16,980)	36.77 (30.73-42.29)	22,969 (18,438-27,916)	40.41 (32.44-49.11)	-0.11 (-0.38-0.16)
30-34 years	23,805 (20,368-27,165)	68.42 (58.54-78.08)	40,704 (32,594-49,669)	73.69 (59-89.91)	-0.12 (-0.43-0.18)
35-39 years	38,054 (32,641-43,248)	134.28 (115.17-152.6)	70,677 (56,125-85,534)	135.1 (107.28-163.5)	-0.24 (-0.45--0.04)
40-44 years	62,528 (54,162-70,937)	289.38 (250.66-328.29)	138,231 (110,299-167,067)	281.71 (224.78-340.48)	-0.24 (-0.37--0.12)
45-49 years	105,572 (92,804-120,455)	587.02 (516.03-669.78)	250,271 (200,391-303,199)	563.57 (451.25-682.75)	-0.3 (-0.4--0.19)
50-54 years	173,407 (150,966-197,383)	1,096.03 (954.19-1,247.57)	411,245 (327,753-496,158)	1,020.64 (813.42-1,231.37)	-0.34 (-0.41--0.27)

55-59 years	221,989 (196,238-254,445)	1,677.4 (1,482.82-1,922.64)	545,029 (440,227-650,333)	1,564.26 (1,263.48-1,866.49)	-0.37 (-0.43--0.31)
60-64 years	252,194 (217,215-285,924)	2,380.99 (2,050.76-2,699.45)	639,791 (517,522-752,027)	2,240.66 (1,812.45-2,633.72)	-0.44 (-0.52--0.37)
65-69 years	213,873 (182,137-243,437)	2,814.72 (2,397.04-3,203.79)	588,350 (480,196-688,480)	2,790.95 (2,277.91-3,265.94)	-0.27 (-0.37--0.17)
70-74 years	141,379 (123,333-161,609)	2,815.33 (2,455.98-3,218.19)	405,697 (331,510-474,229)	2,987.47 (2,441.17-3,492.12)	-0.05 (-0.16-0.05)
75-79 years	73,390 (62,654-84,312)	2,393.58 (2,043.42-2,749.79)	229,759 (187,713-267,111)	2,780.21 (2,271.43-3,232.19)	0.29 (0.18-0.4)
80-84 years	32,334 (27,872-37,718)	1,831.09 (1,578.43-2,136.02)	120,101 (95,897-141,586)	2,488.34 (1,986.86-2,933.48)	0.75 (0.62-0.89)
85-89 years	13,168 (11,034-15,313)	1,672.15 (1,401.14-1,944.48)	48,999 (39,546-59,095)	2,102.77 (1,697.1-2,536.01)	0.67 (0.58-0.76)
90-94 years	2,785 (2,260-3,281)	1,287.37 (1,044.92-1,516.5)	15,618 (11,715-19,172)	1,863.67 (1,397.88-2,287.7)	0.78 (0.59-0.98)
95+ years	528 (402-682)	889.35 (677.89-1,149.64)	4,034 (2,875-5,089)	1,688.71 (1,203.44-2,130.45)	1.81 (1.47-2.14)

Table S7 Number of incidence and age-standardized incidence rates due to TBL cancer in 1990 and 2021, and trends in Southeast Asia from 1990 to 2021.

Characteristics	**Number of incidence cases (95% UI) in 1990**	**The age-standardized incidence rate/100000 (95% UI) in 1990**	**Number of incidence cases (95% UI) in 2021**	**The age-standardized incidence rate/100000 (95% UI) in 2021**	**EAPC (95% CI)**
Southeast Asia	47,601 (42,047-53,436)	18.69 (16.44-21.05)	131,740 (108,216-152,398)	20.13 (16.5-23.18)	0.03 (-0.06-0.13)
Sex					
Female	13,343 (11,391-15,906)	9.75 (8.33-11.62)	41,969 (32,660-50,578)	11.99 (9.36-14.34)	0.37 (0.23-0.51)
Male	34,258 (29,478-40,277)	29.18 (24.89-34.21)	89,771 (74,616-105,516)	29.97 (25.07-34.94)	-0.08 (-0.16-0)
Age					
15-19 years	102 (81-118)	0.21 (0.16-0.24)	136 (106-166)	0.24 (0.19-0.29)	0.47 (0.4-0.54)
20-24 years	154 (125-179)	0.35 (0.28-0.4)	226 (183-282)	0.4 (0.32-0.5)	0.24 (0.13-0.36)
25-29 years	249 (209-288)	0.62 (0.52-0.72)	400 (323-487)	0.7 (0.57-0.86)	-0.01 (-0.28-0.26)

30-34 years	443 (380-505)	1.27 (1.09-1.45)	783 (627-953)	1.42 (1.14-1.73)	-0.02 (-0.33-0.29)
35-39 years	816 (703-926)	2.88 (2.48-3.27)	1,572 (1,254-1,907)	3 (2.4-3.65)	-0.12 (-0.33-0.08)
40-44 years	1,417 (1,231-1,605)	6.56 (5.7-7.43)	3,252 (2,593-3,932)	6.63 (5.28-8.01)	-0.11 (-0.24-0.01)
45-49 years	2,605 (2,295-2,969)	14.49 (12.76-16.51)	6,411 (5,162-7,728)	14.44 (11.62-17.4)	-0.17 (-0.27--0.06)
50-54 years	4,749 (4,115-5,422)	30.01 (26.01-34.27)	11,673 (9,292-14,022)	28.97 (23.06-34.8)	-0.22 (-0.28--0.16)
55-59 years	6,712 (5,931-7,701)	50.72 (44.82-58.19)	17,043 (13,814-20,343)	48.92 (39.65-58.39)	-0.26 (-0.32--0.2)
60-64 years	8,591 (7,393-9,748)	81.11 (69.8-92.03)	22,517 (18,335-26,579)	78.86 (64.21-93.09)	-0.34 (-0.42--0.26)
65-69 years	8,309 (7,111-9,510)	109.35 (93.59-125.16)	23,544 (19,217-27,487)	111.68 (91.16-130.39)	-0.18 (-0.28--0.07)
70-74 years	6,334 (5,494-7,245)	126.13 (109.4-144.26)	18,682 (15,305-21,835)	137.57 (112.7-160.79)	0.05 (-0.05-0.15)
75-79 years	3,871 (3,300-4,438)	126.26 (107.62-144.74)	12,479 (10,203-14,558)	151 (123.46-176.16)	0.4 (0.29-0.51)
80-84 years	2,023 (1,744-2,351)	114.58 (98.76-133.16)	7,734 (6,161-9,113)	160.24 (127.65-188.81)	0.85 (0.72-0.98)
85-89 years	968 (809-1,127)	122.96 (102.7-143.13)	3,723 (2,897-4,499)	159.77 (124.32-193.06)	0.77 (0.68-0.85)
90-94 years	218 (174-258)	100.58 (80.61-119.14)	1,255 (944-1,546)	149.77 (112.7-184.49)	0.87 (0.68-1.07)
95+ years	40 (30-53)	67.66 (50.87-88.55)	311 (220-394)	130.13 (91.9-164.86)	1.91 (1.59-2.22)

Table S8 Number of prevalence and age-standardized prevalence rates due to TBL cancer in 1990 and 2021, and trends in Southeast Asia from 1990 to 2021.

Characteristics	**Number of prevalence cases (95% UI) in 1990**	**The age-standardized prevalence rate/100000 (95% UI) in 1990**	**Number of prevalence cases (95% UI) in 2021**	**The age-standardized prevalence rate/100000 (95% UI) in 2021**	**EAPC (95% CI)**
Southeast Asia	50,621 (44,912-56,693)	18.51 (16.36-20.77)	142,581 (117,611-165,258)	20.6 (16.94-23.81)	0.15 (0.06-0.24)
Sex					
Female	14,391 (12,270-17,127)	9.8 (8.39-11.67)	45,539 (35,531-55,028)	12.45 (9.76-14.95)	0.48 (0.34-0.62)
Male	36,230 (31,362-42,558)	28.47 (24.53-33.42)	97,042 (80,639-115,085)	30.11 (25.12-35.46)	0.02 (-0.05-0.1)
Age					
15-19 years	181 (143-209)	0.37 (0.29-0.43)	248 (194-303)	0.44 (0.34-0.54)	0.56 (0.49-0.64)
20-24 years	280 (227-325)	0.63 (0.51-0.73)	423 (342-526)	0.75 (0.61-0.93)	0.35 (0.23-0.46)

25-29 years	626 (523-723)	1.56 (1.3-1.8)	1,036 (836-1,262)	1.82 (1.47-2.22)	0.09 (-0.18-0.36)
30-34 years	1,109 (953-1,265)	3.19 (2.74-3.63)	2,027 (1,623-2,463)	3.67 (2.94-4.46)	0.1 (-0.21-0.41)
35-39 years	1,565 (1,349-1,776)	5.52 (4.76-6.27)	3,149 (2,507-3,810)	6.02 (4.79-7.28)	0.03 (-0.17-0.23)
40-44 years	1,872 (1,627-2,121)	8.67 (7.53-9.82)	4,550 (3,629-5,516)	9.27 (7.4-11.24)	0.08 (-0.04-0.21)
45-49 years	3,435 (3,030-3,911)	19.1 (16.85-21.74)	8,978 (7,223-10,831)	20.22 (16.27-24.39)	0.04 (-0.06-0.14)
50-54 years	6,225 (5,392-7,106)	39.34 (34.08-44.91)	16,271 (12,969-19,505)	40.38 (32.19-48.41)	-0.01 (-0.06-0.05)
55-59 years	8,229 (7,269-9,435)	62.18 (54.92-71.29)	22,225 (17,914-26,513)	63.79 (51.41-76.09)	-0.05 (-0.11-0)
60-64 years	9,219 (7,940-10,473)	87.04 (74.97-98.88)	25,744 (20,977-30,350)	90.16 (73.46-106.29)	-0.14 (-0.22--0.06)
65-69 years	7,981 (6,837-9,131)	105.04 (89.98-120.17)	24,069 (19,635-28,117)	114.17 (93.14-133.38)	0.03 (-0.08-0.13)
70-74 years	5,226 (4,531-5,973)	104.07 (90.23-118.94)	16,407 (13,420-19,103)	120.82 (98.82-140.67)	0.25 (0.15-0.36)
75-79 years	2,732 (2,328-3,133)	89.1 (75.94-102.18)	9,348 (7,642-10,934)	113.12 (92.47-132.31)	0.61 (0.5-0.71)
80-84 years	1,265 (1,090-1,474)	71.66 (61.74-83.46)	5,102 (4,058-6,001)	105.72 (84.07-124.33)	1.04 (0.91-1.16)
85-89 years	540 (450-629)	68.52 (57.19-79.83)	2,158 (1,677-2,620)	92.59 (71.96-112.41)	0.89 (0.81-0.98)
90-94 years	116 (93-137)	53.52 (42.89-63.46)	689 (520-850)	82.26 (62.02-101.39)	0.97 (0.78-1.16)
95+ years	20 (15-26)	33.92 (25.5-44.39)	156 (110-198)	65.47 (46.21-82.97)	1.92 (1.61-2.23)

Mortality and DALYs were highest in the 60-69 year age group. ASDR was highest in the 90-94 year age group. (**Figure 5A**). Number of deaths, DALYs, incidence, and prevalence were significantly greater in men than women **(Figure 5B**).

Between 1990 and 2021, TBL cancer-related deaths and DALYs in Southeast Asia increased 1.72-fold and 1.56-fold, respectively. However, ASR of DALYs (EAPC: -0.03 (95% UI: -0.12-0.07)) and ASDR (-0.16 (EAPC: 95% UI: -0.25-0.07)) decreased (**Figure 5C**).

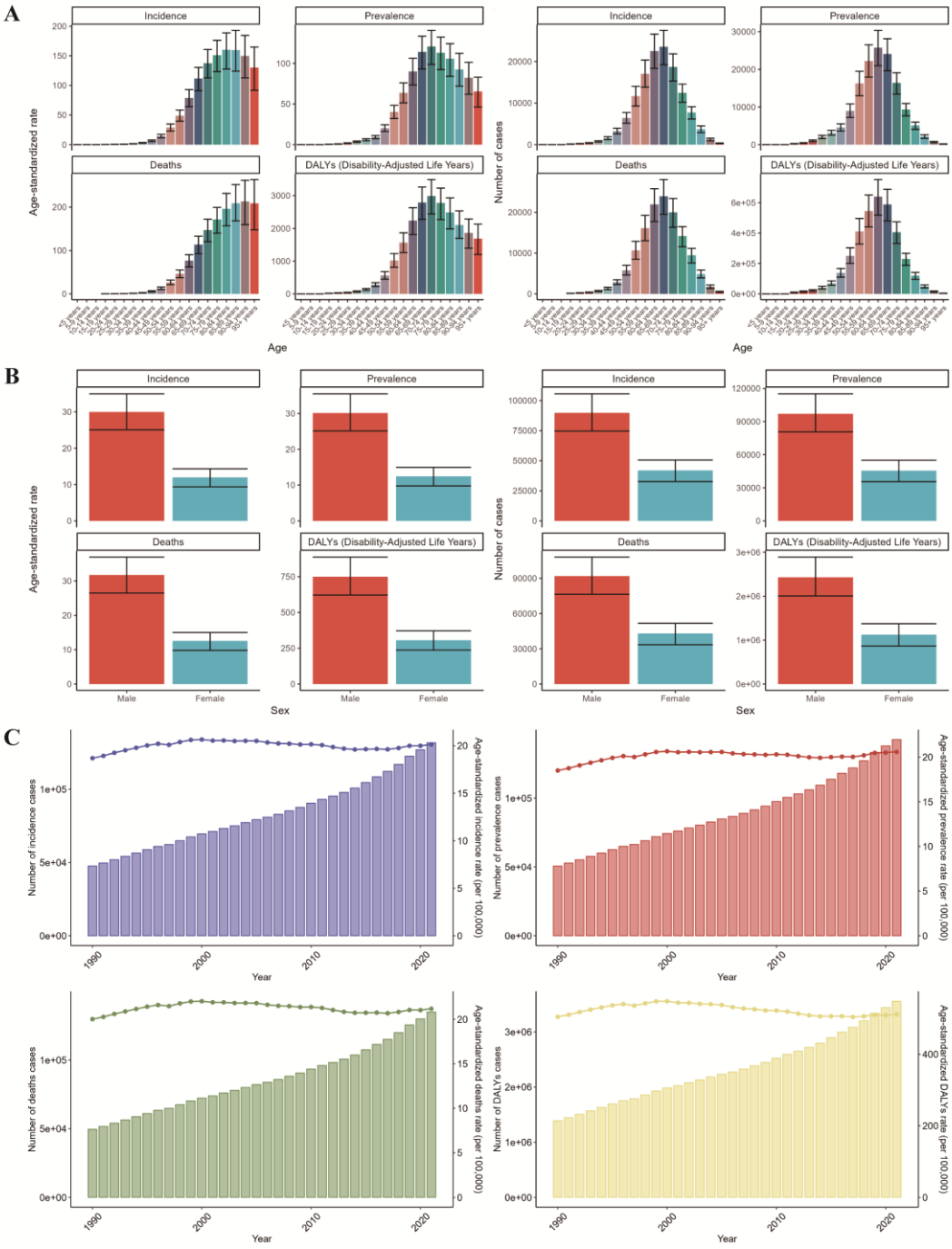

Figure 5 (A-B) Distribution of TBL cancer disease burden by age and sex in Southeast Asia in 2021. (C) Trends in the burden of disease for TBL cancer in Southeast Asia, 1990-2021.

Increases in TBL cancer-related deaths were most pronounced in the 60-69 age group, with a more significant increase amongst men (**Figure 6A-B**). According to our model's projections, mortality, DALYs, incidence, and prevalence of TBL cancer in Southeast Asia will continue to increase through 2050, but the corresponding ASRs will level off (**Figure 6C**).

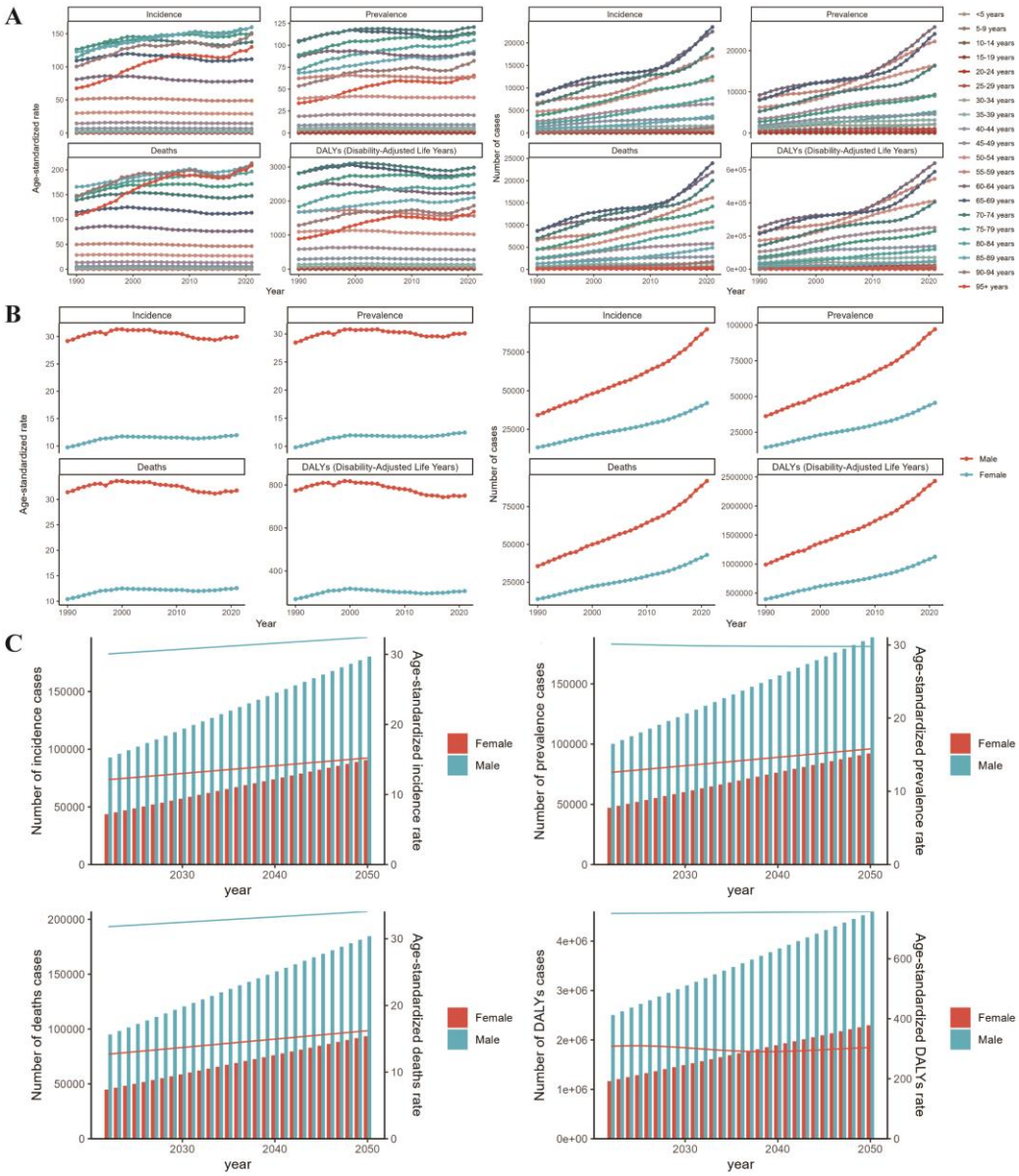

Figure 6 (A-B) Trends in the Burden of Disease for TBL cancer by age and sex in Southeast Asia, 1990-2021.（C）Trends in TBL cancer disease burden in Southeast Asia through 2050 as projected by the ARIMA Predictive Model

The main risk factor for TBL cancer in Southeast Asia was smoking, followed by household air pollution from solid fuels and ambient particulate matter pollution. From 1990 to 2021, the proportion of risk attributable to household air pollution from solid fuels gradually decreased, while the proportion of risk attributable to ambient particulate matter pollution gradually increased (**Figure 7A-D**).

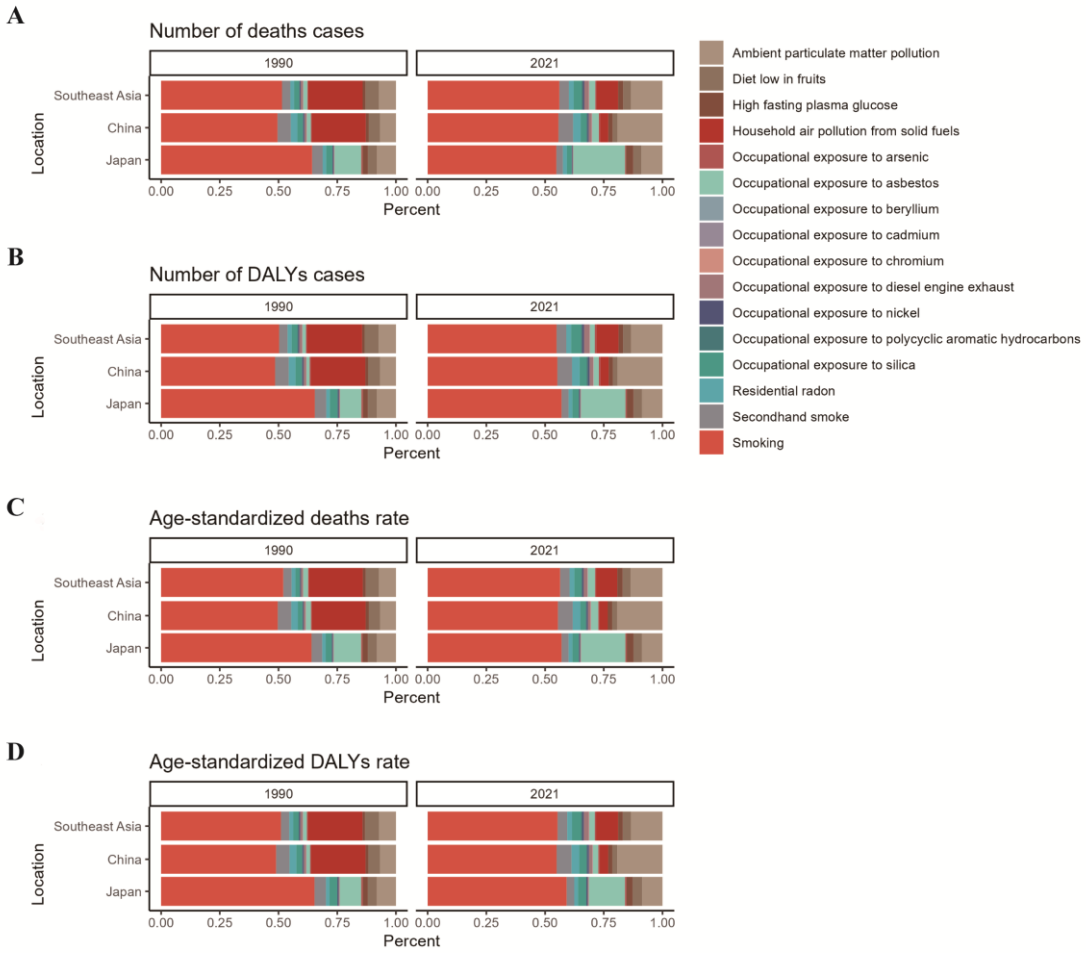

Figure 7 (A-D) Risk factors for TBL cancer.

Discussion

From 1990 to 2021, the burden of disease related to TBL cancer has been slowly increasing in China, with a more pronounced trend in men. However, TBL cancer-associated ASDR and ASR of DALYs in China reached a peak in 2005, and have continued to decline since then. Our prospective model suggested that TBL cancer-related disease burdens will decline over the next 25 years, especially among men. Over the past three decades, the global TBL cancer disease burden has been gradually decreasing, and although China's ASDR and DALY ASRs have decreased over time, ASIR and ASPR have continued to increase. The TBL cancer disease burden in China is higher than both global and Asian regional levels [10, 11]. TBL cancer occurs as a result of the interaction between genetic and environmental factors. Several previous studies have found that polymorphisms in some genes are associated with an increased risk of lung cancer in Chinese populations, including rs3200401 in lncRNA MALAT1[12] , rs28757157 in CYP19A1 [13], rs2099361 in CYP2B6 [14], Tyr113His and His139Arg polymorphisms in the mEH gene, rs2736098G/A polymorphisms in the TERT gene, rs6495309 polymorphisms in the CHRNA3 gene, GSTT1 deletions, GSTP1 Ile105Val, GSTM1 deletions, the ERCC2, XRCC2, and XRCC1 genes involved in DNA repair, the CYP1A1, CPY2E1, and CYP2D6 genes with five polymorphisms, and the VEGF, P53, MTHFR, APE1, and NQO1 genes [15]. These genetic predispositions may contribute to the disproportionately high disease burdens in Chinese populations. We also analyzed the risk factors for lung cancer, and found that the proportion of risk attributable to smoking and household air pollution from solid fuels gradually decreased over time, while the proportion of risk attributable to ambient particulate matter pollution generally increased. Smoking has long been the leading risk factor for TBL cancer, and China is the world's largest producer and consumer of tobacco. There is also a much higher prevalence

of smoking amongst Chinese men than in women, which likely contributes to gender-based disparities in TBL cancer-related outcomes. In response to this enormous public health challenge, the Chinese government launched the"Healthy China 2030" national strategy, which aims to reduce smoking prevalence to less than 20% by increasing the cost and taxation of tobacco and banning smoking in public spaces [16]. At the beginning of the 21st century, almost all rural Chinese residents, along with a small percentage of urban residents, relied on solid fuels (wood, crop residues, and coal) for cooking or heating [17]. However, household solid fuel-related pollution has continued to decrease as China urbanizes, and most Chinese cities plan to eliminate the use of household coal and transition to cleaner fuels (e.g., liquefied petroleum gas (LPG), biogas, or electricity). Declining smoking rates and reduced pollution from solid fuels appear to have reduced the burden of TBL cancer-related disease to some extent. However, alongside rapid economic development and urbanization, ambient particulate matter pollution from industrial and automobile exhaust has rapidly increased [18], and is another prominent risk factor for TBL cancer. The Chinese government has addressed these increases in air pollution with several policy measures, including limiting gas emissions from factories, promoting the use of new energy products, and encouraging people to travel sustainably. The introduction of immunotherapy and other targeted therapies over the past several decades has also improved survival rates amongst lung cancer patients [19]. Thus, changes in environmental exposures and improved treatments may help explain the projected decreases in TBL cancer disease burden.

Between 1990 and 2021, the TBL cancer-associated disease burden in Japan trended downward, especially after 2010. The TBL cancer-related disease burden is lower in Japan compared to global and regional Asian levels. In Japan, the proportion of risk for TBL cancer attributable to smoking has decreased over time, but it remains the number one risk factor for these conditions. Additionally, the proportion of risk attributable to occupational exposure to asbestos has increased over time. Japan enacted the Health Promotion Law, which prevented passive smoking, in 2002. In 2020, the law was further amended to strengthen penalties and prohibit smoking indoors, except in public facilities, public transportation, and restaurants used by a small number of citizens [3]. Smoking is also explicitly prohibited in schools, hospitals, children's facilities, and government buildings. Taken together, these measures have helped significantly reduce the prevalence of smoking [20], which has been declining amongst Japanese men since 1995, and amongst women since 20024. Low-dose computed tomography (CT) screening has also become an important means of detecting early-stage lung cancer, and Japan ranks first amongst the Organization for Economic Cooperation and Development (OECD) countries in terms of the number of CT scanners, MRI scanners, and PET machines owned per capita. Even small family clinics are equipped with CT scanners, and the low cost and high availability have greatly increased the penetration of early lung cancer screening in Japan. This means the country has higher early diagnostic rates and survival rates for lung cancer than other countries, resulting in a relatively small burden of disease [19]. Asbestos exposure is another important risk factor for lung cancer, and in Japan, there was a dramatic increase in asbestos imports between 1960 and 1974. Seventy-seven thousand tons of asbestos were imported in 1960, and a peak of 352,316 tons were imported in 1974 [21]. The median latency period for asbestos exposure to lung cancer development is 47 years [22]. Thus, to maintain decreases in TBL cancer-related disease burdens, Japan still needs to strictly control smoking prevalence and exposure to asbestos, as well as address other environmental factors that can cause TBL cancer.

The burden of TBL cancer-associated disease in Southeast Asia decreased between 1990-2021, with a lower ASDR than China, Japan, and South Korea. The largest risk factor for TBL cancer in this region is also smoking. Southeast Asian countries are among the highest-ranked tobacco producing and consuming regions of the globe, with India being the world's second-largest consumer and third-largest producer of tobacco. 42% of adult men and 14.2% of adult women in India currently smoke or use smokeless tobacco. With the introduction of anti-tobacco legislation in various Southeast Asian countries in the 21st century, the overall prevalence of tobacco use in the region has declined from 47% in 2000 to 29% in 2018, and is projected to further decline to 25%

by 2025 [23]. The significant decline in smoking prevalence has had a large impact on TBL Cancer rates. However, previous research has also demonstrated that a large proportion of lung cancer patients in Southeast Asia have never smoked. For example, an Indian study showed that the proportion of TBL cancer patients who had smoked ranged from 40%-50% [24, 25]. The remaining cases may be associated with household air pollution from solid fuels and/or ambient particulate matter pollution. Our present results also suggest that the proportion of risk for TBL cancer attributable to ambient particulate matter pollution in Southeast Asia has increased in recent years, both in relation to increases in vehicle emissions and pollutant gases from factories and in relation to increases in particulate air pollution from fires. Previous studies have shown that particulate matter air pollution from fires disproportionately affects poorer populations in Southeast Asia and that reducing exposure to particulate matter and ozone pollution from fires would relay considerable public health benefits throughout the region [26].

Through this study, we were able to detail changes in TBL cancer-related disease burdens over time throughout China, Japan, and Southeast Asia, as well as to help identify gender-based and geographic disparities in TBL cancer. However, our study also had some limitations. First, the quality and incompleteness of the raw data likely affected our estimations and predictions of TBL cancer burdens. In the 1990s, Internet technology was not fully available and disease registry systems were incompletely developed, which could have decreased case registrations and led to missing data, especially in low- and middle-income countries. Second, the GBD lacks robust data sources for countries with small populations, meaning that disease estimates for these countries rely on predictive covariates and neighboring regions, which may further affect their accuracy. Third, the lack of genetic information in the GBD for patients with TBL cancer prevented us from analyzing risk factors other than environmental factors. Finally, the heterogeneity of risk factors across histologic types of TBL cancer prevented us from assessing risk factors that may have corresponded to specific pathologic subtypes.

Conclusions

Between 1990 and 2021, age-labeled ASDR and ASR of DALYs for TBL cancer in Japan and Southeast Asia decreased. In China, however, the age-labeled ASDR and ASR of DALYs for TBL cancer increased. The burden of disease was significantly greater in men than in women. The major risk factor for TBL cancer in China, Japan, and Southeast Asia was smoking, but the proportion of risk attributable to smoking gradually decreased over time, while the proportion of risk attributable to factors related to air pollution gradually increased. Our systematic analysis of the disease burden and risk factors associated with TBL cancer in China, Japan, and Southeast Asia between 1990 and 2021 provides insights to help policymakers promote the early prevention and treatment of these cancers and improve public health.

Statement of Ethics

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Conflict of Interest Statement

We declare that we have no financial and personal relationshipswith other people or organizations that can inappropriately influenceour work, there is no professional or other personal interest of any nature or kind in any product, service and company that could beconstrued as influencing the position presented in, or the review of,the manuscript entitled.

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Author Contributors

Pengkhun Nov and Duanyu Wang designed the overall research, Duanyu Wang collected data and verified the accuracy of the data; Duanyu Wang and Minghao Tan prepared manuscript and images; Duanyu Wang, Minghao Tan, Socheat Touch, Syphanna Sou and Virak Vichet analyzed and interpreted data; all authors contributed to revise manuscript. All authors read and approved the final manuscript.

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Data Availability Statement

This study follows the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER). To download the data used in these analyses, please visit the Global Health Data Exchange (GHDx). https://ghdx.healthdata.org/gbd-2021.

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