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Online links

DATABASES
The following terms in this article are linked online to:
CancerNet: http://cancernet.nci.nih.gov/index.html
chronic myeloid leukaemia
LocusLink: www.ncbi.nlm.nih.gov/LocusLink/
APC | *BRCA1* | *BRCA2* | HRAS | *TP53* | *Trp53* | *RB*
OMIM: www.ncbi nlm.nih.gov/Omim/
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FURTHER INFORMATION
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http://zygote.swarthmore.edu/fert6b.html
Computer models of cellular signalling:
www.cellularsignaling.org
Human Genome Sequence: http://www.ncbi.nlm.nih.gov/
Mendel's Genetics:
http://anthro.palomar.edu/mendel/mendel_1.htm
MendelWeb: www.netspace.org/MendelWeb/

TIMELINE

Tobacco and the global lung cancer epidemic

Robert N. Proctor

Tobacco is the world's single most avoidable cause of death. The World Health Organization has calculated that the 5.6 trillion cigarettes smoked per year at the close of the twentieth century will cause nearly 10 million fatalities per year by 2030. Lung cancer is the most common tobacco-related cause of cancer mortality, with one case being produced for every 3 million cigarettes smoked. How was the global lung cancer epidemic recognized, and what can we expect in the future?

The tobacco plant is native to the Americas; archaeological evidence indicates that Mayans were smoking the leaf as early as the first century BC (FIG. 1). Columbus discovered the Arawaks using dried tobacco leaves in several curious rituals, and was offered the plant as a gift. Several of his men took up smoking, and the habit was soon exported to Europe and the rest of the world. Tobacco was used sporadically throughout the seventeenth and eighteenth centuries, although objections were sufficiently strong in many places to have bans enacted. A Chinese imperial edict of 1612 barred growing or smoking the leaf, and the city of Berlin banned smoking in 1723[1]. Smoking was illegal in 14 American states as late as 1921, although none of these bans would survive the decade.

Tobacco has been used in many different forms. Native Americans 'drank' the smoke in hand-rolled palm or maize leaves, whereas European sailors tended to prefer chewing to avoid the hazards of fire. Cigarettes were not popular until the nineteenth century; the French Revolution gave snuff an aristocratic odour and cleared a path for 'little cigars'[2]. Health effects were limited in these early years, however, as the methods most commonly used to cure the leaf made the smoke too harsh to inhale. Cigarettes were also time-consuming to manufacture: the women and girls who hand-rolled cigarettes in the mid 1800s could usually roll only about 200 per day.

Cigarette production was given an enormous boost in 1880 with the invention of the Bonsack cigarette-rolling machine (FIG. 2), which could churn out more than 100,000 cigarettes per day. W. Duke, Sons and Company of Durham, North Carolina, installed two such machines in 1884, allowing them to produce an unprecedented 744 million cigarettes in a single year. When combined with mass marketing and the invention of safety matches (in 1855), cigarettes quickly became a popular consumer item. Americans smoked only about eight cigarettes per person per year in the 1880s; by the end of the century, this figure would more than quadruple. Cigarettes were included with the rations of soldiers in the First World War, and many of the young men who entered the war as abstainers returned home as addicts. Consumption was further increased by new methods of advertising and government encouragement, following the recognition that tobacco could supply an impressive streak of tax revenues. Tobacco taxes in the United States, for example, went from about $13 million in 1910 to nearly $5 *billion* ($10^9$) some 60 years later. Tobacco provided 8% of Germany's entire national tax income in the 1930s , and China today earns an even higher percentage (~ 10%). Dependence on tax revenues is one of the main reasons why governments have been reluctant to challenge the tobacco juggernaut. One tobacco company

Figure 1 | **The oldest existing illustration of a smoker — a Mayan god.** (Image courtesy of Imperial Tobacco.)

has even argued that cigarettes can actually save a nation money by killing off the burdensome elderly, obviating the need to pay for medical care and costly pensions[3].

The cancer connection

Cancers caused by tobacco were among the earliest discovered environmental cancers (see TIMELINE). John Hill in England in 1761 warned that "an immoderate use of snuff" could cause cancer of the nose, and Samuel T. von Soemmerring in Germany in 1795 cautioned that pipe smokers were excessively prone to cancer of the lip[4,5]. Such studies fit with an increasing interest in environmental cancer — Percival Pott's 1775 demonstration, for example, that the 'soot wart' of chimney sweeps was an epithelial cancer of the scrotum, and Bernardino Ramazzini's earlier (and less sound) speculation that nuns suffered from high rates of breast cancer as a result of failing to bear children[6].

The nineteenth century saw further efforts to buttress a tobacco–cancer link, using elementary statistics. In 1858, for example, a Montpellier surgeon by the name of Etienne-Frédéric Bouisson recorded that 63 of his 68 patients who suffered from cancer of the mouth were pipe smokers[7]. The famous German pathologist Rudolf Virchow corroborated the connection in the 1860s[8], by which time the tobacco historian Friedrich Tiedemann had reported several cancers of the tongue brought on by smoking[9].

Tobacco cancers of the oral cavity and lip were among the first to be recognized, primarily because they are easily visible, both to doctors and to the suffering patient. Links to cancers of the internal organs — notably bladder and lung — were not discovered until the twentieth century. Internal cancers were more difficult to diagnose, but there was also the already mentioned fact that tobacco smoke was rarely inhaled until the invention of 'flue-cured' tobacco (also known as 'bright' or 'Virginia' tobacco) in the nineteenth century. Charcoal-based fermentation at high temperatures (yielding a bright yellow, flue-cured leaf) allowed a milder, nicotine-rich smoke to be rapidly delivered to the lungs, which helped cigarettes replace cigars and pipes as the favoured form of smoking. Inhalation of cigarette smoke also allowed a new kind of tobacco-related cancer to come to the fore.

Lung cancer was extraordinarily rare before the twentieth century. It was not even described until the eighteenth century (by Giovanni Battista Morgagni), and for many years thereafter was notoriously difficult to diagnose. Only 140 cases had been reported in the world medical literature by 1898[10], and only 374 were known to Adler when he composed his 1912 review[11]. As late as 1919, physicians were still being called in to observe a case, believing they might never see another[2]. The invention of X-ray photography in 1895 made it easier to distinguish pulmonary malignancies from tuberculosis or influenza, although the discovery that many diseases were caused by pathogenic microbes also fostered the impression that cancer, too, might be caused (exclusively) by some kind of infectious agent. The bacteriological revolution made it easier to diagnose lung cancer, but it also diverted attention from what would turn out to be its primary cause.

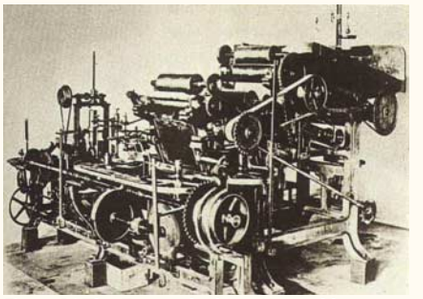
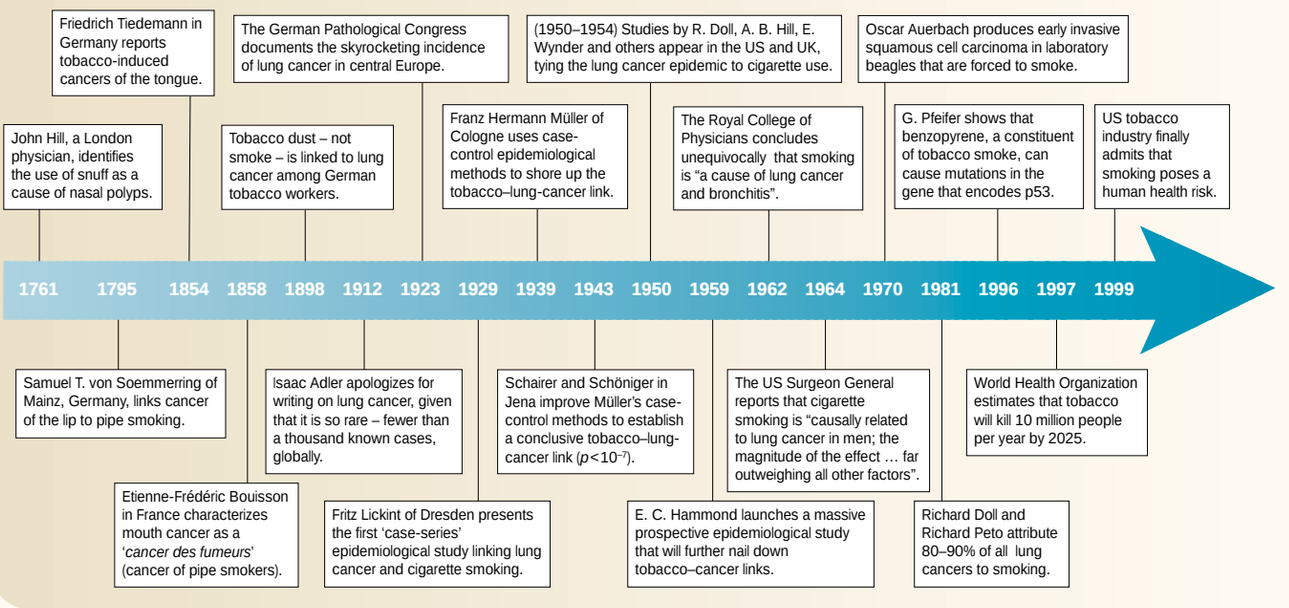


Figure 2 | **The Bonsack cigarette-making machine**. (Image courtesy of Imperial Tobacco.)

In the second decade of the twentieth century, physicians began to notice an increased incidence of the disease. Isaac Adler in 1912 noted that although lung malignancies were "among the rarest forms" of cancer, the disease seemed to be showing "a decided increase"[11]. This was confirmed in 1923, at the annual meeting of Germany's Pathology Association. German pathology was known for its rigour — many German cities required autopsies to identify the cause of death, and several boasted sophisticated cancer registries. It was therefore increasingly difficult to argue that the lung cancer epidemic was purely an artefact of diagnosis.

Timeline | Key events in the discovery of tobacco–cancer causation



There was not yet agreement on what the cause might be: air pollution and traffic exhaust were blamed, as were the delayed effects of the 1919 influenza epidemic, the increasing use of X-rays, increased racial mixing, and exposures to poisonous gas in the First World War[12].

Discovery of the link to cigarettes was made difficult by the fact that lung cancers typically have a time lag between exposure and the onset of symptoms of more than 20 years. This was not yet a familiar phenomenon in medicine, and not something to be expected if cancer was caused by a quick-acting infectious agent. As many other causes seemed possible, and as statisticians did not initially distinguish cancer type by site in the body, it is not surprising that it took some time for the true cause of the epidemic to be appreciated.

The lung cancer link

Adler in 1912 was apparently the first to suggest that cigarettes might be a cause of the lung cancer epidemic. Hermann Rottmann had previously blamed exposure to tobacco-factory dust, an interesting early example of a bias towards occupational causes[13]. A number of observers in the 1920s suggested a tobacco–lung-cancer link, but the first quantitative analysis to support this came from Fritz Lickint — a Dresden physician and ardent tobacco opponent — who, in 1929, showed that lung cancer sufferers were more likely to be smokers[14]. German interest in this issue was given a boost by the rise of Nazism, which tended to frown on tobacco as an unhealthy vice. In 1939, Franz Hermann Müller, a Cologne physician, produced the world's first case-control epidemiological study on the relationship between tobacco and lung cancer, concluding that smoking was the main cause of the epidemic. In 1943, Eberhard Schairer and Ernst Schöniger at the University of Jena published further work with even more careful controls, establishing (with "high probability")[15] that tobacco was the primary cause of the lung cancer epidemic[12,16].

The same conclusion was also reached by a number of other scholars in the German-speaking world — Adam Syrek of Cracow, for example[17], along with Franz Högler in Vienna and the German expatriate, Wilhelm Hueper (although Hueper would later protest what he saw as the exaggeration of the relationship)[6]. In 1942, Berthold Ostertag reported that the increased incidence in lung tumours among smokers was "well established and undisputed"[18]. Angel H. Roffo of Argentina had, by this time, induced cancers on the ears of rabbits by rubbing them with tobacco tars, and though subsequent critics objected that he had burnt his tobacco at unrealistically high temperatures[19], his work nonetheless helped shift attention from nicotine to tar as the carcinogenic agent in tobacco smoke.

After the Second World War, British and American scholars further nailed down the link, while German research was in disarray. Richard Doll, A. Bradford Hill, Ernst Wynder and others published epidemiological studies showing more rigorously than before that tobacco was the culprit behind the modern rise of lung cancer[20–24]. These were followed by Ernst Wynder's animal experimental work[25] and the large prospective study by E. Cuyler Hammond of the American Cancer Society in the United States[26], along with further studies by Doll, Hill and others, including cohort studies[27,28]. These new studies used much larger sample sizes and quantified the statistical significance of the results in new ways, enabling Britain's Medical Research Council to assign formal blame to tobacco in 1957[29]. London's Royal College of Physicians summarized these findings in 1962, concluding that smoking was a significant cause of cancer and that steps were needed "to curb the present rising consumption of tobacco"[30]. The United States Surgeon General concluded 2 years later that smoking was "causally related to lung cancer in men" and that the evidence "pointed in similar directions" for women[31].

Despite well-funded attacks and denials from scientists in the pay of the tobacco industry[6], knowledge of the hazards eventually reached a broader public. Cigarette consumption in the wealthier parts of the world began to decline in the 1980s, and tobacco companies shifted their attention to previously untapped markets in Asia, Africa, South America and the new nations spawned by the break-up of the Soviet Union. The Philip Morris company in its 1997 *Annual Report* stated that global opportunities for cigarette sales were "larger than ever"[32].

Lawsuits against the industry have increased in recent years, following the release of secret documents showing that the main United States tobacco companies knew about the smoking hazard long before they admitted

Box 1 | The evolution of tobacco industry strategies

The tobacco industry has been creative in finding new ways to keep cigarettes on the market. In the 1950s, the industry developed the strategy of insinuating doubt about the hazards of tobacco. When epidemiological studies showed higher rates of cancer and heart disease, the industry responded by saying that the hazard had not yet been proven in animals. When the hazard was demonstrated in animals, the industry responded that the link was "merely statistical". Since the 1950s, when the Tobacco Institute and Council for Tobacco Research were established, the industry has spent hundreds of millions of dollars on basic tobacco biochemistry, directing attention away from the simple fact that stopping smoking can save lives.

It wasn't until the late 1990s that the tobacco industry conceded, following the release of secret internal documents[33], that tobacco was a "risk factor" in the development of certain diseases. The concession was part of a larger legal strategy to argue that the risks of smoking have been well-known for decades, and that people therefore voluntarily assume such risks when they take up the habit.

With the decline in smoking in developed nations, marketing targets have shifted to the developing world and nations with weak anti-smoking movements. Some of the strategies now being used to extend global cigarette use include:

- mass advertising, including billboards, television advertisements and film implants (including paying actors to smoke on camera)
- sponsorship of sporting and cultural events
- marketing in countries where health regulations are weak
- political lobbying to keep down cigarette tax rates and to counter tobacco legislation
- aggressive marketing to children and teenagers
- marketing using sexual and 'adventure' imagery
- encouragement of smuggling to circumvent taxation (e.g., in Canada)
- targeting of women to increase 'gender equity' in smoking.

Such efforts have been accompanied by continued attempts to challenge anti-smoking programmes; there have also been efforts to discredit the credentials of anti-smoking advocates and to re-orient public debate from 'health versus the tobacco industry' to 'smokers versus the anti-tobacco lobby.'

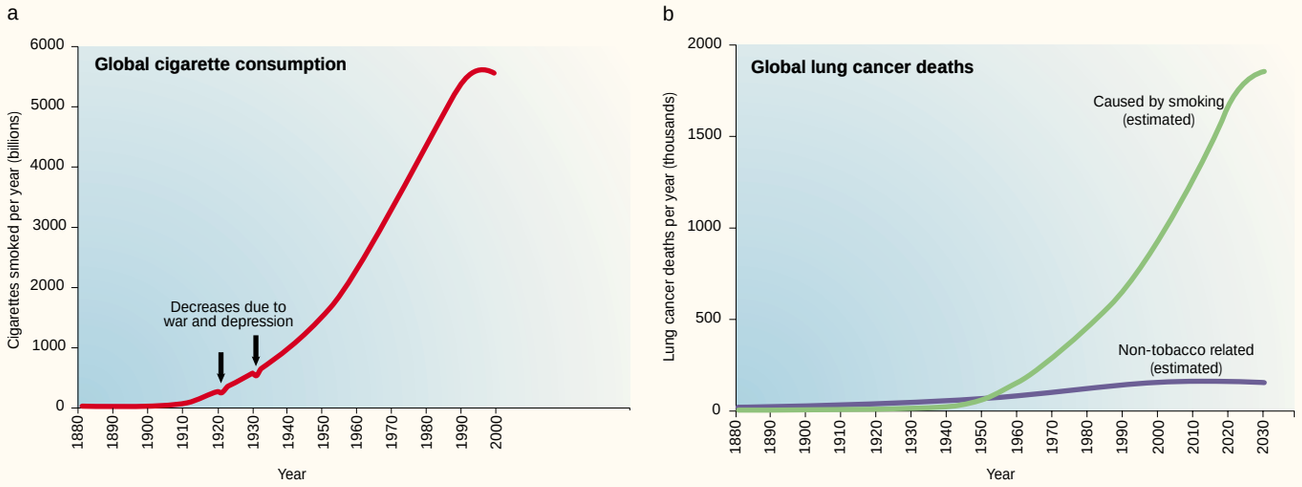


Figure 3 | **Global cigarette consumption (a) and lung cancer mortality (b), 1900–2030.** Consumption peaked in the 1990s; lung cancer rates will not peak until 2020 or 2030. Consumption figures for the pre-1950 period are based on data from P. N. Lee[46] and estimates of United States production and global market share. Consumption is assumed to be roughly equal to production in both cases. Production (= consumption) data for 1950–1998 are from the Worldwatch Institute and the United States Department of Agriculture. Post-1950 figures are minimum values, as hand-rolled cigarettes are ignored. Pre-1990 lung cancer rates are calculated from the assumption that one lung cancer death is generated for every 3 million cigarettes smoked, with a 35-year time lag between consumption and mortality. Non-tobacco-related lung cancers are those from 'background' sources such as naturally occurring radon, occupational exposures such as asbestos, petrochemical products, inhaled radioactive gases from mining, spontaneous tumours, and tumours from X-rays or unknown causes. Post-2000 projections assume no improvements in lung cancer treatment.

it, and that they later tried to cover up that knowledge[33]. The legal strategy of the tobacco companies shifted in the mid-1990s — from denying the health 'risk' flat-out, to arguing that it has been known for centuries, and that people therefore have only themselves to blame for taking up the habit (BOX 1).

Global cancer consequences

The scientific case against tobacco was essentially closed by the 1950s, though subsequent work would add new ways to prove the causal link, along with new insights into carcinogenic mechanisms. The pathologist Oscar Auerbach in 1970 showed that several of the beagles he had taught to smoke had developed lung cancer[34] and, in 1981, Doll and Peto published their conclusion that cigarettes must be considered a cause "of all, or nearly all, of the excess of lung cancers observed among smokers"[35]. That same year, Takeshi Hirayama, in Japan, showed that second-hand smoke could cause lung cancer[36] and, in 1996, Gerd Pfeifer *et al.*[37] showed that tobacco smoke caused mutations in one of the best-known tumour-suppressor genes, *TP53*, encoding the famous p53 protein. In recent years, epidemiologists have begun to examine the nature and extent of the global tobacco catastrophe, also exploring approaches that might help slow the epidemic[38].

The World Health Organization (WHO) has estimated that tobacco will cause about 10 million deaths per annum by the year 2020 or 2030 (REF. 39). That figure could prove to be a slight overestimate, but only if tobacco consumption rates decline dramatically. Recent figures indicate that total world consumption peaked in the mid 1990s, and has actually begun to fall (*per capita* consumption culminated in 1990)[40]. Even if we see a decline from this point on, however, deaths from smoking-induced heart disease and cancer will continue to grow over the next two or three decades (because of the time lag), assuming no dramatic breakthroughs in the treatment of heart or lung disease. Roughly a quarter of these deaths will be from lung cancer, and most will be in developing nations. The WHO has estimated that more than 100 million people will die from tobacco-related disease over the next 30 years — more than from AIDS, tuberculosis, car accidents, homicide and suicide combined[41].

One convenient way to think about the lung cancer epidemic is in terms of how many cigarettes it takes to generate a given kind of cancer. Cigarette smoke is unlike radon, asbestos, aniline dye or most other carcinogens in that the dosages delivered to the body are remarkably uniform. Cigarettes are pretty much the same size and composition throughout the world, as are the routes by which the body is exposed. And as consumption rates are carefully recorded by governments (primarily for taxation purposes), it is fairly easy to predict the long-term cancer consequences of a given level of consumption. How many cigarettes does it take — on average — to produce a lung cancer? And what does this tell us about the future of global cancer rates?

Max Parkin *et al.*[42] have estimated a global annual lung cancer toll of 1,240,000 new cases (incidence) and 1,100,000 deaths (mortality) for the year 2000. Assuming that 85% of all lung-cancer deaths are caused by tobacco[43], this gives a global toll of about 935,000 lung-cancer deaths per annum. As a nation's lung cancer burden seems to be an expression of smoking levels that were in existence roughly 35 years previously (on average), this means that the 3×10^{12} cigarettes smoked per year in the mid-1960s gave rise to about 900,000 lung-cancer deaths, or about one lung-cancer death for every 3 million cigarettes smoked. This is consistent with the tobacco–cancer trajectory of many individual nations. In the United States, for example, there were about 162,000 lung-cancer deaths in the year 2000[44]. The 510 billion cigarettes that were smoked in 1965 yielded a harvest of $0.9 \times 162{,}000 = 146{,}000$ tobacco lung-cancer deaths in the year 2000, assuming that 90% of all lung cancers were tobacco induced. (In 'late-stage' epidemic countries such as the United States, we can assume that a slightly higher fraction of all lung cancers are due to tobacco, hence the 90% figure.) That turns out to be about one lung-cancer death for every 3 million cigarettes. This is also consistent with what we know about lifetime individual risks of smoking, as a person who smokes 10,000 cigarettes per year for 50 years has a one in

six chance of dying from lung cancer. Again, this means that one lung cancer is produced for every 3 million cigarettes smoked in a given society (FIG. 3).

There are obviously a number of assumptions built into such estimates: that cigarettes are pretty much the same throughout the world (and over time), that most lung cancers are caused by tobacco, that lung cancer treatment contributes negligibly to survival rates, that dose-response curves are essentially linear, and so on. Some variance might be expected according to changing tar content, what kind of ingredients are mixed with tobacco and differences in national smoking patterns, such as how much of a cigarette is smoked. In Germany after the Second World War, for example, it seems that it took only about 2 million cigarettes to generate a lung cancer, perhaps because of the practice of gathering and smoking cigarette butts[45]. Such estimates might err on the low side, however, if large numbers of cigarettes were being smoked 'unofficially' (for example, from home-grown tobacco). The number of cigarettes required to generate a lung cancer might also be expected to vary according to the stage of the epidemic. In an early stage, for example, a higher cigarette/lung cancer ratio might be expected, if people were smoking fewer cigarettes per person and, therefore, taking longer to develop cancer (from a population point of view). There is also the obvious fact that the fraction of lung cancers due to tobacco will be lower in the early stages of an epidemic, as non-tobacco causes will exercise more of an influence.

In 1997, the World Health Organization estimated that in the developed world, where cigarette smoking has a longer history, lung cancers account for about 27% of all smoking-related deaths. In China, by contrast, lung cancer seems to account for only about 15% of all smoking fatalities (and tobacco has a more important role in causing diseases such as liver and stomach cancer)[43]. The percentage of lung cancer fatalities (among all tobacco-related fatalities) is expected to grow, as global smoking history comes to look more like that of the developed nations. In countries such as India and China, the tobacco epidemic seems to be unfolding much as it did in the United States and in Europe some 40 years previously. China's per capita consumption of cigarettes more than quadrupled from 1965 to 1995, for example. The world's most populous nation now produces — and smokes — 1.7 trillion cigarettes each year, about a quarter of the world's supply.

A billion tobacco deaths?

Tobacco caused the deaths of about 100 million people in the twentieth century. If consumption rates do not decline from present rates, there could be as many as 1 billion deaths from tobacco in the twenty-first century, including 250 million from lung and other cancers. Hopefully, this is an overestimate. Even if everyone on the planet were to quit tomorrow, however, the death toll from that point on would still be in the tens of millions. Much depends, of course, on what kinds of approaches are taken in China, India, Japan and the nations once ruled by the Soviet Union — although it should not be forgotten that US-based firms are still the world's leading exporters of finished tobacco products. Until governments take the problem of global tobacco control seriously[38], the golden leaf of the Americas will remain the world's leading cause of preventable death, and a black mark on our ability to turn knowledge into a force for human health and well-being.

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Online links

FURTHER INFORMATION
Action on Smoking and Health (ASH) Tobacco Global Trends:
www.ash.org.uk/html/international/html/globaltrends.html
American Cancer Society: www.cancer.org
Centers for Disease Control and Prevention: www.cdc.gov
Tobacco Control Archives from the UCSF Library:
www.library.ucsf.edu/tobacco
Tobacco Timeline:
www.tobacco.org/History/Tobacco_History.html

Action on Smoking and Health (ASH) Tobacco Global Trends
www.ash.org.uk/html/international/html/glob-altrends.html

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Biography

Robert N. Proctor is Distinguished Professor of History at Pennsylvania State University and the author of, most recently, *The Nazi War on Cancer* (Princeton Univ. Press, 1999) and *Cancer Wars* (Basic Books, 1995). His research interests coalesce around the political history and philosophy of science; he has also written on environmental policy, bioethics, molecular anthropology, theories of cancer causation and the "social construction of ignorance". He has held positions as Senior Scholar in Residence at the United States Holocaust Memorial Museum in Washington, DC (1994), and as Visiting Fellow at the Max–Planck–Institute for the History of Science in Berlin (1999–2000). He is now working on a book on human origins, a book on Darwinism and a book on agates.