The International Epidemiology of Lung Cancer

Geographical Distribution and Secular Trends

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Abstract: This review presents the latest available international data for lung cancer incidence, mortality and survival, emphasizing the established causal relationship between smoking and lung cancer. In 2002, it was estimated that 1.35 million people throughout the world were diagnosed with lung cancer, and 1.18 million died of lung cancer—more than for any other type of cancer. There are some key differences in the epidemiology of lung cancer between more developed and less developed countries. In more developed countries, incidence and mortality rates are generally declining among males and are starting to plateau for females, reflecting previous trends in smoking prevalence. In contrast, there are some populations in less developed countries where increasing lung cancer rates are predicted to continue, due to endemic use of tobacco. A higher proportion of lung cancer cases are attributable to nonsmoking causes within less developed countries, particularly among women. Worldwide, the majority of lung cancer patients are diagnosed after the disease has progressed to a more advanced stage. Despite advances in chemotherapy, prognosis for lung cancer patients remains poor, with 5-year relative survival less than 14% among males and less than 18% among females in most countries. Given the increasing incidence of lung cancer in less developed countries and the current lack of effective treatment for advanced lung cancers, these results highlight the need for ongoing global tobacco reform to reduce the international burden of lung cancer.

Key Words: Lung cancer, International, Epidemiology, Smoking.

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Lung cancer continues to be the leading cause of cancer-related deaths worldwide.[1] Despite improvements in survival for many other types of cancer in recent years, 5-year survival for lung cancer has remained relatively poor, mainly because by the time a diagnosis is made, lung cancer is often well advanced and treatment options are limited.[2–4]

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The most important risk behavior for lung cancer is tobacco smoking. The relationship between smoking and lung cancer is one of the most thoroughly investigated issues in biomedical research,[5] and compelling evidence has built up since the middle of the twentieth century to indicate that smoking is the predominant causal factor for lung cancer.[6–10] A large number of studies have found that smokers have a 15- to 30-fold increased risk of developing lung cancer compared with nonsmokers.[9] There is also sufficient evidence to conclude that exposure to second-hand smoke (commonly known as 'passive smoking') can cause lung cancer.[6,11]

However not all lung cancers are due to smoking, and it is likely that the proportion of lung cancer patients who have never smoked may increase in the future.[12,13] Exposure to indoor radon (a naturally occurring radioactive gas) is considered to be the second most important environmental risk factor for lung cancer behind tobacco smoke in the United States,[14] and was recently estimated to be responsible for 9% of all lung cancer deaths in Europe.[15] A family history of lung cancer has been shown to result in a twofold increase in lung cancer risk, independent of smoking.[16,17] Air pollution, pre-existing diseases of the lungs such as tuberculosis or pneumonia, high doses of radiation, and exposure to industrial or chemical carcinogens such as asbestos, silica, and arsenic have also been associated with an increased risk of developing lung cancer.[5,12,18,19] Factors such as household air pollution from cooking and heating fumes appear to play a greater role in the etiology of lung cancer for nonsmokers within less developed countries, especially among women.[20–22]

The purpose of this review is to describe current international patterns in lung cancer incidence, mortality and survival, including recent trends, along with a discussion of the impact of smoking on the observed data. (Throughout this article, lung cancer has been defined as codes C33–C34 using the International Classification of Diseases, 10th revision [ICD-10].[23]) An international perspective has been provided wherever possible; however, when detailed information was only available for a specific country (for example, incidence by stage), data from that country is presented alone.

LUNG CANCER INCIDENCE

An estimated 1.35 million people were diagnosed with lung cancer worldwide during 2002 (12% of all invasive cancers),[1] an increase of about 110,000 compared with the number of lung cancers diagnosed in 2000.[24] About 71% (or about 960,000) of these lung cancer diagnoses were among males,[1] with age-standardized rates (using the World Health Organiza-

tion World Standard population)[25] of 40 and 13 new cases per 100,000 population for males and females respectively.[26]

Globally, lung cancer has been the most common cancer diagnosed each year since 1985.[1] Lung cancer had a higher incidence among males worldwide than any other cancer, followed by prostate cancer (more common in developed countries) and stomach cancer (particularly in developing countries). Among females, lung cancer was the fourth most diagnosed cancer, behind breast cancer, cervical cancer (mostly in developing countries), and colorectal cancer.[1]

For both sexes, the estimated number of lung cancer cases diagnosed in more developed countries during 2002 was similar to that in less developed countries.[1] However, after allowing for differences in population size and age structures, lung cancer incidence rates were around twice as high in more developed countries (61/100,000 among males and 19/100,000 among females) compared with less developed countries (29/100,000 among males and 10/100,000 among females).[26]

Sex-specific incidence rates varied substantially between countries (Fig. 1). For males, estimated lung cancer incidence rates ranged from 104/100,000 in Hungary to less than 5/100,000 in many African countries (such as Kenya). The highest estimated rate for females was in the United States (40/100,000 population) compared with a rate of between 2 to 3/100,000 in a range of less developed countries including India, Algeria, Kenya, and Iran (Table 1).[26]

Text Box 1

GLOBOCAN data

The main source of data used in this article was GLOBOCAN 2002. GLOBOCAN is a database constructed by the World Health Organization (WHO) which contains estimates of incidence, mortality and prevalence data for different types of cancer for every country as at 2002.[26] GLOBOCAN 2002 was published in 2004, and remains the most recent source of international cancer data currently available. Data from GLOBOCAN can be reported in terms of more developed and less developed countries. More developed countries included those in Europe and North America along with Australia, New Zealand, and Japan, whereas less developed countries were defined as those in Africa, Central and South America, Asia (excluding Japan), and all other island nations (i.e., those in the Caribbean, Melanesia, Micronesia, and Polynesia).[27] Care should be taken when interpreting any comparisons of international data. For example, the accuracy of cancer data in GLOBOCAN varies from region to region. Incidence and mortality data for countries including Australia, Canada, and the United Kingdom were based on national data collections. In contrast, national estimates for many countries throughout Asia (including China and India) were based on cancer registries that only cover part of the population, whereas in Africa estimates were often obtained by averaging results from neighboring countries.[26] Similarly, the accuracy of premature mortality data reported later in this article ranges from a relative uncertainty of less than 1% in countries with comprehensive death registration systems up to 25% in countries where the collection of mortality data is limited.[28]

Incidence by Age

Worldwide during 2002, 5% of lung cancer cases were diagnosed among people aged 0 to 44 years, 14% in the 45 to 54 age group, 25% in the 55 to 64 age group, and 55% among those aged 65 years and over.[26] These proportions were fairly uniform for both sexes.

Age-specific lung cancer incidence rates were between 1.5 to 2.3 times higher for more developed countries compared with less developed countries within each age group. There was also a significantly higher proportion of lung cancer patients aged 65 years and over at diagnosis within more developed countries (62% compared with 49% in less developed countries).[26] This primarily reflects the higher life expectancy and different age distribution in more developed countries compared with less developed countries.

Although current smokers are at an increased risk of developing lung cancer compared with nonsmokers within every age group (20–25 times higher among males and 10–12 times higher among females across most age groups),[7] there does not appear to be any clear link between median age at diagnosis and smoking status.[12,29,30] It is possible that the apparent parity of age at diagnosis by smoking status may stem from biologic differences between lung cancer among never smokers compared with lung cancer among smokers.[12,30]

Text Box 2

Worldwide smoking prevalence

In 2005, it was estimated that around 1.25 billion adults throughout the world were smokers–around 1 billion men and 250 million women.[31] This represented approximately 35% of men and 22% of women in more developed countries, compared with 50% of men and 9% of women in less developed countries.[31] Smoking rates were highest for men in Afghanistan (82%), Yemen (77%), and Djibouti (75%) and for women in the Cook Islands (71%), Nauru (59%), and Guinea (47%).[31]

Incidence by Histology

Lung cancers can be divided into two main types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLCs are the most aggressive form of the disease, having greater potential to metastasis than other types of lung cancer. Nearly all patients (over 95%) diagnosed with SCLC are current or ex-smokers.[32]

NSCLCs are a heterogeneous group, of which the most common subtypes are squamous cell carcinomas and adenocarcinomas. Squamous cell carcinomas are also predominantly linked to smoking.[33] These tumors tend to grow in the center of the lung and have the capacity to grow to large sizes.[34] Adenocarcinomas usually occur in the periphery of the lung.[34] Although it is the most common type of lung cancer seen in nonsmokers,[19] smoking has been increasingly associated as a cause of adenocarcinoma in more recent years.[6,35]

The distribution of lung cancer incidence by histology and sex for selected countries is shown in Table 2. Within each of these countries, squamous cell carcinoma

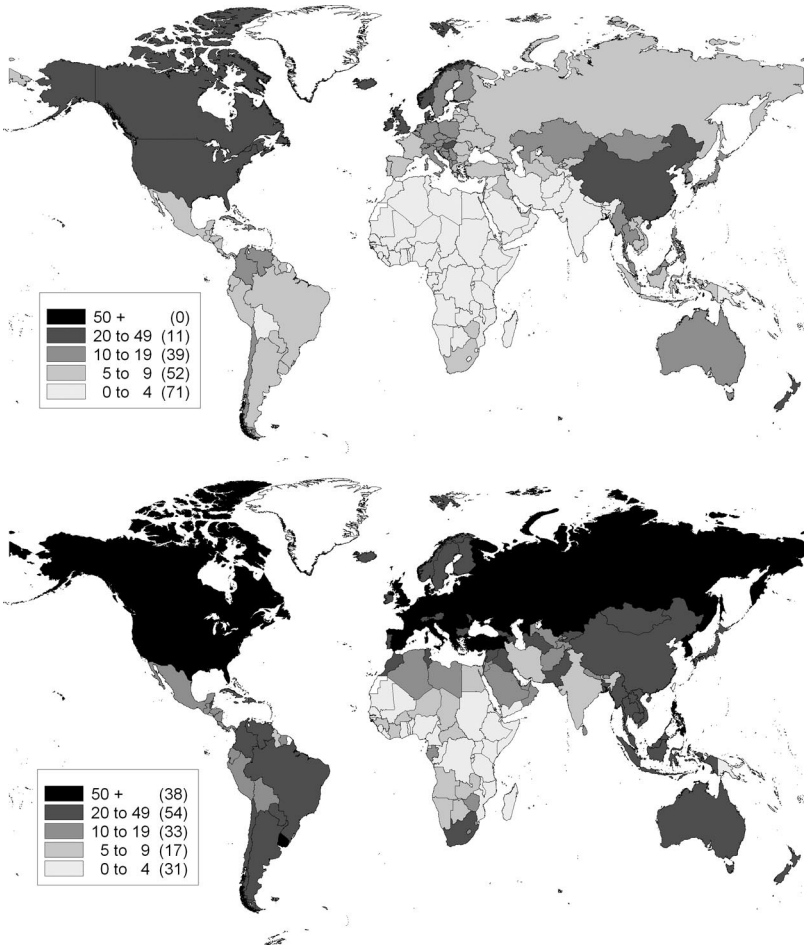

FIGURE 1. International variation in age-standardized lung cancer incidence rates (per 100,000 population) in 2002. Notes: 1. Rates age-standardized to the WHO World Standard Population.[25] Source: GLOBOCAN 2002, International Agency for Research on Cancer (IARC).[26] 2. Lung cancer incidence rates for females are represented in the top map and for males in the bottom map. 3. The numbers in brackets shown in the legend signify how many countries are included in that incidence range.

comprised a much higher proportion of lung cancers diagnosed among males than females, whereas adenocarcinoma comprised a greater proportion of lung cancers diagnosed among females compared with males. Among males, squamous cell carcinoma was the most common histologic type of lung cancer in Korea (46%), France (41%) and the United Kingdom (40%), whereas adenocarcinoma was the most common type in the United States (31%), Canada (31%), Sweden (30%), and Australia (29%). With the exception of the United Kingdom (where 28% of lung cancer cases among females were squamous cell carcinomas), adenocarcinomas made up the greatest proportion of lung cancers among females for all of the countries shown (ranging from 38% in the United States up to 69% in Japan).[36] Small cell cancers comprised between 14% (Australia and Japan) to 17% (Korea and the United Kingdom) of lung cancers among males, and between 9% (Japan) to 22% (United Kingdom) of lung cancers among females.

Incidence by Stage

Lung cancer is typically asymptomatic in its early stages of development, and even when symptoms appear, they are usually nonspecific.[37] As a result, the majority of lung cancer patients are diagnosed after the disease has progressed to a more advanced stage. In the United States between 1996–2003, only 16% of lung cancer cases were localized when diagnosed (compared with 91% for prostate cancer, 80% for melanoma and 61% for female breast cancer), 35% were regional and 41% were distant, with the remaining 8% unstaged.[38] Females were slightly more likely than males to be diagnosed with localized lung cancer (18% and 15% respectively), whereas a higher proportion of males had distant metastases at diagnosis (43% males, 39% females).[38]

Incidence Trends

The estimated number of lung cancer cases rose by 51% worldwide between 1985 and 2002, with a larger increase among females (76%) compared with males (44%).[1] After adjusting for population increases and ageing, age-standardized rates decreased slightly (−3%) among males over this period, whereas rates increased (22%) among females.[1]

Lung cancer incidence rates peaked among males in North America, Australia, New Zealand, and many countries in North-Western Europe during the 1980s and have since been declining.[27,39,40] In contrast, the incidence rates

TABLE 1. Age-Standardized[a] Lung Cancer[b] Incidence and Mortality Rates (Per 100,000 Population) by Sex for Selected Countries, 2002

	Males					Females			
	Incidence		Mortality			Incidence		Mortality	
	Cases	ASR	Deaths	ASR		Cases	ASR	Deaths	ASR
World	965,241	39.5	848,132	34.9	World	386,891	13.5	330,786	11.5
More developed countries	481,950	61.0	423,507	53.2	More developed countries	194,731	18.9	161,472	15.2
Less developed countries	481,029	28.7	422,681	25.5	Less developed countries	191,192	10.4	168,481	9.2
More developed countries									
Hungary	6461	103.7	5,773	92.3	United States	86,024	40.1	65,792	30.0
Poland	19,478	90.4	16,354	75.9	Canada	8096	34.8	6808	28.5
Belgium	6,518	83.9	6235	78.5	Denmark	1515	32.8	1475	30.8
Russia	53,654	73.4	50,658	69.5	United Kingdom	15,424	27.8	13,390	23.7
Belarus	3825	72.3	3482	66.0	Hungary	2276	27.1	2097	24.4
United States	118,873	69.2	94,640	54.8	New Zealand	607	22.8	574	21.2
Italy	30,384	64.8	26,990	56.3	Australia	2679	18.8	2246	15.4
Canada	12,552	62.6	11,032	54.7	Poland	4534	15.9	3960	13.5
Spain	17,983	61.7	16,253	54.7	Sweden	1253	15.7	1197	14.3
France	23,044	57.5	21,760	52.6	Japan	18,889	13.8	15,257	10.9
United Kingdom	24,300	54.3	21,959	48.6	Belgium	1189	13.3	1052	11.1
Denmark	2011	50.8	2045	51.0	Italy	6784	11.8	5788	9.5
Australia	5565	44.5	4936	39.3	France	4507	9.6	4465	8.8
Japan	47,564	43.2	41,110	36.9	Russia	8909	7.3	8743	6.9
New Zealand	974	42.1	911	39.3	Spain	2038	5.9	1870	5.2
Sweden	1736	23.7	1896	25.5	Belarus	466	5.0	421	4.7
Less developed countries									
Kazakhstan	4794	85.0	4095	73.7	China	126,718	20.9	109,059	18.1
Uruguay	1202	65.4	1017	53.3	Cuba	1229	18.1	1227	18.1
Philippines	10,823	55.8	10,064	51.8	Philippines	3358	15.0	3120	14.0
Turkey	12,862	52.3	11,884	48.4	Kazakhstan	1085	12.7	947	11.1
China	269,650	47.2	231,301	40.9	Thailand	3026	11.4	2858	10.8
Cuba	2826	44.7	2699	42.6	South Africa	1203	8.2	1,099	7.6
Thailand	6429	28.1	6070	26.6	Brazil	5498	7.9	5524	8.0
South Africa	3043	27.4	2788	25.2	Mexico	2633	7.6	2567	7.4
Brazil	13,635	24.0	12,728	22.5	Indonesia	6227	7.5	5736	7.0
Indonesia	15,432	22.3	14,299	20.7	Uruguay	160	7.2	158	6.4
Mexico	5622	19.2	5477	18.8	Zimbabwe	195	6.6	190	6.5
Algeria	1552	18.5	1510	18.1	Turkey	1572	5.8	1453	5.3
Zimbabwe	353	13.8	344	13.4	Egypt	772	3.1	747	3.0
India	35,495	9.9	30,706	8.7	Iran	506	2.4	466	2.3
Egypt	1886	9.5	1837	9.3	Kenya	176	2.3	167	2.2
Iran	1502	8.0	1386	7.5	Algeria	209	2.3	205	2.2
Kenya	296	4.6	288	4.5	India	8046	2.1	6934	1.9

[a] Rates age-standardized to the WHO World Standard Population.[25]
[b] Based on International Classification of Diseases, Version 10 (ICD-10)[23] codes C33–C34–malignant neoplasms of the trachea, bronchus, and lung.
Data source: GLOBOCAN 2002, International Agency for Research on Cancer (IARC).[26]

for males in many Southern and Eastern European countries, Japan and China, and for females from most developed countries, either continue to increase or have recently begun to plateau (Figure 2).[27,39–41] Although trend data is scarce for less developed countries, there is some evidence that lung cancer rates among females in Latin America are increasing,[42] and the incidence of lung cancer is predicted to increase substantially throughout Asia and Africa, particularly among males.[20]

As a result of these differing trends, the global burden of lung cancer has shifted towards less developed countries. In 1980 it was estimated that 31% of new lung cancers were diagnosed in developing countries, but by 2002 this had risen to about 50%.[1]

TABLE 2. Distribution of Lung Cancer by Histological Type and Sex for Selected Countries, 1998–2002

	Small Cell (%)	Squamous (%)	Adenocarcinoma (%)	Other/Unspecified (%)	Microscopically Verified (%)
Males					
Australia	14.2	27.2	29.1	27.9	82.6
Canada	15.0	30.0	31.3	22.5	78.7
France	15.7	40.8	26.0	16.2	95.6
Japan	14.2	32.5	40.8	7.3	74.8
Korea	17.1	45.7	26.2	9.4	74.7
Sweden	15.5	29.2	30.4	22.6	97.7
UK (excluding Wales)	17.3	39.6	18.0	23.6	66.6
USA	15.2	26.9	31.0	25.7	88.1
Females					
Australia	16.7	16.8	37.2	28.0	73.8
Canada	17.1	17.9	41.1	22.8	78.4
France	16.3	19.6	44.3	18.2	94.6
Japan	9.0	11.4	68.5	4.9	70.1
Korea	11.8	16.5	58.7	10.6	62.0
Sweden	17.5	17.1	39.7	23.1	97.1
UK (excluding Wales)	22.4	28.1	23.5	24.4	62.6
USA	18.4	17.9	37.6	24.8	87.0

Data source: Cancer Incidence in Five Continents, Vol IX (IARC).[36]

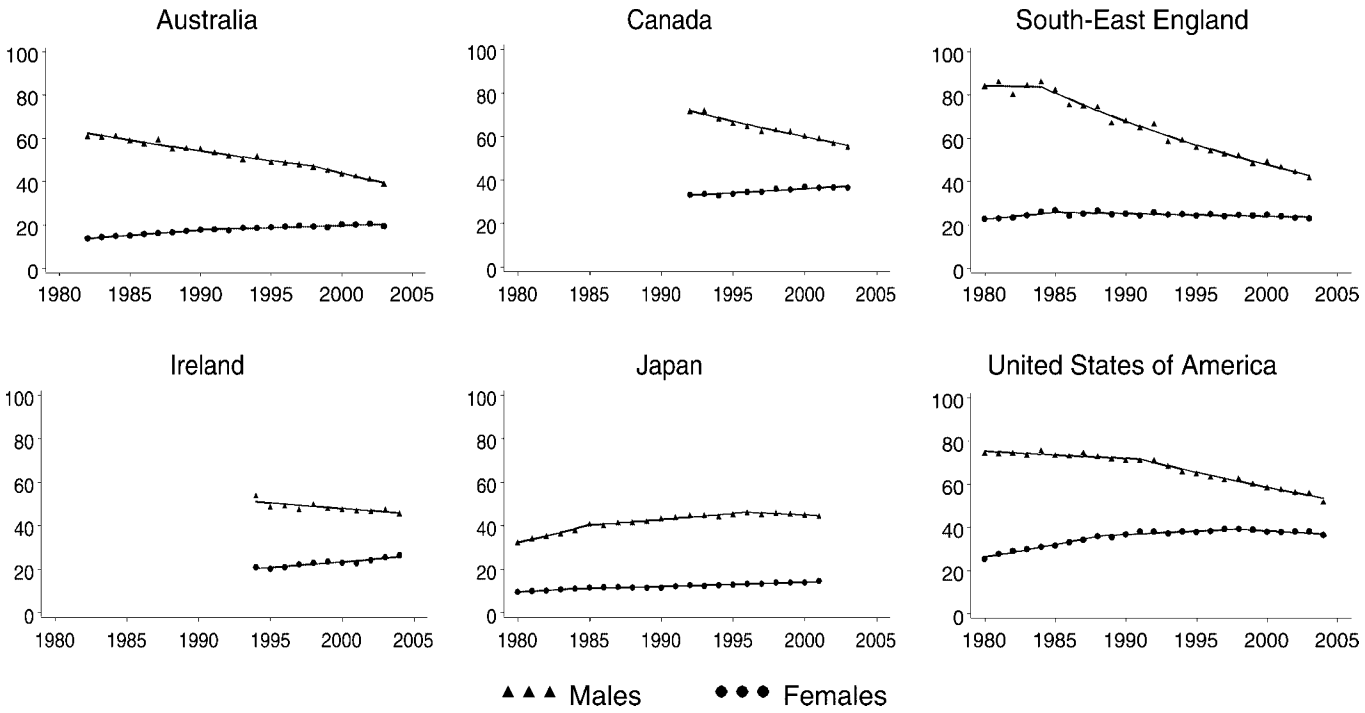

FIGURE 2. Recent trends in lung cancer incidence by sex for selected countries/registry areas, 1980–2004. Data sources: Australian Institute of Health and Welfare (Australia); Public Health Agency of Canada (Canada); Thames Cancer Registry (South-East England); National Cancer Registry of Ireland (Ireland); National Cancer Centre (Japan); National Cancer Institute (USA). Notes: 1. *y* axis represents 'Incidence rate per 100,000 population per year' and *x* axis represents 'Year'. 2. Incidence rates have been age-standardized to the WHO World Standard Population.[25] 3. Trends modeled using Joinpoint software (version 3.0), National Cancer Institute.[43]

Lung cancer incidence and mortality trends closely reflect patterns in smoking prevalence from 20 to 30 years earlier,[37,44,45] due to the characteristically long latency period between when a person starts to smoke and when they are diagnosed with or die of lung cancer.[46] The link between lung cancer trends and smoking behavior is further demonstrated

by changes in the distribution of the histologic subtypes of lung cancer over time.

Modifications to cigarette design (particularly the shift to filter cigarettes in the 1960s and 1970s), cigarette composition, and smoking behavior are widely believed to be the major reasons behind the relative increase in the incidence of adenocarcinoma compared with other types of lung cancer.[47–50] Smoke from lower yield (i.e., low tar, low nicotine, or filtered) cigarettes tends to be inhaled more deeply, resulting in a higher concentration of carcinogens in the outer areas of the lungs where adenocarcinomas tend to form. In addition, the tobacco blends used in cigarette manufacturing were changed to include higher levels of nitrates, which have also been linked to the development of adenocarcinoma.[47–49] The rapid increase in adenocarcinoma means that it has now overtaken squamous cell carcinoma as the most common form of lung cancer diagnosed among males in some countries, and has continued to be the dominant type of lung cancer diagnosed among females.[40,47]

LUNG CANCER SURVIVAL

Although there is some variation in lung cancer survival rates between countries, the prognosis for people diagnosed with lung cancer remains poor worldwide, with 5-year relative survival typically between 6 to 14% among males and 7 to 18% among females (Table 3).

One reason for the low lung cancer survival rates relates to the lack of observable symptoms for early stage lung cancer. Lung cancers diagnosed based on symptoms alone are usually well advanced and treatment options are limited.[37,51,52] Surgical resection remains the most effective treatment for early localized tumors,[53,54] but only a minority of lung cancers are diagnosed at that stage. Another probable reason for poor survival among lung cancer patients is the effect of smoking, in that smoking-related comorbidities such as cardiovascular diseases or chronic obstructive pulmonary disease may have an additional negative impact on survival.[55,56] There is also some evidence that current or previous smoking reduces the effectiveness of radiotherapy or chemotherapy when treating lung cancer.[57,58]

International comparisons of lung cancer survival data can be problematic (see Text Box 3). However, even after considering these caveats, survival for lung cancer patients diagnosed in Japan seems to be higher than in other more developed countries (Table 3), followed by North America, whereas generally lower survival rates were reported for European countries.

Data on cancer survival among less developed countries is limited,[59] with 5-year survival for lung cancer averaging around 9% in developing countries for both males and females combined (based on areas where population cancer registry data was available).[1] Although this is considerably lower than the survival reported for some developed regions such as Japan and North America, it is similar to the average 5-year survival for lung cancer of just under 11% for all persons that was recently estimated for Europe.[60]

TABLE 3. Lung Cancer 5-yr Relative Survival for Selected Countries

			5-Year Survival (%) (95% Confidence Interval)	
Country	**Yr**	**Method**	**Male**	**Female**
Australia	1992–1997	Cohort	11.0 (10.6–11.4)	14.0 (13.3–14.7)
Austria	1990–1994	Cohort	13.4 (11.0–16.4)	16.0 (11.9–21.6)
Canada	1997–2002	Period	13.3 (12.6–14.0)	18.5 (17.5–19.4)
Czech Republic	1990–1994	Cohort	6.3 (5.0–7.8)	8.2 (5.1–13.1)
Denmark	1990–1994	Cohort	6.1 (5.5–6.7)	5.9 (5.3–6.6)
England	1990–1994	Cohort	7.4 (7.2–7.6)	7.7 (7.4–8.0)
Estonia	1990–1994	Cohort	6.8 (5.5–8.4)	11.9 (9.0–15.9)
Finland	1990–1994	Cohort	7.8 (7.2–8.6)	10.9 (9.4–12.7)
France	1990–1994	Cohort	13.1 (11.6–14.8)	15.9 (12.2–20.7)
Germany	1990–1994	Cohort	10.8 (9.4–12.5)	10.5 (8.0–13.7)
Iceland	1990–1994	Cohort	8.0 (5.2–12.4)	10.6 (7.0–16.0)
Italy	1990–1994	Cohort	9.8 (9.4–10.2)	10.5 (9.6–11.5)
Japan	1993–1996	Cohort	20.7 (21.1–20.3)	27.6 (28.2–27.0)
Netherlands	1990–1994	Cohort	11.7 (10.9–12.6)	12.4 (10.8–14.2)
New Zealand	1994–2003	Cohort	9.5 (8.8–10.4)	11.1 (10.1–12.1)
Norway	1990–1994	Cohort	8.0 (7.2–8.9)	10.5 (9.2–12.0)
Poland	1990–1994	Cohort	6.1 (5.3–6.9)	6.8 (5.7–8.2)
Scotland	1990–1994	Cohort	7.0 (6.5–7.6)	6.8 (6.2–7.4)
Slovakia	1990–1994	Cohort	6.9 (6.2–7.8)	12.0 (9.9–14.5)
Slovenia	1990–1994	Cohort	8.0 (6.8–9.3)	9.3 (7.2–12.0)
Spain	1990–1994	Cohort	12.4 (11.6–13.2)	12.8 (10.4–15.8)
Sweden	1990–1994	Cohort	8.5 (7.8–9.2)	11.5 (10.4–12.6)
Switzerland	1990–1994	Cohort	9.7 (7.9–11.9)	16.2 (12.5–20.9)
USA	1996–2003	Cohort	13.0 (12.8–13.2)	17.4 (17.0–17.8)
Wales	1990–1994	Cohort	8.0 (7.3–8.7)	7.5 (6.5–8.5)

Data sources: Australia,[61] Canada,[62] Europe,[63] Japan,[64] New Zealand,[65] USA.[66]
Confidence intervals are provided to indicate the precision of the estimate, but are not meant for comparative purposes (see Text Box 3).

Text Box 3

Interpreting survival data

Reported differences in lung cancer survival between countries do not necessarily translate into real differences, but may be due to characteristics of the underlying data. Some of the factors to consider when comparing survival results include completeness of population coverage, data quality (including linkage to mortality records), consistency of analysis methodology, the time period that the estimates are from, demographic differences (e.g., age, sex, socioeconomic status), tumor-related characteristics such as histology and stage at diagnosis, and health system issues including access to treatment.[67,68]

Lung cancer survival is generally, but not always, better for females and for younger patients.[69–74] Although the exact mechanisms for potential differences in survival by sex and age at diagnosis remain unclear, possible explanations include gender-related differences in tumor biology and/or

hormonal factors,[75,76] whereas some commentators have suggested that any survival advantage among younger lung cancer patients may be due to more aggressive treatment compared with older patients.[74,77]

Prognosis for SCLC is usually inferior compared with NSCLC. In the United States, the 5-year relative survival rate by type of lung cancer was about 17% for patients with NSCLC and only 6% for those diagnosed with SCLC between 1996–2003.[38] Similar differences in survival by histology have been reported for Canada, Australia, and throughout Europe.[78–80]

Survival for patients with lung cancer has shown only modest, if any, improvement over the last two or three decades, both in terms of all lung cancers combined[38,80–82] and within the individual histology groups.[39,80,83,84] However, it is anticipated that the development of more effective and well-tolerated chemotherapy drugs (such as gemcitabine and pemetrexed), in conjunction with an improved understanding of the biology of lung tumors, will help improve survival rates and quality of life for both NSCLC and SCLC patients within the foreseeable future.[85,86]

The results from several large, recent studies have indicated that nonsmokers who develop lung cancer have a better prognosis than smokers, after taking into account other factors such as demographic characteristics and existing comorbid diseases.[30,55,87] That a differential exists in lung cancer survival between smokers and nonsmokers after adjusting for histology, stage, comorbidities and treatment most likely suggests a biologic difference in cancer progression (possibly as a result of late mutational effects, immune suppression or oxidative tissue damage) between smoking-related lung cancer and other forms of lung cancer.[55]

LUNG CANCER MORTALITY

Lung cancer is the leading cause of cancer-related deaths worldwide. In 2002 there were about 1.18 million deaths caused by lung cancer internationally,[1] an increase of over 70,000 deaths since 2000.[24] Lung cancer deaths caused almost 18% of total cancer mortality[1,88] and around 2% of all mortality worldwide during 2002.[88]

Nearly three-quarters (72% or 850,000) of lung cancer deaths throughout the world during 2002 occurred among males,[1] equating to an age-standardized rate (World Health Organization World Standard population)[25] of 35/100,000 population for males compared with a rate of 11/100,000 population for females.[26] Worldwide lung cancer was clearly the leading cause of cancer-related deaths among males, after stomach cancer and liver cancer, and ranked second among females behind breast cancer.[1] However, in some countries (notably the USA since 1987[89] and more recently some European countries including the UK, Sweden, and Denmark[90]) lung cancer has overtaken breast cancer as the leading cause of cancer death among females.

Similarly to incidence, the estimated average age-standardized mortality rates (MR) for lung cancer during 2002 in more developed countries (53/100,000 among males and 15/100,000 among females) were about twice that of less developed countries (26/100,000 among males and 9/100,000 among females).[26] For males, the MR was highest in Hungary (92/100,000 population) compared with rates of less than 5/100,000 in parts of Africa (such as Kenya), whereas among females the MR varied from 31/100,000 in Denmark to below 2/100,000 in India (Table 1).[26]

The MR and incidence rate for lung cancer are generally quite similar within a given population, which is indicative of the poor survival prospects of most lung cancer patients.[27] The ratio of MR: incidence rate was the same (0.89) for both males and females in less developed countries, but was lower for females (0.81) compared with males (0.87) within more developed countries,[26] reflecting the slightly better survival prospects of females living in more developed countries.

A higher proportion of lung cancer deaths were attributable to smoking than for any other disease.[91] It has been estimated that nearly three quarters (71%) of lung cancer deaths worldwide were caused by smoking in 2000.[91] By 2015, this would result in a projected 1.18 million smoking-related lung cancer deaths per year.[88] The influence of smoking on lung cancer was particularly strong in more developed countries, causing 91% of lung cancer deaths among males and 71% among females. In less developed countries, the contribution of smoking to lung cancer deaths was substantially lower (66% for males and 25% for females),[91] further emphasizing the greater impact of other risk factors for lung cancer (such as coal smoke and occupational exposure to carcinogens) in places like Asia and Africa.[92]

Text Box 4

Do people with lung cancer always die specifically from lung cancer?

There is a common perception that almost all people diagnosed with lung cancer die of lung cancer.[55] However between 20 and 40% of early stage lung cancer patients die of other causes,[55] which are often smoking-related comorbidities such as ischemic heart disease or stroke.[93,94] In Australia lung cancer patients were more than four times as likely to die of a noncancer cause compared with the general population,[93] whereas in the United States lung cancer patients who died of other causes were more likely to be males and in the older age groups.[95]

Premature Mortality

Due to the poor survival for lung cancer patients, the main burden of lung cancer is due to premature mortality rather than long-term illness. Estimates from the Global Burden of Disease Study[96] reveal that in 2002, lung cancer caused nearly 11 million years of life lost. Lung cancer was the leading cause of cancer-related premature mortality among males (20%) and ranked second for females (10%) behind breast cancer (17%). In contrast, lung cancer was estimated to be responsible for approximately 233,000 years lost due to disability during 2002, comprising 11% of cancer-related years lost due to disability among males and 3% among females.[96]

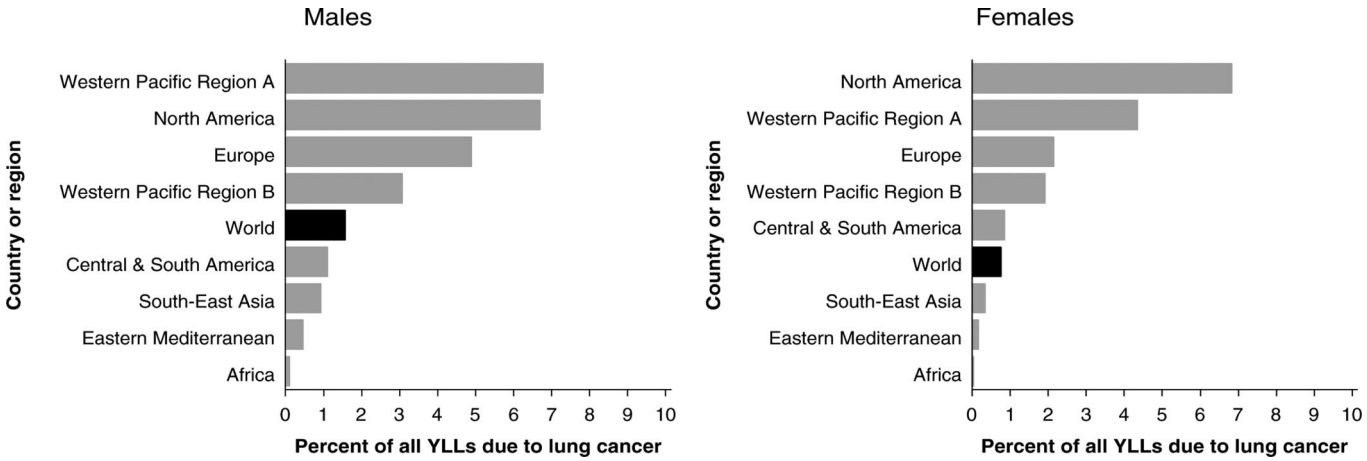

FIGURE 3. Percent of total Years of Life Lost (YLLs) due to lung cancer, by region, 2002. Data source: World Health Organization (WHO).[96] Note: Western Pacific Region A includes Australia, Brunei, New Zealand, Japan and Singapore. Western Pacific Region B incorporates all other countries in this region, including China, Mongolia, Republic of Korea and the Pacific Island nations.[97]

In terms of premature mortality from all causes, lung cancer was estimated to be responsible for 1.6% of premature mortality among males and 0.7% among females in 2002.[96] There was substantial variation in these proportions between regions (Figure 3). Lung cancer was most prominent as a cause of premature mortality among both males and females in North America (6.7% and 6.8% of total premature mortality, respectively) and among males in Western Pacific Region A (6.8%); however, lung cancer caused very little premature mortality in Africa (less than 0.1% for both sexes).[96] This is most likely as a result of smoking prevalence in Africa being historically lower in comparison to many developed countries (particularly among females),[98,99] combined with shorter life expectancy and much higher MRs from infectious diseases such as HIV/AIDS (which was estimated to have caused almost 60% of premature mortality throughout Africa compared with less than 4% in North America[96]).

Mortality Trends

Trends in lung cancer MRs between 1980 to 2005 for 24 selected countries (with sufficient quality and quantity of data) are shown in Figure 4. The close association between lung cancer incidence and mortality is again evidenced by the similarities in the incidence and MR trends within particular countries (compare with Figure 2).

Mortality rates for males were decreasing significantly in all of the countries shown except for Bulgaria, where the rates were stable, and China, Israel, Romania, and South Korea where rates were rising. The greatest decreases were recorded in the United Kingdom and Australia, where the lung cancer MRs among males had been dropping by 3.5% per year between 1991 and 2004 and 3.2% per year between 1994 and 2003, respectively. In contrast, the largest increase was in South Korea, where the yearly MR rose by 9.9% per year from 1985 to 1994, and then continued to grow by 1.8% per year between 1994 and 2004.

Among females, lung cancer MRs were increasing in most of the countries included in Figure 4. Exceptions were stable trends in Bulgaria, Canada, Denmark, and the USA, and decreasing trends in Hong Kong, Japan, Russia, Singapore, and the UK. The decreases were greatest in Hong Kong and Russia, where the lung cancer MRs had been falling by 2.3% and 2.0% per year, respectively, since 1990. The largest rises were occurring in Spain (5.3% increase per year between 1999–2004). Female lung cancer MRs are also continuing to rise rapidly in France (4.3% per year between 1993–2003) and the Netherlands (4.2% per year between 1994–2004).

Of the countries shown in Figure 4, the most recent lung cancer mortality trends by sex can be summarized into the following 5 general patterns:

- An increasing trend for both sexes eg, China, Israel, Romania, South Korea;
- An increasing trend for females and a decreasing trend for males e.g., Australia, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, New Zealand, Poland, Spain, Sweden;
- A decreasing trend for both sexes e.g., Hong Kong, Japan, Russia, Singapore, United Kingdom;
- A decreasing trend for males and stable for females e.g., Canada, Denmark, United States; and,
- Stable trends for both sexes e.g., Bulgaria.

Since a previous report on country-specific trends between 1971 to 1995,[100] lung cancer MRs for both sexes are now decreasing in Japan, trends for males have begun to decrease in several European countries, Canada and the USA, trends have stabilized for females in Canada, Denmark, and the USA, and rates for women have started to decrease in the UK.

Lopez et al.[101] suggested a model consisting of four stages to explain the link between past smoking behavior in a population and lung cancer mortality trends (see Text Box 5). Although the model may not exactly describe the

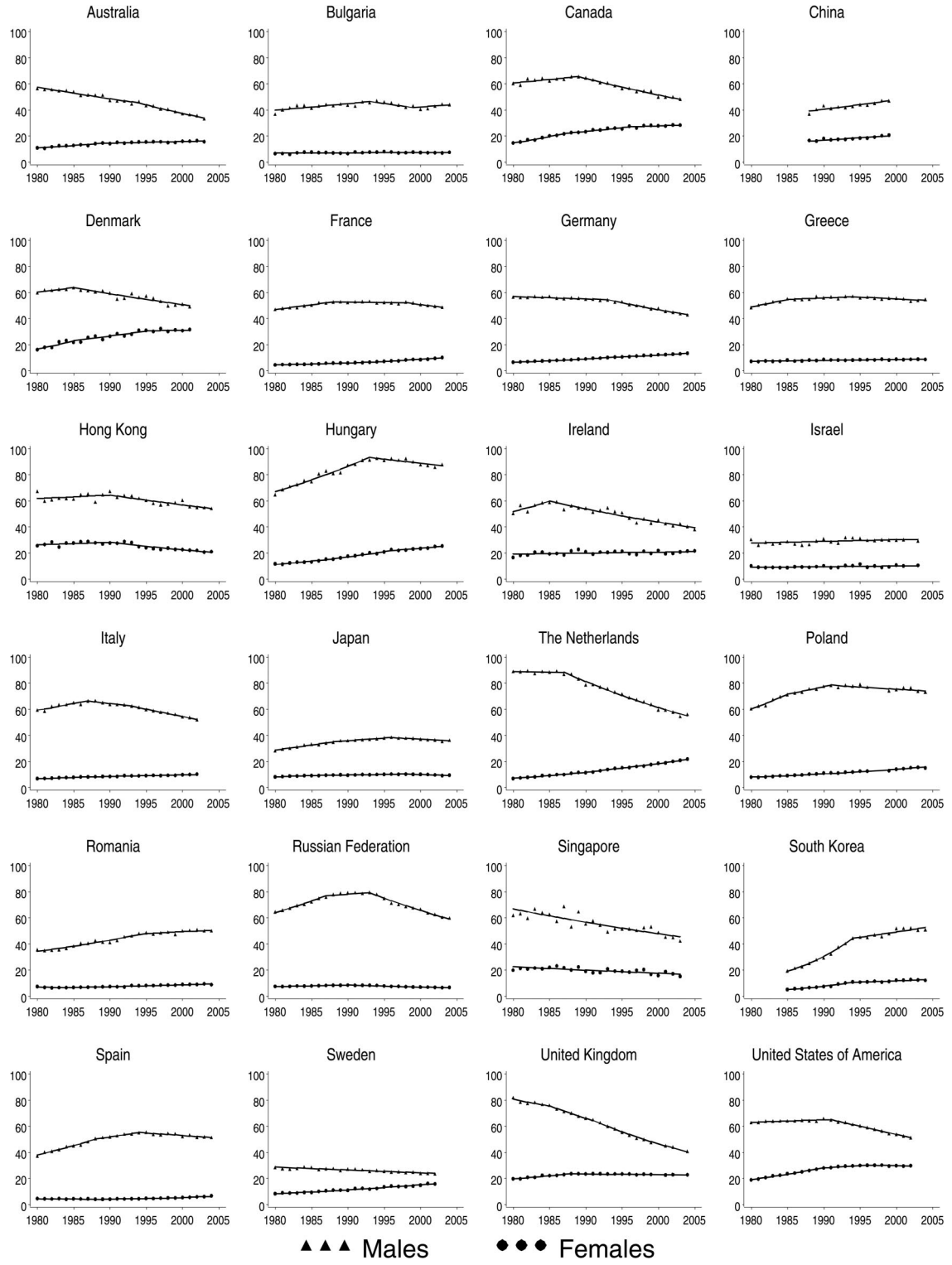

FIGURE 4. Recent trends in lung cancer mortality by sex for selected countries, 1980–2005 Data source: World Health Organization (WHO).[102] Notes: (1) Countries were selected on the basis of having lung cancer mortality data of sufficient quality (at least 80% of all deaths registered, except China, which was based on a sample of less than 10% of all deaths) and quantity (average of at least 300 lung cancer deaths per year for males and 250 deaths per year for females). (2) *y* axis represents 'Incidence rate per 100,000 population per year' and *x* axis represents 'Year.' (3) Rates age-standardized to the WHO World Standard Population.[25] (4) Trends modeled using Joinpoint software (version 3.0), National Cancer Institute.[43]

relationship experienced between smoking and lung cancer in every country, it provides a framework for understanding how the health effects of smoking become evident after a delay of a few decades.[101]

Text Box 5

Evolution of the worldwide lung cancer epidemic

Researchers from the World Health Organization have suggested a four stage model based on tobacco consumption to explain broad differences in lung cancer trends around the world.[101] The model emphasizes the need for sustained commitment at every stage to reduce tobacco use.[103]

- Stage 1—Includes countries where the smoking epidemic has not yet taken off but the population is vulnerable to the tobacco industry. Lung cancer is rare, with incidence rates generally comparable to a nonsmoking population. Examples include many countries throughout Africa.
- Stage 2—There is a rapid rise in smoking among males, with smoking also becoming more common among females. The proportion of ex-smokers is low, and tobacco control is limited, with smoking typically seen as a socially acceptable behavior. Lung cancer becomes increasingly common, particularly for males. Many countries in Asia, North Africa, and South America are at this stage.
- Stage 3—Characterized by a public perception that smoking is a health hazard, allowing the introduction of comprehensive tobacco control legislation. Smoking rates are falling for males and have typically plateaued among females. Lung cancer rates continue to rise sharply before peaking towards the end of this phase. Countries in Eastern and Southern Europe are current examples.
- Stage 4—Smoking rates for both males and females continue to decline, although smoking remains more common among males and differences in smoking by socio-economic status will persist and perhaps even widen. Legislation allowing a smoke-free environment becomes a key issue. Lung cancer rates for males continue to decrease, but may still be rising among women in response to the later peak in smoking prevalence for females. Many developed countries are now at this stage, including North America, North-Western Europe and Australia.

Age-period-cohort modeling using lung cancer mortality data from European Union countries and North America has found that lung cancer MRs have been declining for males under 65 years of age and had either reached a plateau or were starting to fall among older males.[104,105] Mortality rates for females were generally increasing across all age groups in European countries, but were falling or had stabilized among women aged under 65 in the United Kingdom, Ireland, Canada, and the United States.[104,105] Some evidence is also starting to emerge that lung cancer MRs may be declining among younger females (20–44 years) in several other countries throughout Europe.[106] In countries where lung cancer MRs were decreasing for either males or females, the cohort results generally show that MRs were decreasing among successive generations,[104,105] although there seems to have been some moderation in these trends within the United States among people born after 1950.[107]

ISSUES AFFECTING THE FUTURE INTERNATIONAL BURDEN OF LUNG CANCER

Despite the declining or plateauing trends in lung cancer rates in some countries, experts are predicting that lung cancer will continue to be a major cause of death throughout the world within the foreseeable future, particularly due to the ageing of the global population. It is estimated that by 2030 lung cancer will be the sixth most common cause of death, compared with its current ranking of ninth.[88]

The shift towards a higher proportion of lung cancer cases occurring in developing countries appears set to continue.[27,44] It is thought that by the year 2025, 85% of the world's smokers will live in less developed countries,[108] and by 2030 it is expected that around 70% of all tobacco-related deaths (including lung cancer) will occur in the world's poor and middle income nations, compared with the current estimate of 50%.[31,109]

Smoking patterns in China are likely to strongly influence the global burden of lung cancer within the next 10 to 20 years. China consumes about one in three of all the cigarettes produced in the world,[110] due to a combination of its huge population and the high prevalence of smoking among Chinese males (67%).[31] Lung cancer MRs are already increasing among both sexes, in all age groups, and in both urban and rural areas of China.[110] If current smoking patterns persist in China, a massive rise in smoking-related deaths is predicted.[110–112]

The prevalence of smoking among young people is another important international issue, particularly the increasing use of tobacco products among girls in many countries.[31,113,114] The American Cancer Society has reported that nearly 100,000 children and adolescents become addicted to tobacco worldwide every day,[31] and recent data from the Global Youth Tobacco Survey indicates that about one out of every 6 (17%) school students aged 13 to 15 have either smoked cigarettes and/or used other tobacco products.[113]

These issues highlight the ongoing need for targeted tobacco control in an attempt to permanently arrest the worldwide spread of lung cancer,[44,115–117] especially within less developed countries. Tobacco control programs have proven to be successful in reducing smoking prevalence and uptake in some developed countries, including the USA and Australia,[118–120] although further opportunities for progress in tobacco control remain among inveterate smokers[121] and people in high-risk smoking groups, such as those who are socioeconomically disadvantaged.[122–124] The World Health Organization has recently released a report which promotes six key tobacco control strategies.[125] These strategies are monitoring of tobacco use and prevention policies; protecting people from tobacco smoke; offering help to quit tobacco use; warning about the dangers of tobacco; enforcing bans on

tobacco advertising, promotion and sponsorship; and raising taxes on tobacco.[125]

Although optimism remains that the impending lung cancer epidemic can be averted,[31,44,115] this will only occur if there is ". . . political will to tackle tobacco, and appropriate funding proportional to the magnitude of the epidemic, and individual commitment by smokers to quit."[31]

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