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PLoS MEDICINE

Lung Cancer Occurrence in Never-Smokers: An Analysis of 13 Cohorts and 22 Cancer Registry Studies

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Abbreviations: BWHS, Black Women's Health Study; CI, confidence interval; CPS-I, Cancer Prevention Study; CPS-II, Cancer Prevention Study II; CPS-II Nutrition, Cancer Prevention Study II Nutrition Cohort; HPFS, Health Professionals' Follow-up Study; HR, hazard ratio; KCPS, Korean Cancer Prevention Study; MEC, Multiethnic Cohort; NHS, Nurses' Health Study; RR, rate ratio; SEER, Surveillance Epidemiology and End Results; WHS, Women's Health Study

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ABSTRACT

Background

Better information on lung cancer occurrence in lifelong nonsmokers is needed to understand gender and racial disparities and to examine how factors other than active smoking influence risk in different time periods and geographic regions.

Methods and Findings

We pooled information on lung cancer incidence and/or death rates among self-reported never-smokers from 13 large cohort studies, representing over 630,000 and 1.8 million persons for incidence and mortality, respectively. We also abstracted population-based data for women from 22 cancer registries and ten countries in time periods and geographic regions where few women smoked. Our main findings were: (1) Men had higher death rates from lung cancer than women in all age and racial groups studied; (2) male and female incidence rates were similar when standardized across all ages 40+ y, albeit with some variation by age; (3) African Americans and Asians living in Korea and Japan (but not in the US) had higher death rates from lung cancer than individuals of European descent; (4) no temporal trends were seen when comparing incidence and death rates among US women age 40–69 y during the 1930s to contemporary populations where few women smoke, or in temporal comparisons of never-smokers in two large American Cancer Society cohorts from 1959 to 2004; and (5) lung cancer incidence rates were higher and more variable among women in East Asia than in other geographic areas with low female smoking.

Conclusions

These comprehensive analyses support claims that the death rate from lung cancer among never-smokers is higher in men than in women, and in African Americans and Asians residing in Asia than in individuals of European descent, but contradict assertions that risk is increasing or that women have a higher incidence rate than men. Further research is needed on the high and variable lung cancer rates among women in Pacific Rim countries.

The Editors' Summary of this article follows the references.

Introduction

Most of the more than 1.4 million lung cancer deaths that occur annually worldwide are caused by tobacco smoking [1]. The rest comprise only a small fraction of the total, yet they account for a substantial disease burden. For example, in the United States (US), factors other than cigarette smoking are estimated to account for 10%–15% of all lung cancer deaths [2] on the basis of surveys of smoking in the general population and relative risk estimates from a large American Cancer Society cohort study [2]. This percent range corresponds to between 16,000 and 24,000 of the more than 161,000 lung cancer deaths projected to occur in the US in 2008 [3]. If these deaths were considered as a separate category, they would rank among the seven to nine most common fatal cancers in the US [4].

Not all lung cancers caused by factors other than active smoking occur in people who have never smoked; the background risk resulting from other exposures and their interactions with genetic and epigenetic processes also affects current and former smokers. However, lung cancer occurrence among never-smokers is of special interest for several reasons. First, geographic and temporal variations in risk caused by other environmental exposures and/or differences in biological susceptibility should, in principle, be more easily detected in populations that have never smoked. Second, never-smokers comprise a growing proportion of adults in economically developed countries. Whereas only 44% of US adults (age ≥18 y) reported never having smoked 100 or more cigarettes in 1965 [5], this proportion increased to 59% in 2006 [6]. Third, clinical studies have shown that lung tumors in never-smokers have a different molecular profile and better response to targeted therapy than cancers in smokers, and in some respects represent a different type of cancer [7,8]. Finally, some researchers have hypothesized on the basis of limited data that, among never-smokers, women may have higher risk of developing lung cancer than men but lower risk of dying from it [9,10], that age may influence the gender relationship [11], that African Americans [4] or Asians [7] may be at greater risk than individuals of European descent, and that factors other than cigarette smoking may be contributing to temporal changes in lung cancer risk [12–14].

To examine these issues, we pooled data on lung cancer incidence and death rates among self-reported never-smokers from 13 large cohort studies representing over 630,000 and 1.8 million participants for the incidence and mortality analyses, respectively. The studies spanned the time period 1960 to 2004 and were based in North America, Europe, and Asia. We supplemented the cohort analyses with population-based incidence and death rates from lung cancer for women in 22 cancer registries and ten countries or geographic regions during time periods when the prevalence of female smoking was reportedly low. All of these data are provided in extensive supplemental tables as a resource for other researchers (Tables S1–S23).

Methods

General Population Rates

We abstracted data on lung cancer incidence among women from ten countries (21 cancer registries) [15] reported to have a low prevalence of female smoking [16]. The registries were located in India, China, and selected areas in Asia, Africa, Europe, and the Middle East (Table 1). We selected registries in countries where the prevalence of female smoking was known to be low nationally or regionally in the year 2000 [16], or where cultural or religious prohibitions discourage smoking among women. We chose the time period 1983–1987 [15] rather than more contemporary data to circumvent uncertainties about recent increases in female smoking. The exact time period differed slightly in certain countries. For example, the incidence data for Algeria pertain to the years 1986–1989; Mali to 1987–1989; Thailand-Khon Kaen to 1988–1989; and the Basque region of Spain to 1986–1987 [15].

We also abstracted incidence and death rates among women in the US for the years 1935–1940 using the Connecticut Tumor Registry for incidence [17] and US vital statistics for mortality (Table 2) [18]. The time interval of 6 y (1935–1940) rather than 5 y was chosen for comparability with published data from the Connecticut Tumor Registry [17]. The lung cancer incidence rates in Connecticut and death rates in the US in 1935–1940 were compared to each other and to international rates during the 1980s in other countries where few women were known to smoke. In making temporal and geographic comparisons we focused on the age range 40–69 y, where the diagnosis of primary lung cancer was thought to be less affected by changing diagnostic technologies and more reliable than at older ages [19]. However, Tables 1 and 2 present the data over a broad range of age as a potential resource for future studies. All age-standardized rates were based on the IARC 2000 world population standard.

Cohort Studies

We contacted the principal investigators of large cohorts that included a minimum of approximately 20,000 participants who reported no history of regular tobacco smoking. Never-smokers or lifelong nonsmokers were those who reported never having smoked 100 cigarettes or more in their lifetime or never having smoked any tobacco product regularly. We excluded cohorts that were defined by exposure to specific occupational or environmental toxicants. Researchers were asked to provide age-, sex-, and race-specific data on lung cancer cases and/or deaths and person years at risk among the lifelong nonsmokers. Mortality data were provided for 11 studies (Table S1); incidence data for eight (Table S2). Among the mortality studies, seven were located in North America and Europe (the Black Women's Health Study [BWHS] [20], Cancer Prevention Study I [CPS-I] and II [CPS-II] [4], the Health Professionals' Follow-up Study [HPFS] [21], the Multiethnic Cohort [MEC] [22], the Nurses' Health Study [NHS] [21], and the Women's Health Study [WHS] [23]) and four in Asia (Hirayama or Six Prefecture Study in Japan [24], the Japanese Collaborative Cohort Study [JACC] [25], the Japanese Three Prefectures Study [26], and the Korean Cancer Prevention Study [KCPS] [27]). All of the eight studies that provided incidence data were located in North America or Europe (Table S2). These included BWHS, Cancer Prevention Study II Nutrition Cohort (CPS-II Nutrition) [28], the European Prospective Investigation into Cancer and Nutrition (EPIC) [29], HPFS, MEC, NHS, the Swedish Construction Worker cohort (SCW) [30], and WHS. Only two of these cohorts [24,30] have previously published age-specific rates in never-smokers for the length of follow-up considered here.

We tabulated the number of events, person years at risk,

and age-specific and age-standardized rates among never-smokers in each contributing cohort for mortality (Tables S3–S8) and incidence (Tables S9–S12). Most of the studies included both men and women. The two studies of health professionals (HPFS and NHS) were considered a paired analysis of men and women, respectively. Two mortality studies (WHS and BWHS) were included only in the analyses of women. The total number of incident cases and deaths is shown in Table 3 by gender and race.

Before pooling the data from these cohorts, we tested for heterogeneity of the rates among the cohorts within strata of gender and race. We first used the likelihood ratio test in generalized linear models (SAS GENMOD) [31] to determine whether controlling for "study" improved the fit of the model, within each sex and race combination. Heterogeneity across studies was defined as a $p < 0.05$. Heterogeneity within gender was observed in the mortality data for women of European descent ($p < 0.0001$), Asian women ($p = 0.0007$), and Asian men ($p < 0.0001$) and in the incidence data for women of European descent ($p = 0.0015$), and reached borderline statistical significance for men of European descent ($p = 0.066$). The two smallest studies (WHS and MEC) accounted for the heterogeneity of the mortality rates among individuals of European descent (both WHS and MEC) and Asians (MEC). Their exclusion did not appreciably change the rates, since they contributed less than 4% of deaths to any analysis. We could not account for the higher incidence rates among women of European descent in the CPS-II Nutrition Survey than in the NHS.

To examine whether the age pattern for men and women differed, we again used generalized linear models to assess whether the age-specific rate difference changed with age. The statistical significance of the trend in the rate difference (treated as linear) was tested using two-way interaction terms between gender and age and the likelihood ratio test. Three-way interaction terms between age, gender, and cohort were also tested and were not significant.

Lastly, we evaluated potential effects associated with heterogeneity by conducting sensitivity analyses that compared the rates and rate ratios from the pooled data with the results from random effects models within strata of gender and race where heterogeneity was detected. The results of these two approaches were similar.

Despite some evidence of heterogeneity in both the incidence and death rates among cohorts, we present both pooled and cohort specific results. The pooled mortality data are presented in Tables S13–S16 for individuals of European descent, Asians, and African Americans, respectively; the pooled incidence data are presented in Tables S17–S20. In both the pooled and cohort specific analyses, the age-standardized rates were calculated using direct standardization to the IARC 2000 world population weights. The rates were standardized to four different age ranges (40–69, 40–79, 40–84, and 40+ y) to facilitate comparisons with cancer registry and national vital statistics data and with other published results. We calculated age-specific ratios of the male to female rates only in age strata where both sexes had at least five events.

Two other analyses were conducted to provide additional perspective on these risks. To compare the lung cancer risk in never-smokers to that in smokers, we contrasted the age-specific death rates from lung cancer among never-smokers in the pooled data with those of current smokers in CPS-II for individuals of European descent and KCPS for Asians (Figure 1 and Table S21). These two studies were the only contemporary cohorts for which we had the relevant information on smokers. For validity, we restricted the follow-up of the current smokers to first 6 y after enrollment in order to minimize the effect of cessation, since neither CPS-II nor KCPS collected information on changes in smoking status during follow-up. We also calculated the cumulative probability of dying from lung cancer before age 85 y among male and female smokers and never-smokers. The age category 80–84 y was used as the upper limit in calculating cumulative probability because the category age 85+ was open-ended and undefined. The other analysis compared lung cancer occurrence among lifelong nonsmokers in the pooled data with the incidence and death rates for other cancers in the general population. Population-based incidence rates were based on the Surveillance Epidemiology and End Results (SEER) Cancer Statistics Review for the years 2000–2004 [32]; mortality rates were derived from US vital statistics from the same years and source. Only the data for individuals of European descent are presented here.

Results

International Comparisons Based on Cancer Registry Data

Table 1 presents the age-specific and age-standardized lung cancer incidence rates among women in the 21 cancer registries covering populations where female smoking was thought to be uncommon. The age-standardized rates varied by more than 30-fold even when restricted to the age range 40–69 y where the data were considered most reliable. The lowest recorded incidence rates were among women in Africa (Algeria and Mali) and India (Ahmedabad, Bangalore, Madras, Mumbai). Women in the Basque region of Spain were also in the lowest tertile (≤ 9 cases per 100,000) when the comparison was restricted to the age range 40–69 y. Incidence rates (per 100,000) in the middle tertile ranged from 11.2 in Kuwait to 27.4 in Qidong City, China and included women in all of the registries in Japan, the Malay population of Singapore, the Khon Kaen registry in Thailand, and the Qidong City registry in China. Rates in the highest tertile ranged from 30.9 per 100,000 among women in the Rizal Province in the Philippines to 87.8 per 100,000 in Chiang Mai, Thailand. The variability of the rates within individual countries was greatest in China and Thailand.

Table 1 also presents lung cancer incidence rates among women from the Connecticut tumor registry during the years 1935–1940, a time period when few American women smoked. The lung cancer incidence rate among Connecticut women, ages 40–69 y was 8.5 per 100,000 in the late 1930s, similar to that among women of the same age in the Basque region of Spain (8.6 per 100,000) and Kuwait (11.2 per 100,000) 50 y later. The Connecticut rates reach a plateau at age 70 y and then decrease in the oldest age groups, consistent with under-diagnosis of lung cancer in the elderly. The problem of under-diagnosis in older age groups exists wherever minimally invasive diagnostic technologies are unavailable, as would also have been true in the US during the 1930s.

Table 2 compares the lung cancer incidence rates among women in selected registries with national or regional mortality rates during the same time period. With the

Table 1. Age-Specific and Age-Standardized Lung Cancer Incidence Rates (Per 100,000) among Women in Selected Populations with Low Female Smoking [15]

Country/Region	Region/City	Years	Age Group (y)														Age Standardized Rates[a]
			20–24	25–29	30–34	35–39	40–44[b]	45–49[b]	50–54[b]	55–59[b]	60–64[b]	65–69[b]	70–74	75–79	80–84	85+	
India	Ahmedabad	1983–1987	0.1	0.1	1.0	0.5	1.8	2.1	5.3	7.8	8.2	12.8	15.1	11.3	7.8	—	5.4
	Bangalore	1983–1987	0.1	0.1	—	0.6	2.1	1.7	4.9	5.1	10.2	12.3	6.2	12.0	—	—	5.2
	Mumbai	1983–1987	0.2	0.3	0.3	1.3	1.9	3.3	5.1	10.0	10.2	22.1	21.7	18.1	—	—	7.3
	Madras	1983–1987	—	0.1	0.3	1.3	2.0	2.7	5.0	5.6	3.3	7.4	4.3	3.5	—	—	4.0
Africa	Algeria	1986–1989	—	—	—	2.1	—	2.5	3.5	2.1	8.9	—	—	—	—	—	2.7
	Mali	1987–1989	—	2.3	4.7	—	2.7	3.7	9.4	7.0	8.0	—	—	65.2	—	—	5.2
China	Qidong city	1983–1987	—	0.7	1.7	3.0	6.5	11.1	18.0	33.4	52.9	75.2	74.9	93.6	86.6	66.8	27.4
	Shanghai	1983–1987	0.4	0.5	2.4	4.1	9.2	13.4	26.1	44.4	76.0	125.8	162.6	167.7	157.6	129.8	40.2
	Tianjin	1983–1987	0.5	1.5	1.8	4.4	13.3	29.9	62.7	102.6	179.6	230.2	263.2	200.8	213.7	72.2	85.4
	Hong Kong	1983–1987	1.0	2.4	2.7	6.6	14.2	24.4	43.8	80.8	139.6	195.9	280.5	314.3	344.7	390.2	68.6
Japan	Osaka	1983–1987	—	0.6	0.5	1.6	4.3	7.1	14.8	25.8	39.4	73.4	108.8	154.5	157.7	150.3	22.3
	Saga	1984–1986	—	—	3.0	1.0	7.1	7.1	8.6	22.2	31.4	55.2	82.1	88.0	121.2	137.7	18.2
	Yamagata	1983–1986	—	—	2.7	3.3	7.6	5.7	11.4	22.8	30.9	42.8	73.2	106.5	120.6	86.5	17.1
Philippines	Manila	1983–1987	0.2	1.2	1.6	7.8	8.8	17.6	21.0	40.1	81.5	88.0	129.3	133.1	—	—	36.2
	Rizal Province	1983–1987	0.3	1.3	1.7	2.8	6.3	17.8	23.5	44.4	61.7	59.8	91.8	119.0	—	—	30.9
Singapore	Chinese	1983–1987	0.2	0.6	1.1	4.7	5.0	14.8	29.7	52.8	90.3	138.5	204.4	247.5	227.4	—	44.8
	Malay	1983–1987	—	1.1	2.7	3.9	4.3	11.8	25.4	15.0	50.3	92.7	137.0	128.2	—	—	27.2
Thailand	Chiang Mai	1983–1987	—	2.1	2.6	4.7	23.9	37.2	101.3	140.9	153.2	135.9	93.7	118.4	—	—	87.8
	Khon Kaen	1988–1989	—	3.2	—	1.1	2.6	8.0	9.2	18.1	15.1	34.0	19.2	37.7	—	—	12.3
Other	Spain, Basque	1986–1987	—	0.6	0.7	2.0	2.9	9.6	8.1	7.1	9.2	20.2	25.0	39.4	36.8	24.5	8.6
	Kuwait	1983–1987	—	1.5	—	—	—	2.1	13.5	19.4	18.4	27.1	28.4	37.3	79.1	35.1	11.2
	US, CT	1935–1940	0.2	0.7	1.3	1.0	4.5	4.7	7.6	9.7	13.3	17.5	23.6	23.2	17.5	11.3	8.5

[a]Lung cancer rates at ages 40–69 y standardized to the world population, 2000.
[b]Rates at ages 40–69 y considered most reliable.
doi:10.1371/journal.pmed.0050185.t001

Table 2. Comparison of Incidence and Death Rates (Per 100,000) from Lung Cancer among Women in Five Countries and Two Time Periods

Country/ Region	Variable	Region/ City	Years	Age Group (y)														Age Standardized[a] Rate
				20–24	25–29[b]	30–34[b]	35–39	40–44	45–49[b]	50–54[b]	55–59	60–64	65–69[b]	70–74[b]	75–79	80–84	85+	
United States	Mortality [18]	US	1935–1940	0.2	0.5	0.8	1.3	2.5	4.1	6.5	9.1	11.7	14.7	16.4	15.6	13.6	10.4	7.1
	Incidence [17]	CT	1935–1940	0.2	0.7	1.3	1.0	4.5	4.7	7.6	9.7	13.3	17.5	23.6	23.2	17.5	11.3	8.5
India	Mortality [33]	Mumbai	1984–1987	0.0	0.2	0.2	0.5	1.0	1.6	4.9	6.4	7.2	14.8	20.4	20.7	—	—	5.0
India	Incidence [15]	Ahmedabad	1983–1987	0.1	0.1	1.0	0.5	1.8	2.1	5.3	7.8	8.2	12.8	15.1	11.3	7.8	—	5.4
		Bangalore	1983–1987	0.1	0.1	—	0.6	2.1	1.7	4.9	5.1	10.2	12.3	6.2	12.0	—	—	5.2
		Mumbai	1983–1987	0.2	0.3	0.3	1.3	1.9	3.3	5.1	10.0	10.2	22.1	21.7	18.1	—	—	7.3
		Madras	1983–1987	—	0.1	0.3	1.3	2.0	2.7	5.0	5.6	3.3	7.4	4.3	3.5	—	—	4.0
Hong Kong	Mortality [33]	All	1983–1987	—	0.9	—	5.1	—	22.2	—	76.3	—	185.6	—	259.4	—	—	48.4
	Incidence [15]	All	1983–1987	1.0	2.4	2.7	6.6	14.2	24.4	43.8	80.8	139.6	195.9	280.5	314.3	344.7	390.2	68.6
Thailand	Mortality [33]	All	1983–1987	—	0.3	—	1.0	—	3.7	—	6.8	—	13.6	—	16.4	—	—	5.5
	Incidence [15]	Chiang Mai	1983–1987	—	2.1	2.6	4.7	23.9	37.2	101.3	140.9	153.2	135.9	93.7	118.4	—	—	87.8
		Khon Kaen	1988–1989	—	3.2	—	1.1	2.6	8.0	9.2	18.1	15.1	34.0	19.2	37.7	—	—	12.3
Japan	Mortality [33]	All	1983–1987	—	0.6	—	2.6	—	7.5	—	20.8	—	55.2	—	105.0	—	—	14.4
	Incidence [15]	Osaka	1983–1987	—	0.6	0.5	1.6	4.3	7.1	14.8	25.8	39.4	73.4	108.8	154.5	157.7	150.3	22.3
		Saga	1984–1986	—	—	3.0	1.0	7.1	7.1	8.6	22.2	31.4	55.2	82.1	88.0	121.2	137.7	18.2
		Yamagata	1983–1986	—	—	2.7	3.3	7.6	5.7	11.4	22.8	30.9	42.8	73.2	106.5	120.6	86.5	17.1

a Standardized to IARC World Population, 2000; ages 40–69 y.
b Mortality rates for women in Hong Kong, Thailand, and Japan were reported in 10-y intervals. Two of the age categories (35–44 y and 65–74 y) overlapped with the age range of 40–69 y. We therefore estimated the rates for ages 40–44 y and 65–69 y in the three populations using a weighted average of the 10-y intervals, using the ratio of the incidence rates to distribute the mortality rate into 5-y intervals.
doi:10.1371/journal.pmed.0050185.t002

Table 3. Total Number of Lung Cancer Cases and Deaths among Lifelong Nonsmokers Included in the Pooled Analyses of Cohort Studies

Race/Ethnicity	Deaths			Incident Cases		
	Men	Women	Total	Men	Women	Total
European Descent	899	2,229	3,128	899	2,229	3,128
African American	39	146	185	39	146	185
Asian	486	996	1,482	486	996	1,482
Total	1,424	3,371	4,795	1,424	3,371	4,795

doi:10.1371/journal.pmed.0050185.t003

Rate per 100,000

CPS-II, European descent*

KCPS, Asians†

Legend: Never smokers; Current smokers

* Never smokers rates over 22 years of follow-up of CPS-II (1982–2004)
Current smoker rates over 6 years of follow-up of CPS-II (1982–1988)

† Never smoker rates over 12 years of follow-up of KCPS (1992–2004)
Current smoker rates over 6 years of follow-up of KCPS (1992–1998)
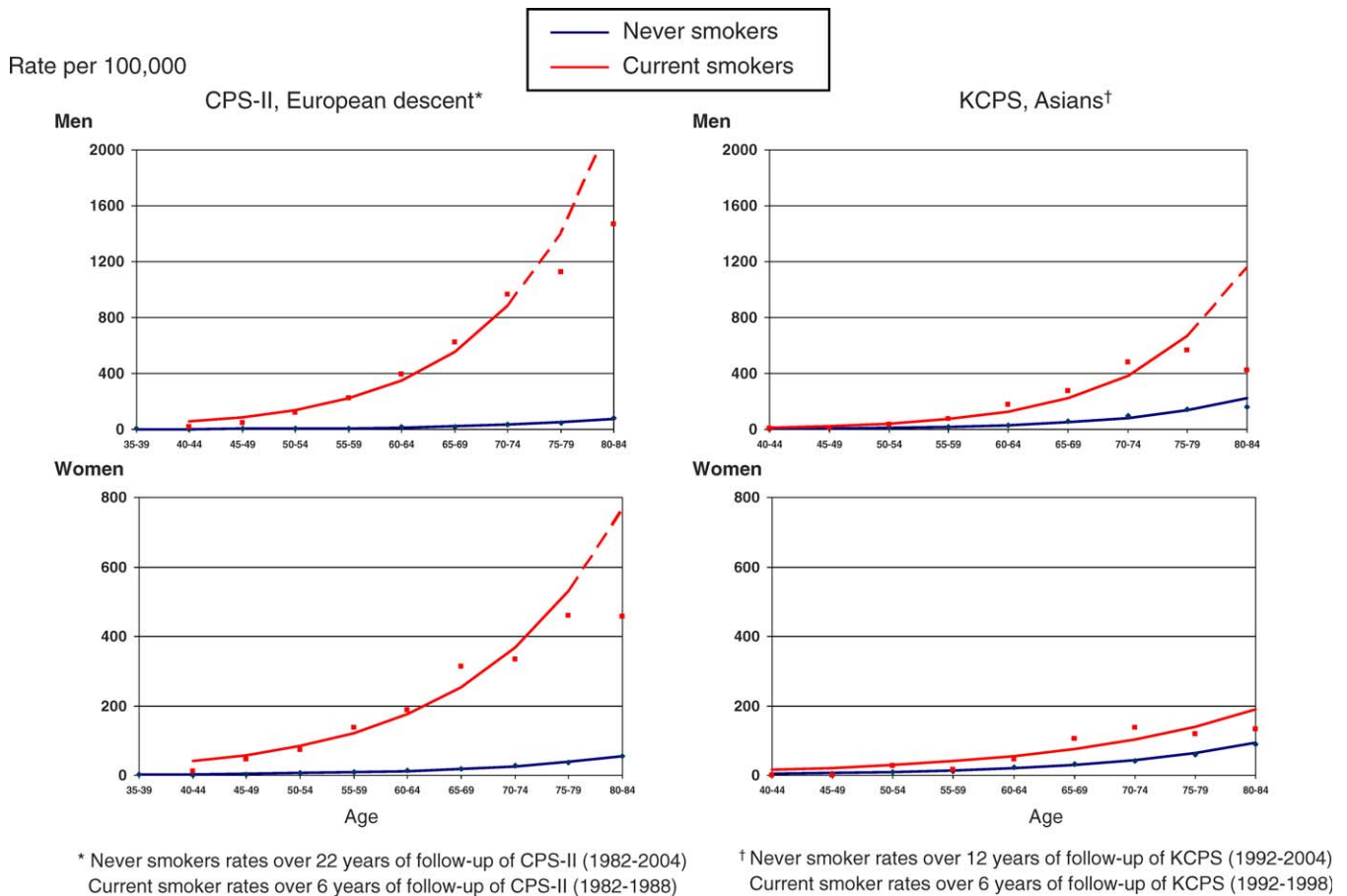
Figure 1. Age-Specific Lung Cancer Mortality Rates Comparing Current Smokers with Never-Smokers in Two Large Cohorts
Blue line indicates never-smokers; red line indicates current smokers.
doi:10.1371/journal.pmed.0050185.g001

exception of Hong Kong and India, the death rates shown [33] pertain to wider geographic areas than the incidence rates and are substantially lower, due to a combination of regional variations in incidence and under-diagnosis of lung cancer in areas outside of the incidence registries. The discrepancy between the regional incidence rate and national mortality rate is especially large in Thailand, where the incidence among women in Chiang Mai is almost 16 times greater than the national death rate, and even the incidence in Khon Kaen is more than twice the national death rate. The issue of regional variability in countries such as Thailand and China is discussed below. Among Japanese women, the regional incidence rates correspond well with the national mortality data, and suggest that lung cancer risk among women in Japan during the 1980s was in fact two to three times higher than that of women in Kuwait or the Basque region of Spain at that time or the incidence rate among US women during the 1930s.

Cohort Studies of Lung Cancer Incidence and Mortality in Never-Smokers

Study populations. As shown in Tables S1 and S2, the cohort studies varied in size, length of follow-up, time period covered, composition (by age, gender, and race), and nature of the cancer endpoint (incidence and/or mortality). The 11 mortality studies are listed first (Table S1), because they are larger and more informative than the incidence studies. Collectively they include 1.4 million women and nearly 440,000 men who reported never having smoked regularly. The eight incidence studies, listed in Table S2, represent more than 630,000 never-smokers (376,600 women and 253,600 men). The total number of lung cancer deaths among lifelong nonsmokers is 4,795, about five times more than the number of incident cases (958) (Table 3). This total is smaller for Asians (1,482) and African Americans (185) than for individuals of European descent (3,128). Most of the incident cases are among women of European descent (511) or men of European descent (284). Fewer than 100 incident cases have been observed to date among Asian (69) or African American (63) women in these cohorts, and even fewer among Asian (22) or African American (9) men (Table 3).

The two American Cancer Society cohorts, CPS-I and CPS-II, contributed over 90% of the mortality data for individuals of European descent (Tables S3 and S4). The age-standardized lung cancer death rate (per 100,000 persons per year) among women of European descent was similar in CPS-I (9.3), CPS-II (10.6), and the NHS (10.3), but lower in the WHS (4.0) when standardized across all ages 40 y and above (Table S3). The death rate (per 100,000) among men of European descent was higher in CPS-I (15.3), CPS-II (13.4), and HPFS (12.6) than in MEC (6.4) when standardized within comparable age ranges. CPS-I represents a time period 20–30 y earlier than

the other cohorts. Larger variations in the death rates were seen between the Asian cohorts from Korea and Japan and the MEC study of Asian Americans (Tables S5 and S6). The age-standardized rates were about twice as high in the massive KCPS cohort and Japanese Three Prefectures study as in MEC. KCPS contributed approximately 90% of all lung cancer deaths in the Asian cohorts.

Comparison of lung cancer death rates between never- and current smokers. Figure 1 shows the age- and sex-specific lung cancer death rates in never-smokers in the pooled data for individuals of European descent (Table S13) and Asians (Table S15) with the death rates among current cigarette smokers in CPS-II for individuals of European descent and KCPS for Asians (death rates in smokers presented in Table S21). The rates for current smokers were based on the first 6 y of follow-up to minimize the effects of smoking cessation, as noted above. Men and women of European descent who smoked actively had lung cancer death rates that were 21.9 and 13.7 times higher, respectively, than the rates of never-smokers, when the rates were standardized to all ages 40+ y.

When expressed as cumulative probability rather than annual death rates, the cumulative risk of dying from lung cancer before age 85 y was 22.1% for a male smoker and 11.9% for a female current smoker, in the absence of competing causes of death. The corresponding estimates for lifelong nonsmokers were a 1.1% probability of dying from lung cancer before age 85 for a man of European descent, and a 0.8% probability for a woman. The actual probabilities are lower because of competing causes of death.

Mortality comparisons by gender and age. Men who reported no history of regular smoking had higher death rates from lung cancer than women in the pooled data for individuals of European descent, Asians, and African Americans (Tables S13, S15, S16, respectively). The rate ratios comparing the male and female death rates reflected significantly higher death rates in men of European descent (rate ratio [RR] = 1.32, 95% confidence interval [CI] = 1.2–1.5) and Asian men (RR = 1.96, 95% CI = 1.4–2.7) than women, at all ages 40+ (Tables S13 and S15, respectively). Age-specific comparisons could not be made among African Americans because of the small number of deaths in men (Table S16). However, the age-standardized death rates were 20%–33% higher in African American men than in African American women, depending on the age range being considered. The gender gap increased with age among individuals of European descent and Asians. Figure 2 illustrates the divergence of the male and female death rates among never-smokers with increasing age in the three largest cohort mortality studies. The gender difference was largest in KCPS for the years 1992–2004, intermediate in CPS-I from 1959 to 1970, and smallest in CPS-II from 1982–2004. When the pooled data were examined by Poisson regression analyses that controlled for study, age significantly modified the association with gender in individuals of European descent ($p = 0.01$) and Asians ($p = 0.0004$) but not African Americans ($p = 0.79$) (Tables S13, S15, S16, respectively). The age-related increase in the rate ratio estimates comparing the male and female lung cancer death rate remained statistically significant in analyses restricted to cohorts or pairs of cohorts that provided data on both men and women (p-trend = 0.002, Table S14).

Mortality comparisons by race. The lung cancer death rates in the pooled analyses were highest in Asians, intermediate in

African Americans, and lowest in individuals of European descent who reported no history of regular smoking (Figure 3 and Table 4). The rate ratio estimates compared to individuals of European descent were statistically significant for Asian men (RR = 1.96, 95% CI = 1.7–2.3), Asian women (RR = 1.69, 95% CI = 1.5–1.8), and African American women (RR = 1.34, 95% CI = 1.1–1.7) when standardized to ages 40–84 y. The rate ratio comparing African American men to men of European descent was similar to that for women (RR = 1.33, 95% CI = 0.9–2.1) (Table 4). It should be noted that among the Asian cohorts (Tables S5 and S6), the age standardized lung cancer death rates were two- to five times lower for Japanese Americans in the MEC study than for men and women in the cohorts from Korea (KCPS) and Japan (Hirayama, JACC, and Three Prefectures). The lung cancer death rates among Japanese living in California and Hawaii were much closer to the rates of individuals of European descent than to the rates of Asians living in Korea and Japan (Tables S5 and S6). Age did not significantly modify the racial differences in risk among lifelong nonsmokers.

Mortality comparisons by time period. The only cohort data that provided meaningful comparisons of lung cancer risk among never-smokers in different time periods were the two American Cancer Society cohorts CPS-I (1959–1972) and CPS-II (1982–2004) [4,34–37]. A previous analysis based on CPS-II follow-up from 1982–2000 found that the lung cancer death rate in never-smokers was higher in CPS-II than in CPS-I among women of European descent (hazard ratio [HR] = 1.25, 95% CI = 1.12–1.41) but not men of European descent (HR = 0.89, 95% CI = 0.74–1.08) [4]. The present analysis extended CPS-II follow-up for 4 additional y and found no statistically significant evidence that the death rate was higher in CPS-II than in CPS-I for women of European descent (RR = 1.11, 95% CI = 0.98–1.25), African American women (RR = 1.15, 95% CI = 0.62–2.13), or men of European descent (RR = 0.83, 95% CI = 0.66–1.05). In other analyses, we divided the CPS-II follow-up into two segments of equal duration and found essentially the same age-standardized death rates among never-smokers during both periods (analyses not shown).

Incidence rates in cohort studies. The lung cancer incidence rates in the cohort studies were based on fewer cases than the mortality studies and were less precise, especially for Asians and African Americans. However, the incidence rate among women of European descent age 40–69 y in the pooled cohort data (Table S17) was very similar to the general population rates among individuals of European descent in populations with a low prevalence of female smoking (Table 1). For example, the age-standardized incidence rate among women of European descent age 40–69 y in the cohort studies was 9.7 per 100,000 (Table S17) compared to 8.5 per 100,000 among US women in the 1930s and 8.6 in the Basque region of Spain during the 1980s (Table 1). At older ages, the female death rates increased more rapidly with age in the pooled cohort data than among women in Connecticut in the 1930s or in the Basque region of Spain during the 1980s. No similar comparisons could be made between incidence rates among Asian women in the cohort studies and women in Asian countries; the only incidence data on Asian never-smokers came from the MEC cohort in North America.

Incidence comparisons by gender and age. The age-specific and age-standardized rate estimates in the cohort studies

Death rates (per 100,000)

A CPS-I, European descent
1959-1972

B CPS-II, European descent
1982-2004
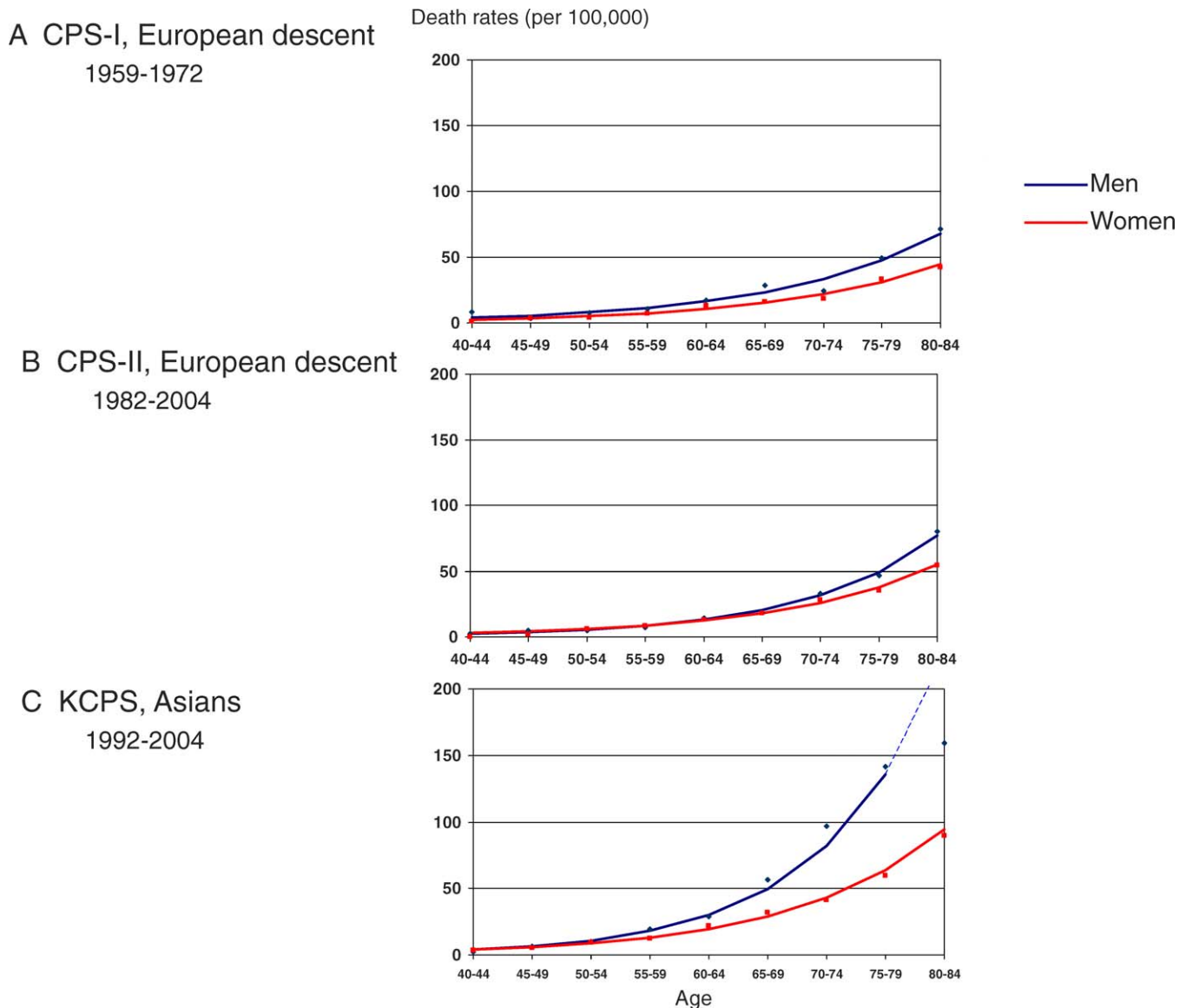
C KCPS, Asians
1992-2004

Age

Figure 2. Sex- and Age-Specific Lung Cancer Death Rates in Three Large Cohorts
(A–C) Blue line indicates men; red line indicates women.
doi:10.1371/journal.pmed.0050185.g002

were much less precise for incidence (Tables S9–S12) than for mortality (Tables S3–S8), even among individuals of European descent. Age-specific comparisons could be made only in this latter group. No meaningful difference was observed between the lung cancer incidence rate in men of European descent (14.0 per 100,000) and women (13.8 per 100,000) who had never smoked, when the rates were standardized to all ages 40 y and above (Table S17). However, the gender relationship observed in the incidence data for individuals of European descent appeared to change qualitatively with increasing age (Figure 4). In the pooled data, women who never smoked had higher incidence rates than men in the age range 40–59 y; similar incidence rates between ages 60 y and 79 y; and lower incidence rates beginning at approximately age 80 y. In only two 5-y age groups (50–54 y and 55–59 y) did the ratio of the male to female rate achieve borderline statistical significance (Table S17). Furthermore, the absolute

difference between the male and female death rates was small, even in these two age groups (absolute difference = 3.9 and 4.4 cases per 100,000 at ages 50–54 y and 55–59 y, respectively). The trend in the rate difference with age was not statistically significant ($p = 0.06$) when all cohorts were included in the pooled analysis. The evidence of a trend was further weakened by restricting the analysis to cohorts or pairs of cohorts that provide incidence data on both sexes ($p = 0.21$) (Table S18).

Incidence comparisons by race and ethnicity. African American women had significantly higher incidence rates from lung cancer than women of European descent who had never smoked (RR = 1.56, 95% CI = 1.1– 2.1). The incidence data available for African American men and Asian men and women were too sparse to make meaningful comparisons. As noted above, incidence data for Asian never-smokers derived entirely from the MEC study in the US (Tables S11 and S12).

Death rate (per 100,000)
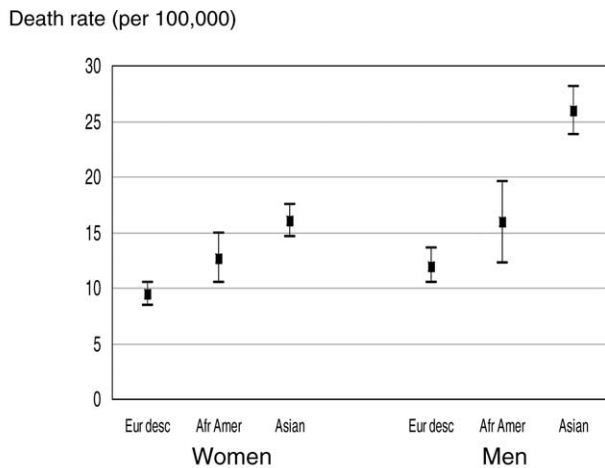
*Rates are age-standardized to the 2000 IARC World population, ages 40-84

Figure 3. Age-Standardized Lung Cancer Death Rates by Race and Sex in the Pooled Analyses

doi:10.1371/journal.pmed.0050185.g003

Frequency of lung cancer in never-smokers versus other cancers in population. We compared the mortality and incidence rates from lung cancer among lifelong nonsmokers in the pooled data for individuals of European descent with US death rates and with SEER incidence rates from other types of cancer in the general population (Tables S22 and S23). The lung cancer death rate in never-smokers was comparable to, and in some cases higher than, the death rate from other types of cancer in the general population, especially at older ages. For example, the death rate among men of European descent who reported never smoking exceeded the general population death rate for melanoma beginning at age 50 y, from cancer of the brain and other nervous system at ages 65+ y, from cancers of the kidney and liver at ages 70+ y, and from cancer of the esophagus at ages 80+ y. The same was observed among women of European descent for cancers of the uterine corpus and liver beginning at age 35 y, for melanoma and cancer of the esophagus at ages 40+ y, for all leukemia at ages 45+ y, for uterine cervix at ages 50+ y, and for cancers of the brain and other nervous system at ages 60+ y.

Using the lung cancer death rates in the pooled data, we estimated the number of lung cancer deaths that would have occurred among individuals of European descent and African Americans in the US in 2004, if the entire population in these two groups, age 40+ y had experienced the death rates of lifelong nonsmokers. We limited the analysis to individuals of European descent and African Americans, because of the lack of reliable death rates or populations at risk for other racial and ethnic groups. The estimated number of deaths (15,943) comprises slightly more than one-tenth the number of lung cancer deaths (154,202) that actually occurred among individuals of European descent and African Americans in 2004. This exceeds the number of deaths reported in 2004 from five of the 12 most common fatal cancers in the US: cancer of the ovary, liver and intrahepatic bile duct, urinary bladder, esophagus, and kidney or renal pelvis.

A similar approach, using the lung cancer incidence rates in the pooled data for never-smokers of European descent and African American never-smokers and the populations, age 40 y and above living in the 17 SEER areas of the US in 2004, estimated that 5,064 incident lung cancers would have occurred if no one smoked. By this estimate, lung cancer among never-smokers would rank 11th among the 12 most common incident cancers in SEER areas of the US in 2004. By comparison, 6,432 cases of leukemia, 4,737 cases of stomach cancer, and 4,516 cases of thyroid cancer were diagnosed among African American residents and residents of European descent of these SEER areas in 2004.

Discussion

To our knowledge, this is the first comprehensive effort to pool and compare data on lung cancer incidence and death rates in lifelong nonsmokers from multiple sources. The combination of data from cohort studies and population registries provides a more coherent picture of how background lung cancer risk varies by age, sex, geographic location, race/ethnicity, and time period than can be obtained from any single study. All of the available data have limitations and unknowns regarding the accuracy of the diagnostic information, the validity and comparability of the exposure information on active smoking or its absence, and the lack of measurements of other exposures that affect lung cancer risk. In the interest of clarity, however, we first discuss the series of questions raised in the introduction and later consider how these data limitations could affect our conclusions.

Table 4. Comparing Pooled Lung Cancer Rates (Per 100,000) among Lifelong Nonsmokers by Race

Variable	Category	Men		Women	
		Age-Standardized Rate[a]	Rate Ratio[b]	Age-Standardized Rate[a]	Rate Ratio[b]
Mortality	European Descent	12.0 (10.5, 13.6)	1.00 (referent)	9.5 (8.5, 10.5)	1.00 (referent)
	African American	16.0 (12.3, 19.6)	1.33 (0.9, 2.1)	12.7 (10.5, 15.0)	1.34 (1.1, 1.7)
	Asian	26.0 (23.8, 28.1)	1.96 (1.7, 2.3)	16.1 (14.6, 17.5)	1.69 (1.5, 1.8)
Incidence	European Descent	11.2 (9.8, 12.6)	1.00 (referent)	12.4 (11.3, 13.5)	1.00 (referent)
	African American	12.3 (3.2, 21.4)	1.10 (0.5, 2.3)	19.4 (14.2, 24.6)	1.56 (1.2, 2.1)
	Asian	12.9 (6.7, 19.1)	1.15 (0.7, 1.9)	15.0 (10.4, 19.7)	1.14 (0.8, 1.6)

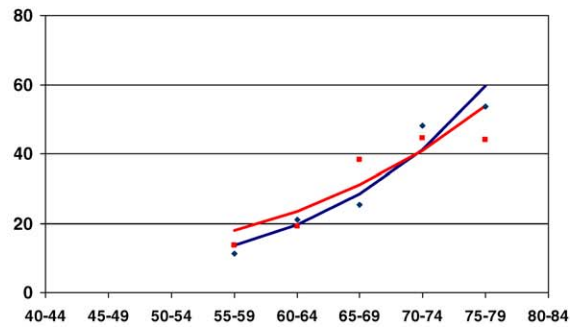[a]Standardized to the IARC World Standard Population for 2000, ages 40–84 y (95% confidence intervals).
[b]Rate ratio in comparison to individuals of European descent.
doi:10.1371/journal.pmed.0050185.t004

A Pooled data

Incidence rates (per 100,000)
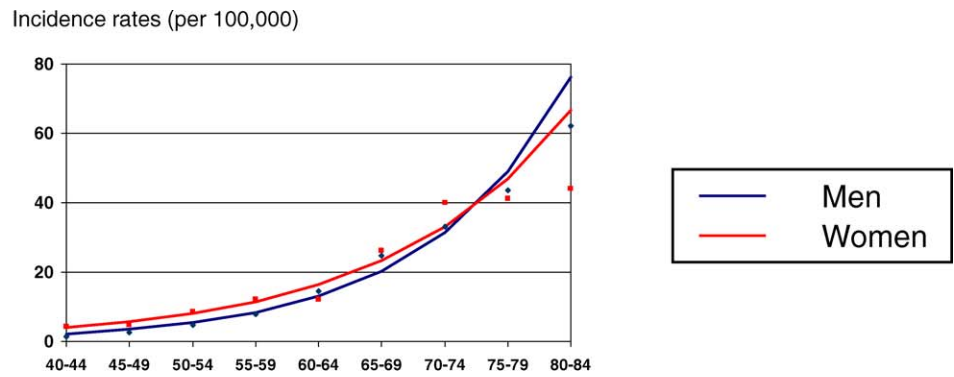
B CPS-II Nutrition

C Pooled data (excluding CPS-II Nutrition Cohort)
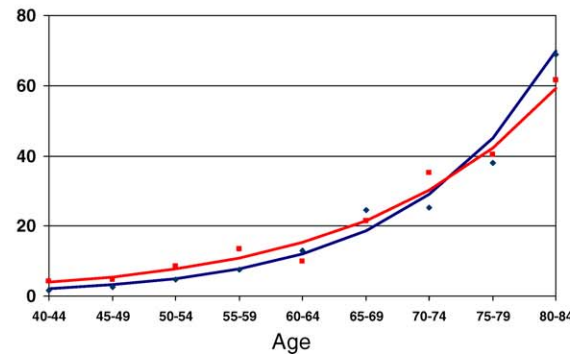

Age

Figure 4. Sex- and Age-Specific Lung Cancer Incidence Rates in Individuals of European Descent, with and without CPS-II Nutrition Cohort
(A–C) Blue line indicates men; red line indicates women.
doi:10.1371/journal.pmed.0050185.g004

How Common Is Lung Cancer in People Who Have Never Smoked Actively?

The incidence of lung cancer among lifelong nonsmokers falls within the National Cancer Institute's (NCI) definition of a "rare" cancer (fewer than 40,000 cases per year, age-standardized incidence rate <15 per 100,000). The incidence rate approximates that of brain cancer (plus other nervous system cancers) in the SEER registries for individuals of European descent under age 70 y. At older ages, the incidence rates increase more rapidly than the incidence of brain cancer and become comparable to the SEER incidence rates for liver and kidney cancer.

The lung cancer incidence and death rates among never-smokers are predictably much lower than those of smokers. Men who report never smoking have a 1.1% cumulative risk of dying from lung cancer before age 85 y in the pooled analysis of individuals of European descent; the corresponding estimate for women is 0.8%. This compares to cumulative risk estimates of 22.1% and 11.9% for male and female current cigarette smokers, respectively, during the first 6 y of

follow-up of CPS-II. Nevertheless, the disease burden from lung cancer would be comparable to that of many other cancers, even if the entire population experienced the death rates of lifelong nonsmokers. While we lack information on the lung cancer death rates among Hispanic, Native American, and Asian never-smokers who live in North America, we can make such estimates for individuals of European descent and African Americans. Our estimate that approximately 16,000 lung cancer deaths would have occurred among individuals of European descent and African Americans, ages 40–79 y in 2004, had the never-smoker rates applied, is larger than the number reported for five of the 12 most common fatal cancers in the US in that year. Lung cancer is obviously a significant public health and medical problem, even beyond the overwhelming disease burden caused by tobacco smoking.

Do Women Have Higher Risk Than Men?

The question of whether women are more susceptible to develop lung cancer than men has been debated since the early 1990s, when reports from case-control studies showed

higher odds ratios in women than in men associated with putatively comparable levels of cigarette smoking [38–40]. These reports were not replicated by large prospective studies in the US [41] or Europe [42,43] that measured lung cancer mortality rates. The prospective cohort studies have consistently found higher lung cancer death rates in men than women, both in the presence [41] and absence [4] of active smoking. The literature is less consistent with respect to incidence, however [44]. The debate has been further complicated by publications from national and international Early Lung Cancer screening studies [9,45], suggesting that the gender relationship may be different for incidence than for mortality. Screening studies have found that women are more likely to be diagnosed with lung cancer than men when high risk smokers are tested with low-dose spiral computerized tomography. Although screening studies measure disease prevalence rather than incidence, Henschke and others hypothesize that lung cancer incidence may be higher in women than in men who smoke, even though the opposite is true for mortality [9]. Wakelee et al. provided limited support for this hypothesis by documenting that lung cancer incidence rates were higher in women than men among never-smokers, age 40–79 y in six cohort studies [11].

Our findings are much clearer for lung cancer mortality than for incidence. The lung cancer death rates are higher in men than women who have never smoked, and the gender difference in mortality increases with age. This has been previously reported for individuals of European descent and African Americans [4]; the addition of new data from Korea [27] and Japan [25,26], extends this finding to Asians. The gender difference in mortality may be narrowing over time, as suggested by the decrease in the HR comparing the male to female rate in CPS-I (HR = 1.52, 95% CI = 1.28–1.79) to that in CPS-II (HR = 1.21, 95% CI = 1.09–1.36). Whether this trend will continue into the future is unknown.

In contrast to the mortality findings, the gender relationship observed for lung cancer incidence is more complex and less convincing. We had no a priori hypothesis that age would modify the relationship between gender and lung cancer incidence rates; the rate was higher in women than men before age 70 y, but lower in women than men at age 80 y and above. Chance may explain this unexpected finding. The incidence rate was significantly higher in women than men in only two age groups (50–54 y and 55–59 y). Age was marginally significant ($p = 0.06$) as an effect modifier when all cohorts are included in the pooled analysis; the association is much weaker when analyses consider only those cohorts or pairs of cohorts that provide incidence data on both sexes ($p = 0.21$). Biases may affect some ages more than others. The gender-specific rates vary across cohorts, and different studies contributed differentially to different age groups. In any case, our analyses do not provide independent replication of the Wakelee et al. results [11], since three cohorts (NHS, HPFS, MEC) were included in both studies.

It is nevertheless provocative that younger women have higher lung cancer incidence rates than men among never-smokers of European descent, and that African American and Asian women have higher age-standardized lung cancer incidence rates than men, even though the differences are not statistically significant. Relative survival is somewhat better in women than men among all patients with lung cancer, especially at younger ages [32]. However, unless the gender difference in survival is considerably larger in never-smokers than smokers with lung cancer, one would not expect a 1-y relative survival of 41.3% in women and 38.3% in men to account for the gender pattern in lung cancer incidence that we observed.

Do African Americans Have Higher Risk Than Individuals of European Descent?

The pooled cohort data strengthen the evidence that lung cancer risk is higher in African Americans than individuals of European descent who have never smoked. The death rate from lung cancer was previously reported to be higher in African American women than in women of European descent in CPS-II [4], but with limited data for African American men, and no information by which to compare incidence rates in individuals of European descent and African Americans. The pooled data in these analyses add new information on mortality rates among African American from BWHS, MEC, and additional follow-up of CPS-II, and new data on lung cancer incidence from BWHS, MEC, and the CPS-II Nutrition cohort. The lung cancer mortality rate among African Americans who report no active smoking, compared to that of individuals of European descent, is higher for both women (RR = 1.34, 95% CI = 1.1–1.7) and men (RR = 1.33, 95% CI = 0.9–2.1) in the age range 40–84 y. Similarly, the incidence of lung cancer is higher in African American women than in women of European descent who have never smoked (RR = 1.56, 95% CI = 1.1–2.1); there are too few cases among African American men to make meaningful comparisons. These data support the hypothesis that lung cancer incidence and death rates are higher among African Americans than individuals of European descent, even in the absence of active tobacco smoking, and that this difference in baseline risk may explain part but not all of the disparity in risk observed between African American and smokers of European descent.

Do Asians Have Higher Lung Cancer Risk Than Individuals of European Descent?

Lung cancer incidence rates were higher and more variable among women in East Asia than in other geographic areas with low prevalence of female smoking. The very high incidence rates observed among women in the Tianjin registry in northeastern China and the Chiang Mai registry in northern Thailand are consistent with the large regional variations that have been reported previously among women in Asia, and especially in China [46–49]. Li et al. reported a 20-fold difference between the lung cancer death rate between Chinese women living in counties at the tenth and 90th percentiles, based on a retrospective mortality survey conducted from 1973 to 1975 [46]. Some of this variation undoubtedly reflects variation in active smoking. The prevalence of active smoking among women in China in 2003 ranged from about 4% in the southern provinces of Hainan and Guangxi to approximately 13% in the northern provinces of Heilongjiang and Inner Mongolia [50]. Other factors likely to contribute to lung cancer risk among Chinese women include indoor air pollution from coal smoke from unventilated coal-fueled stoves [51,52], volatilization of oils from cooking at high temperatures in open woks [53–56], and secondhand smoke [53,57–59]. Older women in northeastern China (Tianjin and Harbin) and northern Thailand (Chiang

Mai and Lampang) have traditionally smoked more than women in other parts of China and southern Thailand. Pipe smoking was once common among older women in northeastern China. A local tobacco product called keeyo was smoked historically by women in northern Thailand. It remains unclear to what extent active smoking versus indoor air pollution from cooking and secondhand smoke contribute to the high rates of lung cancer and chronic obstructive lung disease among women in northeastern China and northern Thailand.

We did not expect that lung cancer incidence rates would be two to three times higher among Asian women, age 40–69 y, living in the Philippines, Hong Kong, Japan, and the Chinese population of Singapore than among Western women of the same age in populations with low female smoking prevalence. Other studies have reported that lung cancer rates have decreased over successive birth cohorts among women in Hong Kong [60] and Singapore [61]. In these countries, the lung cancer incidence rate peaked among women born around 1908 and decreased in later birth cohorts. Further population-based research is needed to characterize lung cancer incidence and death rates among women in Pacific Rim countries by birth cohort, smoking status, and exposure to other factors that may affect risk. The data needed must come from cohort studies and not hospital-based case series that measure proportions rather than rates. Several studies from Korea and other Pacific Rim countries have observed a smaller proportion of active smokers among female lung cancer patients in Asia than in the West [62,63], yet these are difficult to interpret because they measure only the proportion of people who are exposed to the risk factor of interest, not the actual risk (incidence or death rates) among smokers or never-smokers. Active smoking has been considered uncommon among women in most Asian countries, but the relatively high lung cancer rates raise the possibility of incomplete reporting of active smoking.

Has Lung Cancer Risk among Lifelong Nonsmokers Changed over Time?

A challenge in interpreting temporal trends in cancer incidence and death rates is to distinguish actual changes in disease occurrence from artifacts due to changes in disease detection or classification. Technological advances such as bronchoscopy, percutaneous thin needle biopsy, and imaging technologies make it possible to biopsy pulmonary masses without open chest surgery [64]. These technologies particularly affect the rates in older patients, increasing the likelihood that primary lung cancers will be detected, and decreasing the chances that pulmonary metastases will be misdiagnosed as lung cancer. Thus, temporal comparisons are most informative when restricted to the age range 40–69 y, where the diagnostic information was more reliable, even before the advent of these technologies. We find no indication that lung cancer rates have changed among lifelong nonsmokers within this age range in the US since the 1930s. The historical incidence rates among Connecticut women aged 40–69 y in 1935–1940 are similar to the incidence rates in the mid-1980s in other Western countries where female smoking is still uncommon. Likewise, the death rates among US women of this age in the 1930s are similar to the contemporary death rates among never-smokers in the pooled cohort studies. Nor have the lung cancer death rates

changed appreciably among never-smokers from CPS-I (1959–1972) to CPS-II (1982–2004). The death rate was slightly lower in CPS-II than in CPS-I for men of European descent ages 40 y and above (RR = 0.83, 95% CI = 0.66–1.05) but slightly higher for women of European-descent (RR = 1.11, 95% CI = 0.98–1.25) and African American women (RR = 1.15, 95% CI = 0.62–2.13). Even among never-smokers age 80 y and above, the lung cancer death rates in the two studies appear to be converging with longer follow-up of CPS-II.

Our findings do not support assertions by Enstrom, Axelson, and others [12–14,65,66] that lung cancer risk has increased substantially in the United States in lifelong nonsmokers. Most of the increase reported by Enstrom was based on a comparison of national lung cancer mortality rates in 1935 with the much lower death rates recorded in 1914 in a survey of deaths in 24 states conducted by the US Census [67]. However, the 1914 survey was conducted before the International Classification of Diseases (ICD) was modified to include respiratory cancer (1929) or cancers of the lung and pleura (1938) [68]. Furthermore, some of the deaths attributed to tuberculosis in the early 20th century may have involved misdiagnosis of lung cancer. The death rate from tuberculosis decreased by two-thirds between 1915 and 1935 [69], a period when lung cancer mortality was rising, especially in men [70,71]. Several other studies that reportedly found an increase in lung cancer risk among never-smokers [13,14,65,66] relied on statistical modeling rather than direct measurement, and failed to consider the progressive increase in the risks associated with active smoking as the average duration of smoking has lengthened in the population.

Strengths and Limitations of the Analyses

A singular strength of our analysis is its ability to compare incidence and death rates from multiple sources in well-defined populations from different countries, time periods, and demographic subgroups. The general population or ecological data on women cover a 70-y time span and represent the total population—not a selected subgroup—of a diverse range of countries or regions. The pooled cohort data, which provide individual level information on smoking behavior and disease endpoints, yield more stable and statistically precise estimates of age-, sex-, and race-specific incidence and death rates than have been available from individual studies. The use of a common set of weights to standardize for age allows valid comparisons of age-standardized as well as age-specific rates across all groups.

It is reassuring that the pooled incidence and death rates for women age 40–69 y in the cohort studies are similar to those in the general population of countries with a similar level of economic development. It is also noteworthy that the lung cancer incidence rates among male never-smokers in the more affluent cohorts (CPS-II and HPFS) are similar to those in SCW. This argues against the assertion by some [13,14,65] that the CPS-II rates underestimate the occurrence of lung cancer among men in the general population who have never smoked because the participants are less exposed to occupational and environmental pollutants. The incidence and death rates in the different cohort studies are far more remarkable for their similarities than their differences, despite the statistical evidence of some heterogeneity.

Our analyses are limited by uncertainties about the

accuracy and completeness of the diagnostic information, by potential errors in the classification of exposure, and by the paucity of data available to examine risk in relation to race/ethnicity (especially in African American men and Hispanics). Diagnostic errors are especially problematic when comparing lung cancer rates across different time periods or countries at different stages of economic development. Missed diagnoses almost certainly contribute to the low recorded rates of lung cancer in Africa and parts of India during the 1980s, and to the lower incidence and death rates recorded in the oldest age groups. It is not clear how to quantify or minimize this uncertainty, except by restricting comparisons to the age range 40–69 y. Diagnostic errors are less of a concern in the cohort studies than in the ecological data, since most of the follow-up of these cohorts was conducted since 1980 in industrialized countries.

Uncertainties about errors or incompleteness in the exposure information complicate the interpretation of regional variations in lung cancer risk among women in China and other countries in East Asia. Even a small amount of misclassification of smokers among the never-smokers could have a substantial impact on the rates. It is difficult to find historical information on regional variations in active smoking by women or other exposures that may affect lung cancer risk. It is possible that smoking histories may be reported differently in Asia than in the West, and that former smokers or others who consumed relatively few cigarettes over a lifetime were more likely to be classified as never-smokers in the Korean and Japanese cohorts than studies based in Europe or North America.

Our analyses had limited ability to examine risk in subgroups of the population that have been historically underrepresented in cohort studies. Both the incidence and mortality data were especially sparse for African American men and Hispanics. The incidence data were also limited for Asian men and women and African American women. Even in individuals of European descent, the incidence data were not sufficiently robust to resolve whether women under age 60 y have higher lung cancer incidence rates than men, or whether age modifies the gender relationship.

Finally, we did not attempt to identify specific exposures that may contribute to lung cancer risk in various settings. Known risk factors include secondhand smoke, active smoking of other tobacco products, and exposure to other carcinogens such as asbestos, radon, radiation therapy, combustion products, and various other exposures in occupational, environmental, and/or medical settings [4].

Supporting Information

Table S1. Characteristics of Selected Cohorts That Analyzed Lung Cancer Mortality Rates among Lifelong Nonsmokers

Found at doi:10.1371/journal.pmed.0050185.st001 (22 KB XLS).

Table S2. Characteristics of Selected Cohorts That Analyzed Lung Cancer Incidence Rates among Lifelong Nonsmokers

Found at doi:10.1371/journal.pmed.0050185.st002 (20 KB XLS).

Table S3. Lung Cancer Mortality Rates (Per 100,000) among Female Lifelong Never-Smokers of European Descent in Individual Cohort Studies

Found at doi:10.1371/journal.pmed.0050185.st003 (37 KB XLS).

Table S4. Lung Cancer Mortality Rates (Per 100,000) among Male Lifelong Never-Smokers of European Descent in Individual Cohort Studies

Found at doi:10.1371/journal.pmed.0050185.st004 (28 KB XLS).

Table S5. Lung Cancer Mortality Rates (Per 100,000) among Asian Female Lifelong Never-Smokers in Individual Cohort Studies

Found at doi:10.1371/journal.pmed.0050185.st005 (27 KB XLS).

Table S6. Lung Cancer Mortality Rates (Per 100,000) among Asian Male Lifelong Never-Smokers in Individual Cohort Studies

Found at doi:10.1371/journal.pmed.0050185.st006 (27 KB XLS).

Table S7. Lung Cancer Mortality Rates (Per 100,000) among African American Female Lifelong Never-Smokers in Individual Cohort Studies

Found at doi:10.1371/journal.pmed.0050185.st007 (30 KB XLS).

Table S8. Lung Cancer Mortality Rates (Per 100,000) among African American Male Lifelong Never-Smokers in Individual Cohort Studies

Found at doi:10.1371/journal.pmed.0050185.st008 (25 KB XLS).

Table S9. Lung Cancer Incidence Rates (Per 100,000) among Female Lifelong Never-Smokers of European Descent in Individual Cohort Studies

Found at doi:10.1371/journal.pmed.0050185.st009 (35 KB XLS).

Table S10. Lung Cancer Incidence Rates (Per 100,000) among Male Lifelong Never-Smokers of European Descent in Individual Cohort Studies

Found at doi:10.1371/journal.pmed.0050185.st010 (30 KB XLS).

Table S11. Lung Cancer Incidence Rates (Per 100,000) among Asian and African American Female Lifelong Never-Smokers in Individual Cohort Studies

Found at doi:10.1371/journal.pmed.0050185.st011 (30 KB XLS).

Table S12. Lung Cancer Incidence Rates (Per 100,000) among Asian and African American Male Lifelong Never-Smokers in Individual Cohort Studies

Found at doi:10.1371/journal.pmed.0050185.st012 (24 KB XLS).

Table S13. Pooled Lung Cancer Mortality Rates (Per 100,000) among Lifelong Nonsmokers of European Descent

Found at doi:10.1371/journal.pmed.0050185.st013 (40 KB XLS).

Table S14. Pooled Lung Cancer Mortality Rates (Per 100,000) among Lifelong Nonsmokers of European Descent—Only Cohorts with Both Men and Women

Found at doi:10.1371/journal.pmed.0050185.st014 (38 KB XLS).

Table S15. Pooled Lung Cancer Mortality Rates (Per 100,000) among Asian Lifelong Nonsmokers

Found at doi:10.1371/journal.pmed.0050185.st015 (64 KB XLS).

Table S16. Pooled Lung Cancer Mortality Rates (Per 100,000) among African American Lifelong Nonsmokers

Found at doi:10.1371/journal.pmed.0050185.st016 (38 KB XLS).

Table S17. Pooled Lung Cancer Incidence Rates (per 100,000) among Lifelong Nonsmokers of European Descent

Found at doi:10.1371/journal.pmed.0050185.st017 (37 KB XLS).

Table S18. Pooled Lung Cancer Incidence Rates (Per 100,000) among Lifelong Nonsmokers of European Descent—Only Including Cohorts with Both Men and Women

Found at doi:10.1371/journal.pmed.0050185.st018 (39 KB XLS).

Table S19. Pooled Lung Cancer Incidence Rates (Per 100,000) among Asian Lifelong Nonsmokers

Found at doi:10.1371/journal.pmed.0050185.st019 (35 KB XLS).

Table S20. Pooled Lung Cancer Incidence Rates (Per 100,000) among African American Lifelong Nonsmokers

Found at doi:10.1371/journal.pmed.0050185.st020 (35 KB XLS).

Table S21. Lung Cancer Mortality Rates (Per 100,000) among Current Smokers in Two Cohorts

Found at doi:10.1371/journal.pmed.0050185.st021 (32 KB XLS).

Table S22. Comparison between Lung Cancer Mortality Rates in Lifelong Nonsmokers and Mortality of other Cancer Sites in the General Population

Found at doi:10.1371/journal.pmed.0050185.st022 (27 KB XLS).

Table S23. Comparison between Lung Cancer Incidence Rates in Lifelong Nonsmokers and Incidence of Other Cancer Sites in the General Population

Found at doi:10.1371/journal.pmed.0050185.st023 (27 KB XLS).

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Editors' Summary

Background. Every year, more than 1.4 million people die from lung cancer, a leading cause of cancer deaths worldwide. In the US alone, more than 161,000 people will die from lung cancer this year. Like all cancers, lung cancer occurs when cells begin to divide uncontrollably because of changes in their genes. The main trigger for these changes in lung cancer is exposure to the chemicals in cigarette smoke—either directly through smoking cigarettes or indirectly through exposure to secondhand smoke. Eighty-five to 90% of lung cancer deaths are caused by exposure to cigarette smoke and, on average, current smokers are 15 times more likely to die from lung cancer than lifelong nonsmokers (never smokers). Furthermore, a person's cumulative lifetime risk of developing lung cancer is related to how much they smoke, to how many years they are a smoker, and—if they give up smoking—to the age at which they stop smoking.

Why Was This Study Done? Because lung cancer is so common, even the small fraction of lung cancer that occurs in lifelong nonsmokers represents a large number of people. For example, about 20,000 of this year's US lung cancer deaths will be in never-smokers. However, very little is known about how age, sex, or race affects the incidence (the annual number of new cases of diseases in a population) or death rates from lung cancer among never-smokers. A better understanding of the patterns of lung cancer incidence and death rates among never-smokers could provide useful information about the factors other than cigarette smoke that increase the likelihood of not only never-smokers, but also former smokers and current smokers developing lung cancer. In this study, therefore, the researchers pooled and analyzed a large amount of information about lung cancer incidence and death rates among never smokers to examine what factors other than active smoking affect lung cancer risk.

What Did the Researchers Do and Find? The researchers analyzed information on lung cancer incidence and/or death rates among nearly 2.5 million self-reported never smokers (men and women) from 13 large studies investigating the health of people in North America, Europe, and Asia. They also analyzed similar information for women taken from cancer registries in ten countries at times when very few women were smokers (for example, the US in the late 1930s). The researchers' detailed statistical analyses reveal, for example, that lung cancer death rates in African Americans and in Asians living in Korea and Japan (but not among Asians living in the US) are higher than those in people of the European continental ancestry group. They also show that men have higher death rates from lung cancer than women irrespective of racial group, but that women aged 40–59 years have a slightly higher incidence of lung cancer than men of a similar age. This difference disappears at older ages. Finally, an analysis of lung cancer incidence and death rates at different times during the past 70 years shows no evidence of an increase in the lung cancer burden among never smokers over time.

What Do These Findings Mean? Although some of the findings described above have been hinted at in previous, smaller studies, these and other findings provide a much more accurate picture of lung cancer incidence and death rates among never smokers. Most importantly the underlying data used in these analyses are now freely available and should provide an excellent resource for future studies of lung cancer in never smokers.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.0050185.

- The US National Cancer Institute provides detailed information for patients and health professionals about all aspects of lung cancer and information on smoking and cancer (in English and Spanish)
- Links to other US-based resources dealing with lung cancer are provided by MedlinePlus (in English and Spanish)
- Cancer Research UK provides key facts about the link between lung cancer and smoking and information about all other aspects of lung cancer